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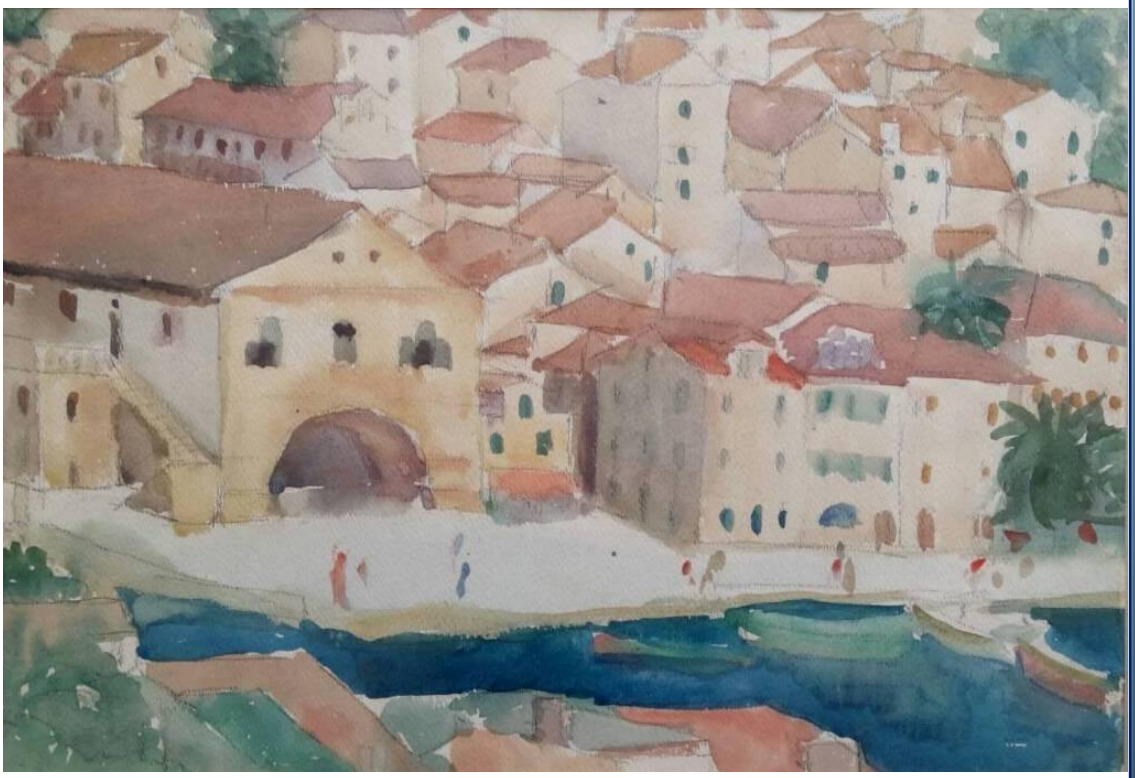

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PATHOLOGICAL FINDING OF AUDITORY EVOKED POTENTIALS IN PATIENTS WITH VERTEBRAL ARTERY HYPOPLASIA ASSOCIATED WITH POSTERIOR CIRCULATION STROKE

Biljana Živadinović, Stefan Todorović, Eva Antić, Mina Stojković, Milan Janković

Abstract: The aim of the paper was to determine clinical significance of pathological finding and characteristics of auditory evoked potentials (AEP) in patients with posterior circulation stroke caused by vertebral artery hypoplasia (VAH). The study enrolled 71 patients, 31 of them had posterior circulation stroke. The results of the examinations showed that pathological AEP finding was statistically significantly correlated with posterior circulation stroke (PCS) finding. Changes in AEP amplitude presented a prominent feature of stroke caused by vertebral artery hypoplasia and require further clinical investigations.

Key words: VAH, VA, PCS, AEP

1.Introduction

The vertebral artery (VA) is the first lateral branch of the subclavian artery. It is rarely a direct branch arising from the aortic arch. Considering the long course of this artery from its origin, it can be divided into 4 topographic divisions: pars prevertebralis, pars cervicalis, pars atlantica and pars intracranialis (1).

Only ¼ of the population have both vertebral arteries of the same caliber.

In general population the VAs are commonly asymmetric in caliber. In about 50% of cases the left vertebral artery lumen is wider, whereas the diameter of the right VA is less commonly larger (25%) (1). Besides these physiological differences in diameter, one of the potential pathological changes on vertebral artery is vertebral artery hypoplasia (VAH). This entity is an uncommon congenital anomaly of blood vessels (2,3). There is a lack of agreement in defining VAH. The current definition means the diameter is equal or less than 2mm, and up to 3mm in some studies (3).

Additionally, VAH definition should be complemented with hemodynamic parameters as well, assessed by Colour Doppler sonography (CDS). Thus, there is reduced blood flow velocity in VAH, systolic velocity less than 40cm/sec, and increased resistance index value (IR)>0.75. Some studies define a clear distinction in the reduction of blood flow in the group of patients with hypoplasia, with VA flow volume of81.6 ± 16.5ml/min, whereas it was 123± 13,5ml/min in the group without VAH (4). Apart from the aforementioned, more common domination of physiological asymmetry of the left VA caliber, right-sided VAH is twice as common as left-sided VAH. (4,5).

VAH results in chronic vascular insufficiency of vertebrobasilar arterial territory and, apart from well known risk factors (age, hypertension, cardiac diseases …), it may also be a risk factor of posterior circulation stroke-PCS. Although PCS is primarily diagnosed by clinical and radiological assessment, useful data and information on determining lesion location may be obtained by electrophysiology, especially by auditory evoked potentials (AEP), being an important predictor of final outcome assessment (6). AEP is an electrophysiological method that has normally been utilized to diagnose pathological changes of the brainstem (7).

Considering the fact that each AEP wave is generated within the brainstem vascularized by posterior circulation arteries (VA and its branches), this method adds relevant information for diagnostics and localization of lesions in the brainstem (8). Special significance of AEP in diagnostic process is also due to the fact that this method is a clinically reliable one, independent of iatrogenic complications of medications: barbiturates and anaesthetics (9).

2. Aims of the paper

1. Investigate the significance of AEP in diagnostics of posterior circulation stroke
2. Determine clinical relevance and potential positive correlation between AEP pathological finding in patients with VAH and posterior circulation stroke.

3. Determine the features of AEP findings in patients with posterior circulation stroke caused by VAH.

3. Patients and methods

This study is a prospective one, enrolling 71 patients. Out of them, 31 patients were in the experimental group, with posterior circulation stroke. The control group included 40 patients with nonvascular etiologic changes in the brainstem. All the patients underwent Computed Tomography (CT) of the brain, which revealed PCS. In cases of small lesions in the brainstem undetectable by CT, magnetic resonance imaging (MRI) of the brain was performed. Carotid arteries colour Doppler imaging was performed in all the patients using Esaote MyLab 70 apparatus, linear probe of 4-11MHz, with pulse repetition frequency PRF of 1-1.8 kHz. The insonation of the V2 segment of vertebral artery was performed in two adjacent intervertebral spaces. Apart from other common parameters (systolic and diastolic velocity, resistance index RI), blood vessel diameter was also measured. The diagnosis of VAH by using the ultrasound with Doppler was specified by the VA diameter of 2mm or less. In patients with suspected VAH observed on Doppler ultrasound, it was verified by computed tomography angiography (CTA), or magnetic resonance angiography (MRA).

All the patients from both groups underwent AEP monitoring on Nihon Kohden's Neuropack M1device, with time base of 10ms, frequency of 5 stimuli per second, a total of 2048 stimuli. A specific type of signal (alternate click of 70dB above hearing threshold) stimulated auditory nerve and the response generated along the auditory pathway and registered at certain points of the scalp by silver disc electrodes was monitored. Active electrodes were placed on the mastoids (A1,A2), reference electrode on the vertex, and ground electrodes on the forehead. In this way both peripheral and central portion of the auditory pathway can be assessed, since seven negative waves within 10ms after stimulation with different amplitude and latency (analyzed later) and interwave latency as well (I-III, III-V, I-V interwave intervals) were obtained as a response to the stimulus. Pathological finding is defined by diminished amplitude of waves (50% less than normal values), poorly formed waves, absence of some waves, as well as prolonged absolute latencies of certain waves and also prolonged inter-wave latencies, IWL. The reference values of all the parameters have already been established as a standard within our institution.

All the obtained results are statistically analyzed and presented in tabular form. Upon admission to the department, patients signed an informed consent for the required therapeutic and diagnostic procedures.

4. Results

Table 1 AEP finding in patients of both experimental and control group

AEP finding	Experimental group	%	Control group	%
Normal	7	22.51 %	33	82.5%
Pathological	24	77.49 %	7	17.5%
Total	31	100 %	40	100 %

The presence of pathological AEP finding is statistically significantly more common in patients with PCS. Chi square is 25.5;$p < 0.01$.

Table 2 Distribution of AEP findings in patients of experimental and control group in relation to the presence and absence of VAH

AEP finding	Experimental group with VAH	Experimental group without VAH	Control group with VAH	Control group without VAH	Total
Normal	3 (23.07%)	4 (22.22%)	2 (50 %)	31 (86.5 %)	40 (56.3%)
Pathological	10 (76.9 %)	14 (77.77%)	2 (50%)	5 (13.88%)	31 (43.6%)
Total	13 (100%)	18 (100 %)	4 (100%)	36 (100%)	71 (100 %)

Statistically significant difference of AEP pathological results between experimental and control group has not been found in relation to the presence of VAH. Chi square was 1.06; $P > 0.05$.

Table 3 Distribution of single, individual characteristics of AEP in patents of experimental and control group in relation to the presence or absence of VAH

AEP finding	Experimental group with VAH	Experimental group without VAH	Control group with VAH	Control group without VAH
Normal finding	3 (23.07%)	4 (22.22%)	2 (50%)	31 (86.1 %)
IWL	2 (15.38%)	4 (22.22 %)	0	1 (2.7 %)
Amplitude	4 (30.76%)	1(5.5 %)	0	1 (2.7 %)
Poorly formed wave	1 (7.69%)	3(16.5%)	0	1 (2.7 %)
Peripheral disorders	1 (7.69%)	1 (5.5 %)	0	0
Retrocochlear lesion	0	1 (5.5 %)	2 (50 %)	2 (5.5 %)
Multiple associated changes	2 (15.38 %)	4 (22.22 %)	0	0
Total	13 (100 %)	18 (100%)	4 (100 %)	36 (100 %)

Changes in the amplitude as an individual characteristic of AEP were statistically significantly observed in patients with VAH in experimental group in comparison to the patients with stroke, but without VAH. Chi square was 7.9; p< 0.01

5. Discussion

VAH is an uncommon congenital anomaly of the VA that results in chronic vascular insufficiency of the posterior circulation of the brain (10). The significance of AEP as an electrophysiological method in diagnosing ischemic changes accompanied with posterior circulation lesions can be found in literature data (11).

The results of our study confirmed that patients with PCS, as the most severe stage of vascular insufficiency, have statistically significantly more common AEP pathological finding (77.49%) in comparison to nonvascular lesions of the subjects in the control group (17.55). This difference is statistically significant. (Chi square was25.5;p<0.01).(Table 1)

Vertebral artery hypoplasia as a separate etiological factor for PCS onset is presented in Table 2. The highest percentage of VAH findings was recorded in the experimental group of patients, 41.93% of them in comparison to the controls (10%).

The relevance of AEP in diagnosing vascular lesions of the brainstem and for lesion site localization originates from the assumption that damage within a region of the brain, being a generator of AEP waves, results in morphological changes, as well as in changes of other characteristics of AEP findings.

Besides a cerebral infarction as the most severe form of posterior circulation ischemia, the significance of AEP in diagnosing transitory ischemic attacks (TIA) has also been described in literature. Usually, TIA patients experience both regression of the disease and improvements of AEPs and clinical manifestation as well. In cases of repeated episodes of TIA (chronic VB insufficiency), permanent changes in AEP analysis have been described. Poorly formed waves, with changes in amplitude (more than 50% drop in amplitude), have been described as a special characteristic of AEP in chronic vertebrobasilar (VB) insufficiency (12).

The results of our study shown in Table 2 illustrate that the percentage of pathological AEP findings was higher in experimental group with VAH in comparison to the controls with VAH (77.9%:50%), but this difference is not statistically significant. Chi square is 1.06;p>0.05.

Table 3 presents characteristics of AEP findings in patients with and without VAH in both experimental and control groups and wave amplitude only was found to be statistically significant. Patients with posterior circulation ischemia associated with VAH had statistically significantly higher percentage of changes in amplitude (30.76%) in comparison to ischemic patients without VAH (5.5%). This difference is statistically significant. Chi square =7.9;p < 0.01.

Similar results related to the relevance of changes in amplitude and waveforms, which are characteristics of AEP in chronic VB insufficiency, have been described by other authors as well (13).

Characteristics of AEP in brainstem infarction, but without distinguishing VAH as an etiological factor, were registered by Wang H in his study. This author identifies prolonged latency of waves III and IV as the most important characteristic of AEP findings in patients with PCS(14).

In one of the papers describing potential complications of stenting of the VA it is pointed out that patients who experienced PCS during

this intervention had prolonged IWL of waves I-V in AEP findings (15).

These changes in aforementioned waves have also been noted by other authors who analyzed AEP findings in patients with basilar artery dolichoectasia and subsequent presence of lacunar infarctions in the posterior circulation (16).

Thorwirth et al described absence of wave III in patients with lesion in pons (17).

Apart from already described changes in amplitude and IWL, changes in absolute latencies of the waves in patients with PCS have been reported in some studies (Drake et al) (18).

5. Conclusion

Pathological AEP finding in patients with VAH has great diagnostic and prognostic value, since it is statistically significantly associated with severe stages of ischemia, that is, with posterior circulation stroke. Alternations in wave amplitude, characteristic of AEP, have been identified as a statistically most significant parameter associated with posterior circulation stroke and concomitant VAH. Further studies,with a larger number of patients are needed, to investigate clinical relevance of AEP findings in patients with ischemic lesions associated with VAH

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ANALYSIS OF ARTERIAL PRESSURE VARIABILITY BY MEASURING PRESSURE ON BOTH ARMS AND AS A FUNCTION OF TIME IN PATIENTS WITH NEWLY DISCOVERED HYPERTENSION

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Summary: INTRODUCTION At the initial office visit, blood pressure should be measured in both arms, ideally with electronic devices that can measure them simultaneously. SBP difference between arms >10 mmHg must be confirmed by repeated measurements. If confirmed, the arm with the higher blood pressure should be used for all subsequent measurements, as its values more accurately reflect the level of blood pressure in the major arteries. Using blood pressure readings on the arm with higher pressure improves outcome prediction. A consistent difference in SBP between the arms >15 to 20 mmHg may be due to atherosclerosis and restriction of the large intrathoracic or supraclavicular arteries, necessitating investigation of arterial disease. The blood pressure values on the right and left brachialis arteries differ in most cases, and the higher one is taken as more accurate. Prognostic significance: for each 10 mmHg difference according to Agarwal (2008), the relative risk of total mortality increases by 24%. In order to accurately assess the degree of hypertension, the spontaneous variability of pressure as a function of time and the pressure difference between the arms must be taken into account. **WORK OBJECTIVES:** 1. Analysis of spontaneous blood pressure variability upon arrival and repeated after 5 to 30 minutes; 2. Blood pressure differences between the left (LR) and right arm (DR). **MATERIALS AND METHODS:** A prospective study was conducted from the database of the "Dr. Bastać" Internal Medicine Practice on 26 patients, average age 58±12 years, with newly discovered hypertension by measuring blood pressure with the indirect manometer method at the first examination immediately after arrival and after 15 minutes. The control group consists of 28 patients who do not have hypertension. The data were statistically processed with the Student's T test. **WORK RESULTS** The mean value (Xsr) of systolic and diastolic blood pressure (SKP/DKP) of the examined group on arrival is 166/92 mmHg on the right hand (DR), and 161/93 mmHg on the left hand (LR). and after rest at DR 153/90 mmHg and LR 149/87. There is a statistically highly significant difference especially between the CAP on the hands - it is always higher on the right hand by an average of 5 mmHg (p=0.002) and 4 mmHg after rest. Spontaneous variability was determined in 10 (40%) subjects where there was a statistically significant drop in tension after rest. After a 15-minute rest, the significance of pressure differences between arms is maintained, but the high variability of 40% post-rest pressure variability is lost. **CONCLUSION**: Pressure on arrival in newly diagnosed untreated patients is always higher on the right arm by an average of 5 mmHg (p=0.002), and after rest 4 mmHg, this difference is maintained. Spontaneous variability was determined in 10 (40%) subjects where there was a statistically significant drop in tension after rest. After 15 minutes of rest, the significance of the pressure differences between the arms is maintained, but the high pressure variability is lost.

Key words: Blood pressure measurement/methods, hypertension/diagnosis, hypertension/pathophysiology, arterial blood pressure variability, blood pressure/difference between left and right brachial artery, hypertension/prognosis

INTRODUCTION:

According to the earlier guidelines and the latest European guidelines from 2023 as well as international guidelines [1-5], the definition of systemic arterial hypertension remains unchanged (short: hypertension) and is defined on the basis of repeated measurements in the doctor's office: equal to and higher than 140 mmHg for systolic pressure and/or ≥90 mmHg for diastolic pressure. Arterial blood pressure (BP) is defined just as

before as optimal, normal, high normal or grade 1, 2, or 3 according to the pressure measured in the office (Recommendation class of evidence I, level of evidence C) [5].

However, it must be known that there is a continuous relationship between BP levels and cardiovascular, renal and fatal events starting with a pressure >115/75 mmHg [6], and that is why the definition is arbitrary and pragmatic due to the simplification of the diagnosis and the treatment.

That is why it is also important that, apart from the degree of hypertension based on the BP value, in reaching the decision on bigger lowering of the pressure, one should follow the classification according to the stages of hypertension: Grade 1 uncomplicated hypertension; Grade 2 presence of HMOD or CKD Grade 3 or diabetes; Grade III presence of CVD or CKD G4 and G5 [5].

Hypertension is the most common cardiovascular disorder and the standardized global prevalence for people aged 30-79 years is 34% for men and 32% for women. That is why it is additionally important that, in addition to the degree of hypertension based on the KP value, in the decision on a greater lowering of the pressure, a classification according to the stages of hypertension is taken: stage 1 uncomplicated hypertension; stage 2 presence of HMOD or CKD grade 3 or diabetes; Grade III presence of CVD or CKD G4 and G5 [5].

Hypertension is the most common cardiovascular disorder and the standardized global prevalence for people aged 30-79 years is 34% for men and 32% for women. [7].

Finding cases or opportunistic screening for hypertension is recommended for all adults (Class I C) [5]. Regular blood pressure measurement is recommended for people over 40 years of age or earlier in patients with high cardiovascular risk (Class I C) once a year, in order to detect hypertension [5].

Reliable determination of blood pressure by devices with a cuff on the upper arm and the indirect method with an aneroid manometer is the cornerstone the diagnosis and management of hypertension. [8].

At the initial office visit, BP should be measured in both arms, ideally with electronic devices that can measure them simultaneously. An interarm SBP difference >10mmHg must be confirmed with repeated measurements. If confirmed, the arm with the higher BP should be used for all subsequent measurements because its values more accurately reflect the BP level in the major arteries. Moreover, using BP taken on the arm with a higher reading seems to improve the outcome prediction [90]. A consistent interarm SBP difference >15 to 20mmHg may be due to atherosclerosis and restriction of large intrathoracic or upper arm arteries, requiring investigation for arterial disease [8,9]. Blood pressure values on the right and left brachialis arteries differ in the majority of cases, and the higher one is taken as more accurate. Prognostic significance: for each 10 mmHg difference according to Agarwal (2008), the relative risk of total mortality increases by 24%. In order to accurately assess the degree of hypertension, the spontaneous variability of pressure as a function of time and the pressure difference between the arms must be taken into account [10].

AIM OF THE PAPER:

1. Analysis of spontaneous blood pressure variability on arrival and repeated after 5 to 30 minutes and
2. Blood pressure differences between left (LA) and right arm (RA).

METHODS:

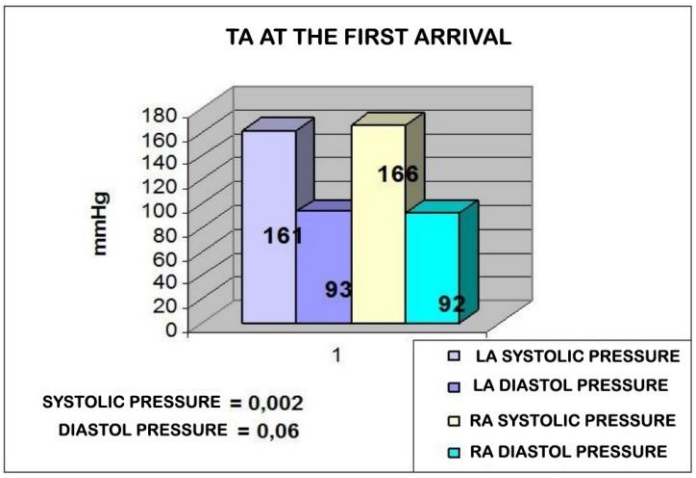
A prospective study was conducted from the database of the Office of Internal Medicine "Dr. Bastać" on 26 patients, whose average age was 58±12 years, with newly discovered hypertension, by measuring blood pressure with the indirect manometer method at the first examination and control examination 15 days later. The control group consisted of 28 patients who didn't have hypertension. The data were statistically processed with Student's T test.

RESULTS

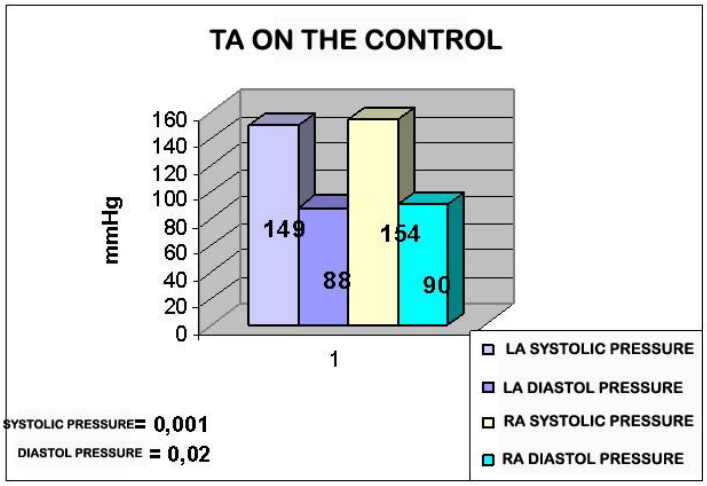
By comparing the mean values of systolic and diastolic pressures between the arms at the arrival of GRAPHIC 1, we note that there is a statistically highly significant difference between the SKP on the arms. The systolic pressure is higher on the right arm by an average of -5 mmHg (p=0.002), which is maintained even after a 15-minute rest and then remains 5 mmHg (p=0.001).

Diastolic pressure does not differ significantly between measurements on the left and right arm (p=0.06) at the first measurement, and after rest it is statistically significantly higher by 2 mmHg (p=0.02), which is not clinically significant.

GRAPH 1. COMPARISON OF SYSTOLE AND DIASTOLE PRESSURES ON THE LEFT AND RIGHT ARMS AT THE FIRST ARRIVAL

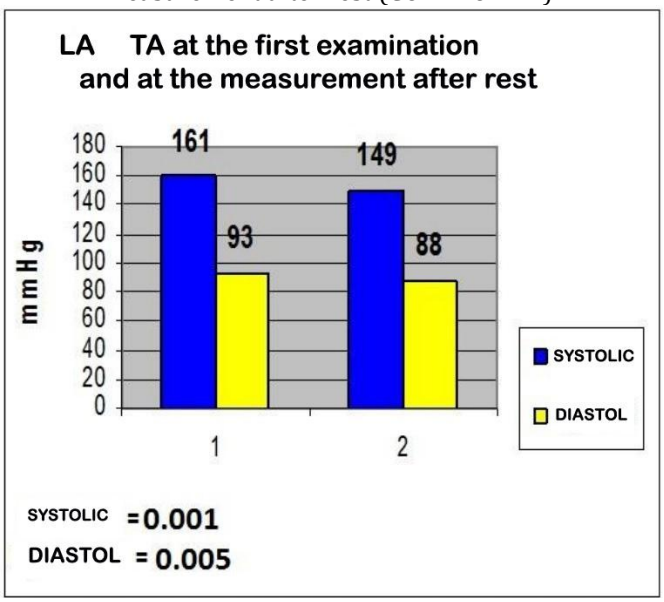


GRAPH 2. COMPARISON OF SYSTOLE AND DIASTOLE PRESSURES ON THE LEFT AND RIGHT ARMS after rest - statistically significant variability



The mean value (Xsr) of systolic and diastolic blood pressure (SKP/DKP) of the studied group on arrival was 161/93 mmHg on the left arm (LR) and 149/88 after rest. (GRAPH 3) which is highly statistically significantly lower pressure after rest: by 12 mmHg systolic (P= 0.001) and by 5 mm Hg diastolic (P=0.005).

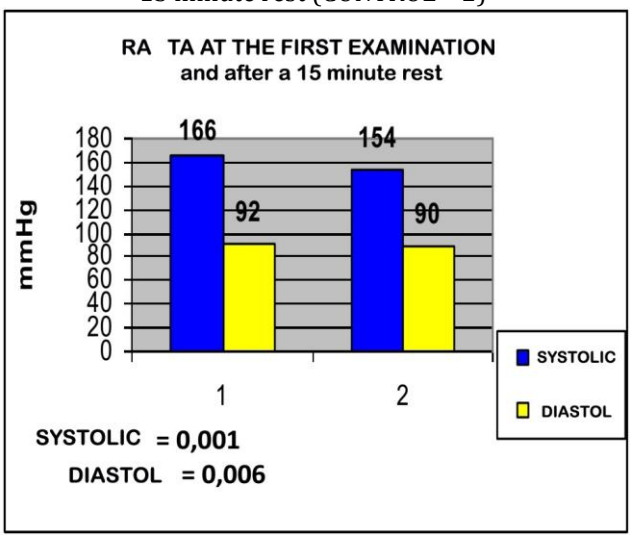
GRAPH 3. AVERAGE PRESSURE VALUES ON THE LEFT HAND AT THE FIRST EXAMINATION - 1 and at the measurement after rest (CONTROL – 2)



The mean pressure values on the right hand (GRAPHIC 4) are at the first measurement 166/92 mmHg (GRAPHIC 4). and after rest they drop to 154/90 mmHg, that is 12 mm systolic pressure and after rest is statistically significantly lower 12 mmHg ($p<0.001$), while diastolic pressure is only 2 mmHg lower without statistical significance ($p=0.06$).

It is similar in the normotensive control group for systolic pressure: the systolic pressure on the right arm decreases after rest by 8 mmHg, and on the left arm by 6 mm Hg. In contrast to hypertensive patients, the diastolic blood pressure in the control group of healthy people at rest decreased significantly more in both arms compared to the examined group of hypertensive individuals, namely on the right arm by 5 mmHg ($p<0.01$) and on the left by 4 mmHg ($P<0,01$).

GRAPH 4. AVERAGE VALUES OF PRESSURE ON THE RIGHT ARM AT THE FIRST EXAMINATION - 1 and after a 15 minute rest (CONTROL – 2)



In the individual distribution, blood pressure dropped by >10% in 24%, and by >20% in 16% of patients - high spontaneous variability. At the follow-up examination, the significance of the differences in pressure between the arms was maintained. On the contrary, the mean value of blood pressure at RA was 154/90mmHg, at LA it was 149/88mmHg, and after rest there was no statistically significant drop in pressure.
On the contrary, the mean value of blood pressure on RA was 154/90mmHg, on LA it was 149/88mmHg. and after rest there was no statistically significant drop in pressure

DISCUSSION

Our results show that the mean systolic blood pressure in the right arm was significantly higher - by 5 mm Hg at the first measurement and by 4 mm Hg after rest. According to data in the literature, the difference in systolic blood pressure values between the arms was associated with all-cause mortality and with increased cardiovascular mortality [10,11]. Systolic difference between arms is associated with increased all-cause mortality, cardiovascular mortality, and cardiovascular events. Blood pressure should be measured in both arms during the cardiovascular assessment. A systolic difference between arms of 10 mm Hg is suggested as the upper normal limit [11].

Clinically, blood pressure variability [12] is classified into 4 main types based on monitoring time: very short-term (beat-to-beat), short-term (within 24 hours), medium-term (within days), and long-term (over months and years) and simultaneous measurement on both arms, for which new blood pressure meters have already been created, is particularly important, [13].

Blood pressure variability is a strong risk factor for cardiovascular disease, chronic kidney disease, cognitive decline, and mental illness. The diagnostic and therapeutic value of measuring and controlling blood pressure variability may offer critical targets in addition to lowering mean blood pressure in the nonhypertensive population [12,14].
Therefore, it is very important to measure blood pressure in both arms in all patients, and doctors who are directly involved in patient care must always keep in mind that failure to measure blood pressure in both arms can lead to misdiagnosis, unnecessary testing, and inadequate therapy. A systolic difference between the arms of 10 mmHg is suggested as the upper normal limit [15,16]. In order to be fully responsible for the patients, it is best that we doctors, measure the patients' blood pressure on both arms ourselves, particularly during the first examination, using the proper functioning validated devices. If we do transfer that responsibility to our medical associates, we must be sure that both they and the equipment they use are reliable.

CONCLUSION

There is an extremely statistically significant difference particularly between the systolic pressure on the arms: it is always higher on the right arm by an average of -5 mmHg (p=0.002) and 4 mmHg after rest. This difference is further maintained. Spontaneous variability was determined in 10 (40%) subjects where there is a statistically significant drop in tension after rest. After the introduction of antihypertensive therapy 15 days later, the significance of differences in pressure between arms is maintained, but the variability of pressure after rest is lost.

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Vol. 48 (2023) No. 2 & 3 TIMOK MEDICAL GAZETTE Review article

BIODIVERSITY AND SEASONAL DISTRIBUTION OF TICKS IN SOUTHEASTERN SERBIA

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Summary: Ticks are a relatively small group of hematophagous arthropods distributed in three families: Argasidae, Ixodidae and Nuttalliellidae. Ticks are found all over the world and we find them on land and on islands, and even in Antarctica, where seabirds are parasitized by the Northern Memoirs endemic species. They find all types of climates favourable, as well as the temperatures from +4°C and up. They are common in places where there is a large fluctuation of animals. The most common hosts are mammals, but in their absence they can be found on birds and reptiles. Ticks belong to a group of arthropods that are of exceptional biomedical importance due to their role as vectors of various types of diseases and the immediate harmful effects caused by the hematophagous diet. During research in domestic animals and humans in the area of southeastern Serbia, the prevalence of Ixodes ricinus, Dermacentor marginatus, D.pictus, Rhipicephalus sanguineus, R.bursa, Haemaphysalis punctata and He.inermis was established.
Key words: ticks, biodiversity, epidemiology, southeast Serbia

INTRODUCTION

Ticks belong to a group of arthropods that are of exceptional biomedical importance for the living world, primarily due to their role as vectors of various types of diseases, and the immediate harmful effects caused by the hematophagous diet. It is a relatively small group of hematophagous arthropods (896 described species so far) from the phylum *Arthropoda* , under the order *Chelicerata,* class *Arachnidae*, subclasses *Acari,* suborder *Parasitoformes*, order *Ixodia and* superfamily *Ixodida* (Like all of arthropods they started their own rise in Devon and the biggest breakthrough they achieved during Mesozoic, especially in the Chalk period, from which the largest Number of fossils come . Evolutionary transition of ticks was closely connected with the evolution of hosts on which they feed .

They are divided into three families: *Argasidae,* the soft-shelled ticks, *Ixodidae* the hard-shelled ticks, and *Nuttalliellidae* , which have the characteristics of both of the aforementioned ticks .

Argasidae, has 183 species distributed in five genera *Argas, Antricol, Nothoaspis, Ornithodoros* and *Otobius*

Ixsodidae has 241 species from the genus *Ixodes* and 442 species from the genera *Amblyomma, A nomalohimalaya, Bothriocroton, Cosmiomma, Dermacentor, Haemaphysalis, Hyalomma, Margaropus, Nosomma, Rhipicentor* and *Rhipicephalus* .

Nuttalliellidae is a monospecies family(has only one representative) *Nuttalliella namaqua*

Ticks are strictly hematophagous arthropods. After reaching sexual maturity, the female tick attaches itself to the host. During feeding on blood, eggs develop in the ovaries of females. When the female finds a good place and starts feeding, she attracts the male by smell. The male clings to the feeding female and fertilizes her. After copulation, the males die, and the females separate from the host, fall to the ground and lay eggs in the grass, bushes or under fallen leaves. The number of eggs ranges from 300 to 9000.

During feeding on blood, the tick stays on the host for a long time. The most common hosts are mammals, but in their absence ticks can be found on birds and reptiles. All developmental stages of the tick, starting with the larva, attach to the host [1,2,3].

When tick eggs hatch into larvae, their hosts are small mammals, primarily rodents, and in their absence, any other type of animal can serve as a host. Larvae, unlike other tick stages, have three pairs of legs. After feeding, they leave the host and change into nymphs. In the nymph stage, they are most often found on bushy vegetation in a "hunting" position. The most common hosts are still small rodents, but also animals such as foxes, dogs, squirrels, as well as

any animal species found there, including humans [1] .

After feeding, they are detached from the host and change into adults, and the waiting place for hosts is usually high vegetation or treetops from where they attack mammals, birds and reptiles [25,26]. Small ruminants are frequent hosts of adult ticks throughout the world [3-10].

EPIDEMIOLOGICAL SIGNIFICANCE OF TICKS

Ticks belong to a group of arthropods that are of exceptional biomedical importance for the living world, primarily due to their role as vectors of various types of diseases and the immediate harmful effects caused by the hematophagous diet.

The most famous tick-borne diseases are: Lyme borreliosis, *Ehrlichia* sp., *Babesia* sp., *Anaplasma* sp., Hemorrhagic fevers: Crimean-Congo hemorrhagic fever (with and without renal syndrome), Marburg hemorrhagic fever, Omsk hemorrhagic fever, Kyasanur forest disease etc.), African swine fever, Spirochetosis a, *Aegiptela* sp., *Theilleria* sp., Hatma virus, Q fever, arboviruses, adenoviruses, Nairobi disease, Tick-born encephalitis (Powassan encephalitis, Russian spring-summer encephalitis), Typhus (Siberian tick-borne typhus, *Typhus endemica, Th.erythromatosa*), bouton fever and other diseases [11-16].

TICKS OF SERBIA

Research on ticks on the territory of Serbia began at the beginning of the last century. These researches are still ongoing and mainly *Ixodidae species have been studied* , primarily exophilic species (given that they are vectors and reservoirs of many infectious diseases).

During the research, the presence of argasid species was recorded only in birds (poultry, pheasants, etc.), namely *Argas pesicus* and *A. reflexus* [17,18].

Endophilic species of ixodids are the most represented. Five genera of ixodid ticks have been recorded in the fauna of Serbia: *Ixodes, Dermacentor* , *Rhipicephalus, Haemophysalis* and *Hyaloma*. Among them, the most frequent ones are of the following types:

Ixodes ricinus, I.concina and *I.persucatus* were identified

Dermacentor marginatus and *D.recticulatus* were identified from the genus Dermacentor

From the genus Rhipicephalus, the following were identified: *Rhipicephalus sanguineus, R.bursa, R.* (*Boophilus*) *annulatus* and *Boophilus calcaratus*

From the genus Haemophysalis, the following were identified: *Haemophysalis punctata, Ha.inermis, Ha.leporis-palustris, Ha.sulcata* and *Ha.concina*

Hyalomma marginatum marginatum, *Hy.exavatum* and *Hy.detritium* were identified from the genus Hyalomma

The geographical distribution of established ticks in domestic and wild animals (mammals) was quite uniform. Here we present the average data for the area of southeastern Serbia.

INFLUENCE OF CLIMATE CONDITIONS ON POPULATION DYNAMICS

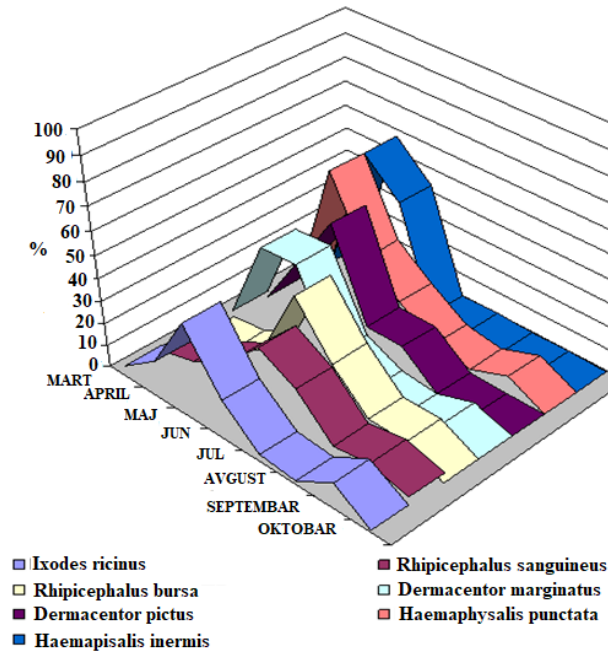
The temperature optimum of activity (the period when the largest number of ticks are looking for a host) is at temperatures of 20-25°C, when more than 40% of adults and 30% of nymphs are active. Air humidity is also an important factor, so the optimal amount is 45-80%. The length of day and night - photoperiod, is also important for tick activity. For species that live in open habitats, solar radiation has a significant impact, which leads to the accumulation of heat in the tick's body and causes the start of activity even at lower temperatures. From the beginning of September until the first snow appears and the temperature drops below 0°C, the new generation has its own natural cycle. In the autumn, when the temperature drops below 5°C, they bury themselves into the surface layer of the soil to a depth of up to 7 cm and remain there until the soil temperature rises above 5-8°C, when they come to the surface again and wait for their victims [2,19-22].

For most species of ticks, the period from mid-March to mid-June is the time when they are most active. At that time, they lay eggs, develop, find the final host on which they will perform their reproductive role. In the period from mid-June to the end of August, there is a time when the new individuals have not yet hatched, so in that period the frequency of finding them is lower. They are mostly found in the grass and shrub communities (forests, parks, steppes, savannas) and ruderal habitats. They can easily adapt to different environmental conditions, so they are found in facilities for housing animals and in residential buildings.

In our climatic conditions, the first appearance of ticks on pastures was observed in the period March-April. In March, we established the presence of: *Ixodes ricinus, Rhipicephalus sanguineus* , *Dermacentor marginatus* and *Haemaphysalis punctata* . In April, the presence of the following specieswas established: *Dermacentor pictus, Rhipicephalus bursa* and *Haemaphysalis inermis* . The species *Dermacentor marginatus, Haemaphysalis punctata* and *Ha.inermis* reach their maximum number in April . In the same month, the presence of *Boophilus calcaratus* and *Hyalomma savignyi* species, which reach their population peak in September was established,. The species *Ixodes ricinus* reaches its maximum number in May, when we also find the maximum number of the species *Dermacentor pictus* . In June, the population peak of the species*Rhipicephalus sanguineus* and *R. bursa* , which are also the most frequently found species in both July and August, is observed. In September, we observe an increase in the population of two types of ticks: *Ixodes ricinus* and *Dermacentor marginatus* , while in October we observe the appearance of the species: *Ixodes ricinus* and *Rhipicephalus sanguineus* .

SOUTH EASTERN SERBIA

Graph 1. Seasonal dynamics of established presence of ticks in southeastern Serbia



Milutinović et al. (1998a) conducted research on the tick fauna in the area of southeastern Serbia and established the presence of: *Ixodes ricinus, Dermacentor marginatus, D.pictus, Rhipicephalus sanguineus, R.bursa, Haemaphysalis punctata* and *He.inermis* in small ruminants. Similar results were obtained [24] during the research on the tick fauna in the autochthonous Zackel breed of sheep in the south of Serbia.

GENDER RATIO IN TICKS IN SOUTHEASTERN SERBIA

The gender ratio of the dominant species of ticks was as follows: of the total number of ticks collected, 52.35% were females and 47.65% were males. The gender ratio of the tick species found showed a larger number of females in four species *Ixodes ricinus, Haemaphysalis punctata, Rhipicephalus sanguineus* and *Dermacentor marginatus* , while a larger number of males were found in two species - *Rhipicephalus bursa* and *He.inermis* and an equal number in *D.pictus ticks.*

SEASONAL DYNAMICS OF TICK SPECIES FOUND

Graph 1 shows the seasonal dynamics of established presence of tick species

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DIAGNOSTIC VALUE OF INFLAMMATORY MARKERS IN PATIENTS WITH ACUTE PANCREATITIS

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Introduction: Acute pancreatitis (AP) is a sudden inflammatory reaction that causes autodigestion of the pancreas, edema, bleeding, and can lead to pancreatic necrosis and necrosis of the surrounding tissue. Since the initial symptoms of mild, moderate and severe pancreatitis are the same, doctors often cannot determine the severity of AP with certainty based on the first examination. Aim of the work: Numerous biomarkers have been studied as potential early predictors of the severity of this disease, so that treatment can be optimally adapted to prevent complications. The aim of the paper is to provide an overview of the most important inflammatory markers that are used, or can potentially be used to determine the severity of acute pancreatitis. Inflammatory markers: Markers of inflammation in AP are: the hormone procalcitonin, then reactants of the acute phase such as C-reactive protein, serum amyloid A, pentraxin 3; enzymes: polymorphonuclear elastase, phospholipase A2, myeloperoxidase; cytokines: interleukins (IL-6, IL-8, IL-17) and tumor necrosis factor (TNF-α). Conclusion: The most frequently determined parameter in clinical practice is CRP, as a non-specific marker of inflammatory diseases. The disadvantage in determining this parameter is that the maximum serum value is reached only 72 hours after the onset of AP symptoms. Numerous biomarkers have proven to be more sensitive for determining the severity of AP, of which procalcitonin stands out, which has been widely used in recent years, for the early prognosis of the development of local complications and multiorgan failure in AP. Cytokine determination is increasingly part of clinical practice. The most commonly used IL-6 is a sensitive and specific marker for predicting organ failure in severe AP.

Key words: acute pancreatitis; inflammatory marker; procalcitonin; acute phase reactants; enzymes; cytokines

INTRODUCTION:

According to the recent classification of acute pancreatitis, there is a division into interstitial pancreatitis (with diffuse enlargement of the pancreas and inflammatory edema, without the signs of necrosis) and necrotic pancreatitis, which is further subclassified into sterile and infectious [2]. Pancreatic necrosis during acute pancreatitis is a key factor predicting outcome, and infection of the necrotic tissue is a serious complication in severe acute pancreatitis. Additionally, intestinal barrier dysfunction leads to infected necrosis, bacteremia, and multiorgan failure [3]. Severity of AP can be classified into three types, mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) [1]. The severity of AP was observed to be related to the type and degree of cell death: severe AP was associated with extensive necrosis of acinar cells, while mild AP showed extensive apoptotic cell death and a minimal degree of necrosis. Therefore, apoptosis is interpreted as a beneficial cell response to an injury, and inducing apoptosis is an effective strategy to reduce the severity of experimental pancreatitis. A newly discovered modality of cell death is necroptosis, which is characterized by both necrosis and apoptosis, namely, it is actively regulated by special genes, and has typical morphological characteristics of necrosis. Necroptosis is gradually becoming an important topic in the field of inflammatory diseases [4]. A variety of agents can cause injury to pancreatic acinar cells. Activation of mononuclear macrophages leads to the activation of neutrophil leukocytes, which further release large amounts of inflammatory mediators responsible for inflammatory effects, by a cascade mechanism. Loss of local control leads to excessive uncontrolled activation ofinflammatory cells and mediators. Proinflammatory cytokines are released through the portal vein and reach the circulation through

the lymph [5]. Mild forms of inflammation of the pancreas, go away within three to four days with adequate therapy, and usually without any consequences. However, the initial symptoms of mild, moderate and severe inflammation are the same, so doctors cannot determine the form based on the first examination. Typical laboratory findings in AP are increased parameters of inflammation, as well as increased values of pancreatic amylase and lipase. According to most guidelines, lipase is more reliable parameter than amylase [6]. The reliability of determination of amylase also depends on the time when the sample is taken.

THE AIM OF THE WORK

Numerous biomarkers have been studied as potential early predictors of the severity of this disease, so that treatment can be optimally adapted to prevent complications. Early identification of patients who could potentially developing severe acute pancreatitis would allow selection of patients for early intensive treatment. Accordingly, the aim of the paper is to provide an overview of the most important inflammatory markers that are used, or can potentially be used to determine the severity of acute pancreatitis.

INFLAMMATORY MARKERS

Aninflammatory reaction is triggered at the site of pancreatic damage and can lead to systemic inflammatory response syndrome (SIRS), which is ultimately responsible for most morbidity and mortality [7]. It is known that extensive damage and necrosis of the pancreas lead to the activation of enzymes - proteases that can cause damage to blood vessels, resulting in hypovolemia, hypotension, increased intra-abdominal pressure and kidney damage. Damage of pancreatic acinar cells stimulates the release of cytokines and the generation of free radicals [8]. Accordingly, it is necessary to detect and determine inflammatory markers whose serum levels are correlated with the degree of pancreatic damage. This article gives a review of some of the most important inflammatory markers of AP.

Procalcitonin (PCT) is a prohormone of calcitonin, and under physiological conditions it is created only in C-cells of the thyroid gland. In pathological conditions, it is also produced by extrathyroidal tissues, such as the liver, lungs, monocyte-macrophage system [9]. In healthy individuals, the level of PCT in the plasma is very low, practically unmeasurable, since active calcitonin is secreted into the blood after its proteolytic breakdown. Elevated PCT values may indicate the presence of a bacterial infection. Serum PCT values increase already 2-4 hours after the onset of the infection, which makes it a potential biomarker for monitoring pathological conditions caused by bacteria - pneumonia, lower respiratory tract infections, abdominal sepsis, urosepsis, myocardial infarction [10]. It has been shown that the development of infectious necrosis of the pancreas in patients with acute pancreatitis can be predicted by PCT values, and accordingly, antibiotic therapy can be applied [11]. A serum PCT value of 3.8 ng/ml or more, within 96 h of symptom-onset indicates pancreatic necrosis with a sensitivity and specificity of 93% and 79%, respectively [12]. The determination of serum procalcitonin has been widely used in recent years, for the early prognosis of the development of local complications and multiorgan failure in AP.

C-reactive protein (CRP) is an acute phase protein. It is a non-specific and most commonly used marker of inflammatory diseases. It is used routinely in clinical practice to assess the severity of acute pancreatitis [1]. Determination of CRP concentration has several advantages, such as accuracy, simplicity, accessibility and relatively low cost. The main limitation of determining this parameter is reflected in the time required for the serum concentration to be optimal - 72 hours from the onset of symptoms [13]. CRP values above 210 mg/ml were used to determine moderate and severe AP, with a sensitivity of 83% and a specificity of 85% [14]. CRP is considered a significant individual indicator of pancreatic necrosis due to the availability of determination of this parameter in clinical practice.

Serum amyloid A is a family of acute-phase proteins synthesized in the liver as response to trauma and inflammation of the tissue. They participate as mediators in cellular communication, within the immune response, acting as propagators of the initiated acute immune response [15]. Research has shown that it can be a more sensitive marker of inflammation than CRP [16]. However, the results of a study of a German center, using a different immune assay in a population that also included healthy subjects and patients with chronic pancreatitis and malignancy, did not support these findings [16].

Phospholipase A2 (PLA2) belongs to a family of enzymes that hydrolyze phospholipids. Apart from the digestive function in the intestinal tract, phospholipase A2 participates in the metabolism of cell membrane phospholipids, including prostaglandin synthesis, transmission of cell signals and metabolism of serum lipoproteins. It has been assumed that activation and release of PLA2 in acute pancreatitis is not only responsible for tissue necrosis associated with pancreatic autodigestion, but is also associated with the development of pulmonary complications [17]. Animal studies have shown that PLA2 can damage dipalmitoyl phosphatidylcholine, a phospholipid that is part of lung surfactant, thus causing alveolar collapse [18].

Polymorphonuclear elastases (PMN-elastases) are enzymes released from polymorphonuclear leukocytes (neutrophils, basophils, eosinophils). It is a sensitive marker of inflammatory diseases, considering that during inflammation their excessive release occurs. In acute pancreatitis, the maximum concentration of this parameter is reached on the first day of the disease, earlier than CRP. One study, showed the importance of values of PMN-elastase levels in plasma for early prognosis of AP severity in clinical practice, with a sensitivity of 92% and a specificity of 91% for the value of 110 mg/L, in the period from 24 to 72 hours from the onset of the disease [19]. Although PMN-elastase could be relevant for assessing the severity of AP, determination of this parameter has not been introduced into routine laboratory use due to assay-related problems, with non-reproducible test results.

Pentraxin 3 (PTX3) is an acute phase protein. It is synthesized and released by macrophages, monocytes and dendritic cells, in response to stimulation by lipopolysaccharide or proinflammatory cytokines. Some studies [20,21] have shown that elevated values of PTX3 correlate with the severity of AP, that the values of this parameter increase in the early phase of AP, and correlate with the values of interleukin-6 (IL-6), a marker whose importance will be explained further. The determination of PTX3 is not yet suitable for clinical use because its concentration can currently only be measured by enzyme-linked immunosorbent assay (ELISA), a relatively expensive method.

Myeloperoxidase (MPO) is an enzyme primarily released by activated neutrophils and is thought to be involved in the body's immune response during inflammation. Excessive release of this enzyme leads to tissue damage, as demonstrated in studies of experimentally induced AP. It is believed that this enzyme has a role in the development of complications on the lungs, considering that the activity of the enzyme has been identified in the lung parenchyma in patients with AP [20].

Cytokines. As previously explained, acute pancreatitis results in excessive activation of leukocytes and increased migration of neutrophils to the inflammatory area with consequent release of pro-inflammatory cytokines. As mediators, they are thought to be involved in the progression of pancreatic infection to necrosis, which subsequently leads to SIRS and multiorgan dysfunction.

Interleukin-6 (IL-6) is an important inflammatory mediator of the acute phase response that may also be significant in assessing the severity of acute pancreatitis. Experimental studies have shown that interleukin-6 induces the production of major acute phase proteins in the liver, including C-reactive protein, serum amyloid A (SAA), haptoglobin, antichymotrypsin, fibrinogen and hepcidin, while inhibiting albumin production [22]. One study showed that elevated levels of IL-6 were detected in 93% of patients on days 3 and 7 of AP. Serum levels of IL-6 were significantly higher in severe pancreatitis compared to mild pancreatitis at day 3 but not at day 7 [23]. One study showed that a serum levels of IL-6 on day 3 of AP are higher than 160 pg/ml indicates a persistent SIRS and potential organ failure [24]. The prediction of severe pancreatitis is very useful for the prognosis of the disease and the decision to transfer patients with suspected severe pancreatitis to the intensive care unit. Accordingly, IL-6 is a sensitive and specific marker for predicting organ failure in severe AP.

Interleukin-8 (IL-8) is a proinflammatory cytokine, released by activated macrophages or endothelial cells. It belongs to the family of chemokines, molecules involved in chemotaxis, activation and degranulation of neutrophils. In a 2009 meta-analysis, IL-6 was shown to have a sensitivity of 83.6% and a specificity of 75.6%, in contrast to a sensitivity of 65.8% and a specificity of 66.5% shown by IL -8. These values suggest that IL-6 is of greater diagnostic value on the first day. However, IL-6 sensitivity appeared to decline slightly over time with

values of 72.1% on day 2 and 81.0% on day 3, although this decline is not statistically significant. The positive likelihood ratio of IL-8 is significantly higher on the second day compared to the values calculated on the first day. This may be of importance in clinical practice, as it showed that this relationship suggests that patients with higher levels of IL-8 on the second day are about 8 times as likely to have a severe course compared to patients with lower levels of IL-8 [25].

Interleukin-17 (IL-17) is a proinflammatory cytokine secreted by activated T-lymphocytes. The most important representative of the IL-17 family is IL-17A, which is produced by activated memory T lymphocytes. It plays a role in stimulating innate immune response. During AP, cellular damage caused by pancreatic autodigestion can cause the activation and aggregation of IL-17-producing CD4+ T helper lymphocytes and stimulate the inflammatory response that is characteristic of this disease. Some studies have shown that IL-17A regulates the transcription of proinflammatory cytokines or chemokines that mobilize neutrophils in acute inflammatory diseases [26]. Compared to healthy controls, AP patients had a significant increase in IL-17 during the first 24 hours, with a positive predictive value of 85.3% [27]. Given its potential prognostic value, IL-17 is considered a promising inflammatory marker of AP.

Tumor necrosis factor alpha (TNF-α) is a pleiotropic cytokine produced by macrophages and which plays one of the main roles in multiple pathophysiological responses to injury and damage [7]. It is a key regulator of other proinflammatory cytokines and leukocyte adhesion molecules, and is a primary activator of immune cells. Additionally, it affects the reduction of T lymphocyte reactivity, which is of large importance for immune homeostasis. Tumor necrosis factor exerts its effect through two receptors, TNFR-1 and TNFR-2 [28]. Tumor necrosis factor alpha also plays a role in the pathogenesis of AP, which is why biological drugs that block TNF-α are being investigated for the treatment of AP[29]. The latest research from 2023 showed that elevated levels of TNF-α correlate with elevated levels of IL-6 and IL-8, and that all three markers are elevated in patients with severe AP [30].

CONCLUSION

In acute pancreatitis, a series of complex chain reactions which lead to damage to pancreatic acinar cells are triggered. Initiation of local and systemic inflammatory response is associated with complications and damage to other tissues and organs. The conventional clinical approach in predicting the severity of AP has limitations and seems to have reached its maximum potential. Given that early identification of patients who can potentially develop severe acute pancreatitis is necessary, various inflammatory markers have been tested to enable early selection of patients with a potentially severe form of AP. The most frequently determined parameter in clinical practice is CRP, as a non-specific marker of inflammatory diseases. Numerous biomarkers have proven to be more sensitive for determining the severity of AP, of which procalcitonin, which has been widely used in recent years, stands out for the early prognosis of the development of local complications and multiorgan failure in AP. Cytokines as mediators in cellular communication play a significant role in all inflammatory processes. In recent years, determination of cytokine has increasingly become a part of clinical practice. The most commonly used IL-6 is a sensitive and specific marker for predicting organ failure in severe AP. The determination of many inflammatory markers that would be used to evaluate AP has both technical and financial limitations; however, with the improvement of molecular methods, it could be expected in the future that their determination will become a part of routine clinical practice.

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DR. SIGISMUND KRAKOW-KLADOWSKI DAYS, "HONOR BEYOND LIFE"

Ranko Jakovljević

NEGOTIN

A man's honor is something that stands above life

- Zygmunt Cracow -

Summary: This paper presents biographical data and details related to service and life in Kladovo in 1903-1907. Dr. Sigismund Krakow and his ancestors

Keywords: doctor, military service, family, Poland, Serbia, Kladovo

Sigmund /Zygmunt/ Krakow was born on 3/15. April 1849 in Warsaw, from father Ludwik "an old revolutionary from the Polish uprisings of 1830 and 1863" and mother Pauline (1813-1882) "from the Radjejowskis, who gave Poland cardinals and marshals, and who herself was a famous Polish writer" (Krakow, 2004, 28). Her literary works are: ''Pamiętniki młody sieroty''; ''Powiesci starego wędrowca''; ''Rozmowy matki z diećmi''; ''Niespodzianka''; ''Wieczory domowe''; ''Obrazy i obrazki''; ''Proza i poezyja polska, wybrana i zastosowana do użytku młodzieży żeńskiej''; ''Wspommenia wygnanki''; ''Nowa ksiaźka do nabożenstwa dla Polek''. According to the father, the genealogy of the family reached 1665, to Jan Kraków, the bearer of the ceremonial sword during the reign of King Mihail Wisniowecki (Stojić 2019, 353). He graduated from Medinica in 1872. at the University of Heidelberg / "Ruprecht-Karl University"/ with the grade cum laude superato, earning the title of doctor of medicine and surgery.

He had a son Ludvik from his first marriage. He had a sister Zofia and a brother Casimir. After the Polish "January Uprising of 1863", in 1865 he settled in Paris, working at the Pasteur Institute (Berec 2017, 164). 1885 he came to Serbia as a volunteer in the Serbian-Bulgarian war, as a military doctor. From the title of "contractual military assistant" 13/27..9.1889.g. he was promoted to the rank of "medical lieutenant"

Medical lieutenant of the Lutheran faith, military doctor of the 14th infantry regiment, Sigismund Kraków married a teacher from Kragujevac, in the extract from the marriage book marked with the data "Persida Đoković, daughter of Aćima and Pelagija Đokić, born 11/23. November 1869 in Prijeljina''. Commenting on the same document, Biljana Stojić indicates that it is "Persida Nedić, sister of Milan, Milutin and Božidar Nedić, distant relative of King Petar Karađorđević" (2019, 353). Milan Nedić was born from the marriage of the teacher Pelagia, the "granddaughter of Prince Nikola Stanojević", through whom they are in contact with the diplomat Konstantin Fotić and the former Minister of Justice of Kranjevina Yugoslavia and the leader of the "Zbor" movement Dimitrije Ljotić. It follows that Sigmund Krakow's wife was the maternal sister of Generals Milan and Milutin and reserve officer - war invalid Božidar Nedić.

The wedding took place on May 3/15, 1892 in the Church of the Assumption of the Blessed Virgin Mary in Kragujevac. It was Sigismund's second marriage, her first. On the occasion of his first marriage and request for divorce, the first-instance court in Kragujevac addressed 7/19/12/1891. To the Ministry of Education with a request that it "get all the rules" from the evangelical pastor-church in Belgrade regarding the fact that the first wife Mihalina "left Sigismund 6-7 years ago". The Ministry of Education responded with information dated January 14, 1892. that "in Germany, the church and the clergy have nothing to do with divorces, because civil courts do it,... rules printed from an ordinary book are sent". The marriage was dissolved and the obstacle to entering into a new one was removed. Stanislav Kraków presents the circumstances of his parents' marriage as something different. According to him, Sigismund left his first wife, a Polish woman, and his eight-year-old son from that marriage in Paris; "since his wife died in the meantime, he decided to stay in Serbia and get married..." (2004, 29). In the obituary from 1910. it was announced that he died after "honoring the act" of military protégé Sava Kelić, to whom the family expresses special gratitude.

From the marriage of Sigismund and Persida on March 16/24, 1895. was born on March 16/24, 1895. in Kragujevac, Stanislav, the writer of the capital works of Serbian literature, "a man with 18 decorations, 14 wounds, three death sentences" (Stojić 2019, 350).

As published by "Male novine" from September 13, 1899. "Sigmund Kraków, contractual medical lieutenant, native of Warsaw, Russian citizen" received Serbian citizenship.

As required by the service, he was assigned to military garrisons in Kragujevac, where he served in 1897-1898. was also the manager of the surgical department of the military hospital, then in Niš /from April 21-

May 4, 1901/, Leskovac /from October 12-25, 1901/, Knjaževac /from May 8-21, 1902 /, Zaječar, Kladovo /from September 9-22, 1903/, Belgrade /from November 13-26, 1907/.

According to the order of the Minister of Military No. 3595 of September 9/25, 1903, according to the needs of the service, "medical lieutenant Sigismund Kraków, until now the corps doctor of the Knjaževac garrison, was appointed as the corps doctor of the Kladovo garrison." Stanislav Krakow wrote about his arrival and life in Kladovo:

''... My father was suddenly transferred from Knjaževac to the border fortress of Kladovo on the Danube. He was satisfied with this change because in Kladovo he had to be not only a military doctor but also the only doctor for the entire area. Like in the Wild West, we traveled for three days in a closed carriage from Knjaževac to Kladovo by the border river Timok and then through the dense oak forests in the Krajina that were never without hajduk... It was already the third night since we left Knjaževac when we saw the lights the small fishing town of Kladovo. Our carriage bounced over the old Turkish cobblestones. He stopped in front of a hotel, which only had a ground floor.

The curious inhabitants of this small town of fifteen hundred souls began to gather around the carriage: - The doctor has arrived. Just at that moment, the door of the tavern opened and the owner of the hotel ran out excitedly:

- Doctor, quickly, save my wife... As my father had his briefcase under his arm, he ran into the tavern. We sat in the carriage and waited. A little later I saw my father coming out smiling. The hotelier's wife got a fish bone stuck in her esophagus and started to choke. My father removed her bone and his reputation as a good doctor was already established on the first night.

The next day we drove into the old Turkish fortress of Fetislam, a few kilometers from the town, where there was a garrison of several hundred people. We drove over the suspension bridge and by the heavy iron gate a guard came out to pay respects to my father...

We got a large separate house, which here, like in the colonies, because of the many snakes, was built so high that it had to be entered via several stone steps. At first, snakes were a real nightmare for me, and for my mother during our entire stay in Kladovo. I got used to them over time. They were everywhere. Every day we found them in the pantry and the kitchen, which were in a separate building, where they were looking for milk, hanging from the ceiling beams, crawling under cupboards, getting into crates. In the barn where my father's horse was, Seiz was never allowed to put his hand in the hay, lest he come across a snake. But most of them were between the stones of the huge city ramparts, under which there were deep casemates, which used to serve as a prison. It was in the casemate, the one closest to our house, where we kept chickens, that the later famous Serbian statesman Nikola Pašić was imprisoned after the rebellion of Eastern Serbia in 1886 against King Milan.

For me, the Kladovo fortress was the promised land. The presence of a large number of soldiers, in whose life I liked to interfere and share it, huge cannons on the bastions, a citadel in the middle of the fortress, with high towers and a suspension bridge, which could only be entered barefoot or in slippers because it was full of dozens of tons of explosives and gunpowder, underground lagumi, all that was miraculous for me. The largest number of civilian patients of my father were alasi - fishermen, and that's why he was always full of caviar and the best Danube fish. Fishermen taught my mother to roast kechiga, wrapped in parchment, on a spit over low heat, and it became my favorite dish.

That's where I first came into contact with abroad - if you can call it that, Kladovo was on the triple border. I often crossed by boat to Turn Severin, in Romania, or to Orshav, just a few kilometers away, in Austria-Hungary. And between those two foreign countries for me, I discovered another one: Turkey. Better to say, a lost part of Turkey. There, near Oršava, in the middle of a river full of eddies, like an enclave, was the small fortified island of Adakale, the last remnant of Turkish rule on the Danube. When I disembarked for the first time from a large fishing boat, which could hardly maintain its balance in the midst of strong rapids, into the greenery of this small island, it was as if I had come to a country that was from another era and from another continent. Adakale theoretically belonged to Turkey, but there

was no government at all, except for one head of the town, who was like the head of a large family. Not the police, not the customs, not the court, not the hospital. People lived a quiet, unchanged life. They watered their gardens and looked after a few sheep and then came to the center in front of the only tavern, under the blossoming trees, to sip coffee or eat rahatlokum there. Life had completely forgotten about them... It was only after the Balkan Wars /1912-13/ that Austria-Hungary settled the island and introduced it to all the obligations, laws and duties that a modern state imposes on its subjects..

In the summer of 1906, I finished the fourth grade of the elementary school in Kladovo as the best student. The director of the school, Milić, was a grateful patient of my father. I was supposed to travel to Belgrade in the fall to stay with my grandmother and uncle in order to study high school there. That was the last summer of my happy childhood in the Kladovo fortress...'' (2004, 19-21).

In the same year, King Petar appointed Dr. Sigismund as his personal physician during treatment at the Brestovačka Banja. Stanislav Krakow concludes his impressions with the words: "when, after more than a month of treatment, King Petar left Brestovačka Banja, my father followed the royal caravan on horseback. The large and dense dust that rose from the country roads when so many carts passed, and in which he rode for days, made my father, when he came to Belgrade with the king, suddenly spit up blood. And when I met my father in the Kladovo fortress, after returning from the capital, he brought a signed picture of the king, fifty gold coins, toys and books for me, but also the beginning of tuberculosis'' (2004, 24).

In the Kladovo fortress there was a hospital and a pharmacy, especially the "marvena pharmacy", as Jovan Mišković noted during the control inspection carried out on October 3, 1884; in addition, he also gives a description of the fortress: "The city of Fetislam is mostly four-sided with 6 bastions /4 on the longer, dry side, and 2 on the corresponding Danube side/, 3 gates and 2 brick round towers facing the Danube. There is a visible redoubt in the middle, with two round towers on the land side. It has a powder store on vaults in two compartments. Besides that, a small hand magazine. The casemates are unusable. There are two out-of-the-ordinary barracks: 1 battalion, and the other one for provisions. Apart from that, about 10 buildings of various sizes and values'' (2020, 2, 116). The fortress is also known for the fact that the latter General Kosta Milovanović, commander of the artillery in Fetislam in 1877, served there. and Duke Živojin Mišić - posted here for duty in 1890. as general staff captain first class, 1893. /then in the rank of major/ Colonel Panta Trifunović, father of the divisional general and Minister of the Army and Navy of the Kingdom of Yugoslavia, Dušan Trifunović.

At the level of the Ključki district in the period 1903-1907, unlike other districts of the Krajinski district, no one was assigned to work in the health profession, so the presence of Dr. Sigmund Krakow meant a lot to the population (Blagojević 2005, 284-333). The presence of another Pole, Siegfried Policer, a pharmacist in the small border town, was of great importance for healthcare in the Kladovo area. Starting from 1906. he ran a pharmacy at the beginning of Kralja Aleksandra Street, equipped according to the highest standards. A herbarium was located in the specially designed apothecary's attic for the storage of herbs intended for the production of medicines. Medicines were kept in a part of the basement partitioned with stone. The pharmacy was characterized by spaciousness and light. In Kladovo, Dr. Sigismund also found the famous pharmacist Jozef Dilber (1828-17-5-1905), a graduate pharmacist from the University of Prague, the owner, the first president of the Pharmaceutical Society of Serbia, who ran a pharmacy here until 17-5-1905.

In the official military gazettes of 1903-1907. there are data on the humanitarian activities of Dr. Krakow through the work of the Red Cross. According to the Report on the activities of the Serbian Red Cross Society 1.1. In 1907, together with him, the following officers of the Kladovo fortress did it: lieutenant colonel Svetozaar Protić, captain II.cl Pavle Jakovljević, lieutenants Milan Matijević, Dobrivoje Mojsilović, Svetozar Ristić and lieutenants Dragiša Predić, Radoje A Pantić and Milivoje Alimpić.

By order of the Minister of Military No. 9320 dated 13/27. In September 1907, instead of medical lieutenant Josif Radulović, Sigismund Kraków, "so far a corps doctor in

the command of the Kladovo fortress", was appointed acting corps doctor of the Eighteenth Infantry Regiment of "Kraljević Đorđe, the Crown Prince" and manager of the temporary spa infirmary.

He died in Belgrade on March 12, 1910. On this occasion, an obituary was published in the Serbian press: "It is with pain in our hearts that we inform our relatives and friends that our dear, never-forgotten husband or son, Dr. Sigismund Kraków, medical lieutenant, died on March 12 at 1:00 a.m. at the age of 60. his own. On this occasion, we cannot fail to express our deep gratitude to Mr. to the doctors who tried to save the deceased from death, and especially to Dr. Pomorišac, who tried to relieve his pain, and vigil all night over the patient's bed, on whose arms he lost his soul. Mr. Sava Kelić against the military, who acted out of honor. Lord to the officers, and military doctors, friends and acquaintances, who escorted the deceased to their eternal home in such a large number. Belgrade, March 17, 1910. Mourners: wife Persida, sons Ludvik and Stanislav and other numerous relatives. The places of service in Timok - Knjaževac, Kladovo, Zaječar have not commemorated dr. Sigismund Krakow was extracted through several data in the publication "150 years of the Hospital in Knjaževac /1851-2001/" by Dragan M Ivanović Šakabenta (2001).

There is a wikipedia entry about his son Stanislav: Kraków is a man of wonderful life and idea verticality. He was always rightly determined and consciously sacrificed for the Serbian idea. He was an example of how to fight, how to write, how to act politically and how to believe in courage. In it, a synthesis of a national, modern, traditional, right-wing and brave Serb was created, who with his example negates the thesis of local writers that only anti-national writing in the genre range from "post-Titoism" to anti-war adulation is the only Serbian literature that is worthwhile and that rules the local scene.

He is the holder of the decorations: White eagle with swords, 4th degree; two gold medals for bravery; Officer of the Romanian Crown; bearer of the Albanian monument; The cross of mercy.

In 1944, he emigrated to Austria, and then to France, where he continued to live. In Belgrade, he was sentenced to death by firing squad in absentia.

He died as a forgotten emigrant in Switzerland, on December 15, 1968, in complete misery.

**** For the help in collecting the material, which we present in the attachment, the author owes special thanks to the Archives of Yugoslavia, Belgrade, and to Mr. Mirko Demić, director of the National Library "Vuk Karadžić", Kragujevac***

SUMMARY

This paper presents biographical data and details related to service and life in Kladovo in 1903-1907. Dr. Sigismund Krakow and his ancestors. With his personal generosity and high moral views, he made a significant contribution to the development of healthcare in Serbia.

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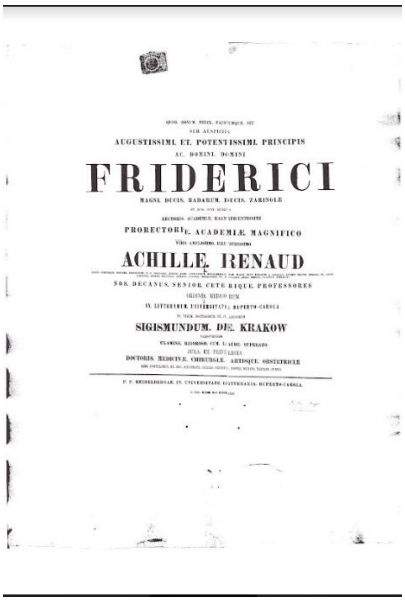


AUGUSTISSIMI ET POTENTISSIMI PRINCIPIS
AC DOMINI DOMINI
FRIDERICI
MAGNI DUCIS BADARUM, DUCIS ZARINGIÆ
PRORECTORIS ACADEMIÆ MAGNIFICO
ACHILLE RENAUD
SIGISMUNDUM DIE. KRAKOW
DOCTORIS MEDICINÆ CHIRURGIÆ ARTISQUE OBSTETRICIÆ

Diploma transcript, Archives of Yugoslavia

У ИМЕ
ЊЕГОВОГ ВЕЛИЧАНСТВА
АЛЕКСАНДРА I.
по милости божјој и вољи народној
Краља Србије
МИ КРАЉЕВСКИ НАМЕСНИЦИ

На предлог Нашег војног министра производимо:

контрактуалног лекарског помоћника I. класе, Сигисмунда Кракова, у чин санитетског поручника, с рангом од 7-ог фебруара 1888-е године

Наш војни министар нека изврши овај указ.

13 септембра 1889 год.,
у Београду.

Јов. Ристић с. р.
К. С. Протић с. р.
J. Бели-Марковић с. р.

У ИМЕ
ЊЕГОВОГ ВЕЛИЧАНСТВА
АЛЕКСАНДРА I.
по милости божјој и вољи народној
Краља Србије
МИ КРАЉЕВСКИ НАМЕСНИЦИ

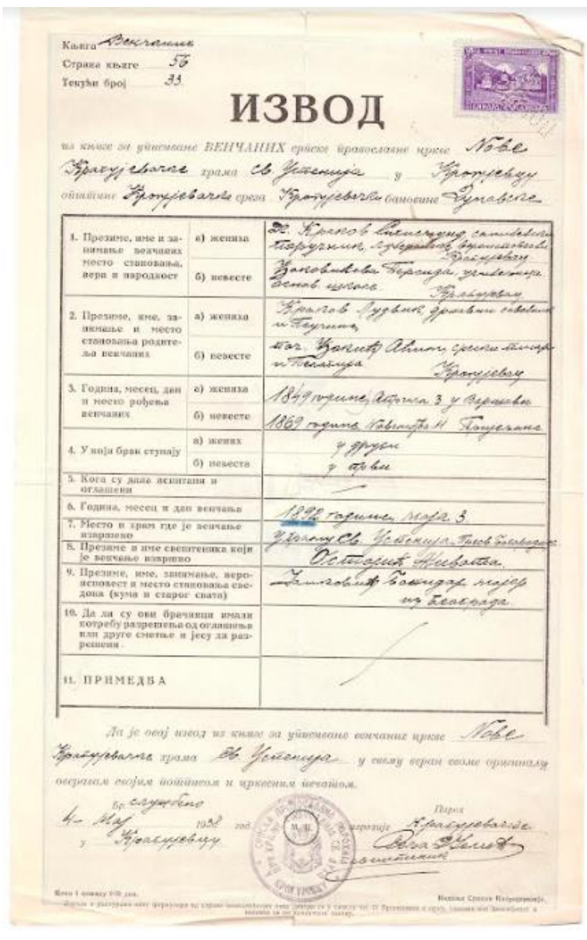
На предлог заступника Нашег министра унутрашњих дела, председника Нашег министарског савета, Нашег министра иностраних дела, а по договору са државним саветом од 11-ог августа ове године Бр. 1467, решили смо и решавамо:

да се Сигисмунд Краков, контрактуални санитетски поручник, родом из Варшаве у Руској Пољској, поданик руски, прими, по молби, својој у српско поданство на основу тачке 8-е највиших правила од 20-ог јануара 1860-е године Вбр. 171 (Збор. XIII. стр. 5.) као српски заштићеник, без отпуста из свога досадашњег поданства.

Заступник Нашег министра унутрашњих дела, председник Нашег министарског савета, Наш министар иностраних дела, нека ово решење изврши.

25 августа 1889 год.,
у Београду.

Јов. Ристић с. р.
К. С. Протић с. р.
J. Бели-Марковић с. р.


Књига [illegible]
Страна књиге 56
Текући број 33

ИЗВОД

из књиге за уписивање ВЕНЧАНИХ српске православне цркве [illegible] храма [illegible] у [illegible] општине [illegible] среза [illegible] бановине [illegible]

1. Презиме, име и занимање венчаних место становања, вера и народност	а) женика	[illegible]
	б) невесте	[illegible]
2. Презиме, име, занимање и место становања родитеља венчаних	а) женика	[illegible]
	б) невесте	[illegible]
3. Година, месец, дан и место рођења венчаних	а) женика	1849 године [illegible]
	б) невесте	1869 године [illegible]
4. У који брак ступају	а) женик	у други
	б) невеста	у први
5. Кога су дана испитани и оглашени		—
6. Година, месец и дан венчања		[illegible] године, маја 3
7. Место и храм где је венчање извршено		[illegible]
8. Презиме и име свештеника који је венчање извршио		[illegible]
9. Презиме, име, занимање, вероисповест и место становања сведока (кума и старог свата)		[illegible] мајор из Београда
10. Да ли су ови брачници имали потребу разрешења од оглашења или друге сметње и јесу ли разрешени.		—
11. ПРИМЕДБА		

Да је овај извод из књиге за уписивање венчаних цркве [illegible] храма [illegible] у свему веран своме оригиналу оверавам својим потписом и црквеним печатом.

Бр. службено
4. Мај 1938 год.
у [illegible]

Парох [illegible]
[illegible]

Extract from the marriage register, Archives of Yugoslavia

Са болом у души јављамо сродницима и пријатељима, да је наш мили никад незаборављени муж односно отац

† Др. Сигисмунд Краков
санитетски поручник

преминуо 12 марта у 1 сат по поноћи у 60 год. живота свога.

Овом приликом неможемо пропустити да не изјавимо нашу дубоку захвалност г. г. лекарима који се труђаху да покојника од смрти спасу; а нарочито г. др. Поморишцу који се труђаше да му болове ублажи, и бдијући целе ноћи над болесничком постељом, на чијим је рукама и душу испустио. Господину Сави Кевићу војном проти, који на почасти чинодејствоваше. Господи официрима, и војним лекарима, пријатељима и познаницима, који у тако великом броју покојника до вечне куће испратише.

Београд, 17. марта, 1910 г.

Ожалошћени: супруга: Персида; синови: Лудвик и Станислав и остала многобројна фамилија. 999,2-2


SZKOŁA PODOFICERSKA I-go OKRĘGU Tow. SOKÓŁ 1 KOMPANJA

ŚWIADECTWO

KURS SZKOŁY PODOFICERSKIEJ

Komisja delegowana przez Komendę Legjonów Polskich

Komisja Egzaminacyjna delegowana przez Komendę Legjonów Polskich.

Diploma of Ludvik Krakow, Archive of Yugoslavia

INSTRUCTIONS TO ASSOCIATES OR AUTHORS

Timok medical GAZZETTE publishes previously unpublished scientific and professional papers bilingually, in Serbian and English language from all fields of medicine and related branches. Original papers, patient case reports, review articles, medical and health history articles, book and journal reviews, editorial letters and other medical information are received for publication. The authors propose a category of their work and the Editorial Board reserves the right to change the category with the consent of the author.

Manuscripts should be prepared in accordance with the Vancouver Recommendations: UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS, recommended by ICMJE (International Committee of Medical Journal Editors - Ann Intern Med. 1997; 126: 36-47), or in accordance with the Serbian languageversion JEDNOBRAZNI ZAHTEVI ZA RUKOPISE KOJI SE PODNOSE BIOMEDICINSKIM ČASOPISIMA, Serbian Archives of Medicine, 2002; 130 (7–8): 293. The digital version is freely available on the ICMJE website, www.icmje.org, as well as at www. tmg.org.rs/saradn.htm

When writing atext in English, one should adhere to the American English language standard and use short and clear sentences. Manuscripts received by the editorial staff are not expected to contain results already published by authors in another journal or similar publication. The original manuscript must be accompanied by the certificate of authorship (you can download the form at: www.tmg.org.rs), scanned signatures of all authors of the article.

The editorial board sends all the papers for peer review - usually two reviewers. Proceedings in supplements are not peer reviewed.

In works where the described patient may be identified, the utmost care should be taken to avoid any details that can identify him/her or obtain written consent for publication from the patient himself or his immediate family. When consent exists, it should be stated in the article.

If the paper receives positive anonymous reviews (2 reviewers) it will be accepted for publication. After receiving a positive review, in order for the paper to be published in electronic version on the website www.tmg.org.rs and printed, it is necessary to pay a fee for the cost of editing the article, proofreading and printing costs for the Timok medical journal **only for the first author**, which amounts to four thousand dinars (4000 RSD) paid to the current account.

Current Account: 205-167929-22
Serbian Medical Association-Zajecar Branch;
purpose: material processing for TMG.

TECHNICAL REQUIREMENTS

The manuscripts are to be submitted exclusively in electronic form, bilingually (starting with volume 45), in Serbian (preferably Cyrillic) and in English. Papers submitted only in Serbian or English only will not be considered. Send the manuscripts in electronic form to: tmglasnik@gmail.com

The electronic format of the manuscript should be in Microsoft Office Word (with a .doc or .docx extension) and should include a final version of the manuscript. All text, references, tables and titles of tables and images and legends of images should be in one document. It is best to form the filename by the first author's last name, one keyword and type of work (for example: paunkovic_tiroidea_originalni.doc).

Use the Times New Roman font, 12p size. Write the paragraph so that only the left alignment is straight. Do not divide words into syllables at the end of the line. Insert only one blank space after the punctuation mark. Allow the titles and subheadings to be aligned with the left edge. Use bold, italic, sub, and superscript and underlined letters only where necessary. **Tables, images and charts should be inserted in the text where they should appear in the paper**. Acceptable formats for tables, charts, illustrations, and photos are doc, xls, jpeg, gif, and npg.

TYPES AND SCOPE OF MANUSCRIPTS

The title of all types of articles is followed by Summary (up to 300 words) and keywords (3 to 8).

The Original Paper (work) is a systematically published research of a problem according to scientific criteria and a clear aim of the research. **The integral parts of the paper are: a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) material and methods**; **c) results; d) discussion; e) conclusion; f) literature**. The length of the text is limited to 3500 words, with a maximum of 5 tables, charts, or pictures (up to 12 pages of text).

A Review Article covers a systematically addressed specific medical problem, in which the author made some contribution, visible on the basis of self-citations. **Integral parts of the paper are: a) introduction**- (the aim of the review paper as the last paragraph of the introduction); **b) the text of the review of literatureonthe problem , with subtitles**; **c) conclusion; d) literature**. The review article is usually commissioned by the Editorial Board, but non-commissioned manuscripts are also considered. Contact the Editorial Board before writing a review article. Text length can be up to 5000 words (18 pages).

A Case Report (patient presentation**)** sheds light on individual cases ofmedical practice. It usually describes one to three patients, or one family. The integral parts of the paper are: **a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) presentation of the patient; c) discussion and d) conclusion**. Unlike the original research, omit the section on methodology and results. The text is limited to 2500 words, max 4 tables, or 4 pictures and up to 25 references (up to 6 pages of text in total). Patient names, initials, or medical history numbers should not be used, especially in the illustrations. Casereportsmust not have more than 5 authors

Articles in the history of medicine and health culture shed light on certain aspects of medical practice in the past. Text length can be up to 2500 words (6 pages). These and the articles statedbelow do not have a prescribed structure, such as original papers, case reports, and review articles. Short contributions from the field of medical practice (diagnostics, therapy, remarks, suggestions and opinions on methodological problems, etc.) are published, too, as well as presentations from various medical meetings, symposia and congresses in the country and abroad, book reviews and articles from foreign journals up to 1000 words, 1-2 tables or images, up to 5 references (up to 3 pages of text). Editorial letters have up to 400 words, or 250 words if they contain comments on published articles. By order of the editorial board, or in agreement with the editorial board, works of didactic character are published.

If the work is part of a master's thesis, or a doctoral dissertation, or is done in the framework of a scientific project, this should be **clearlyindicated in the note after the abstract and before the text**. Also, if the work has been previously announced at a professional meeting, state the official name of the meeting, the venue and time of the event, whether the work has been published and how it has been published (eg the same or a different title or abstract).

ETHICAL CONSENT. Manuscripts on human research should include a statement in the form of a written consent of the persons interviewed in accordance with the WMADeclaration of Helsinki and the approval of the responsible ethics committee that the research can be carried out and is in accordance with legal standards. Experimental research on human material and animal testing should include a statement from the ethics committee of the institution and be in accordance with legal standards. Information on this must be provided in the section

AUTHORSHIP. All persons listed as authors of the work should qualify for authorship. Each author should have participated sufficiently in the work on the manuscript to be able to take responsibility for the entire text and the results presented in the work. Authorship is based solely on: making a significant contribution to the concept of the work, obtaining results or analyzing and interpreting the results; the planning of the manuscript or its critical revision of considerable intellectual importance; the final refinement of the print version of the manuscript. Authors should attach a description of the contributions individually for each co-author within the Submission Letter form. Financing, collecting data or generally overseeing a research team cannot by itself justify authorship. All other contributors who are not the authors of the manuscript should be listed onthe

acknowledgementpage, with a description of their contribution to the work, with written consent, of course.

STATEMENT OF CONFLICT OF INTEREST. The manuscript is accompanied by a signed statement in the form of a Submission Letter stating the authors of each possible conflict of interest or lack thereof. For more information on the different types of conflicts of interest, visit the World Association of Medical Editors' Association (WAME; http://www.wame.org), entitled "Conflict of Interest Statement Policy".At the end of the paper, below the Remarks section, in a separate section Conflict of Interest,each possible conflict of interest or its absence should be declaredfor each author individually (full name of the author or initials) For example Zoran Petrovic: Krka (lecturer) Ljiljana Aleksic: none. Mila Bastac: Pfizer, Sanofi, Bristol-Meyers Squibb (lecturer, honorary consultant, researcher on ascientific project).

PLAGIARISM. As of January 1st, 2019, all manuscripts are subjected to plagiarism / autoplagiarism through the SCIndeks Assistant-Cross Check (iThenticate). Papers containing plagiarism or self-plagiarism will be rejected and the authors sanctioned.

ABBREVIATIONS. Use only when necessary, for very long names of chemical compounds, that is, abbreviations that are already recognizable (standard abbreviations, such as DNA, AIDS, HIV, ATP). For each abbreviation, the full term should be stated when first quoted, unless it is a standard unit of measure. Do not use abbreviations in the title. Avoid using abbreviations in the abstract, but if necessary, explain each abbreviation when first referenced in the text.

ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

MANUSCRIPT PREPARATION

The text of the paper contains first and foremost the title of the paper, in the following lines: full names of the authors and all co-authors; the name, place and address of the institutions from which the author and co-authors come (in parentheses, associate the names of the authors); possibleacknowledgementfor help with elaborationofthe paper;

It is obligatory to submit:

-proposal of the manuscript category (original work, review article, case report, etc.);

-**first and last name, year of birth of the author and all co-authors**;

-**full address, telephone and fax numbers, as well as the author's e-mail for correspondence**.

The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

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Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

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