ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Vol. 6 No 3, December 2022

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, R.N.Macedonia

Apotel® 1000mg/6.7ml

I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:

Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.

i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.

Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:

Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu, R Prabhavathi, 2015

Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.

Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.

На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,

На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**

Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg

Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.

Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

Мултимодално менаџирање на постоперативна болка

I.V. Paracetamol е атрактивна компонента за мултиодално менаџирање на болка.

- **Синергистичко делување**
- **Зголемување на аналгетски ефект**
- **Значително намалување на болка**
- **Редукција на дозата на опоидни лекови за - 40% во првите 24 часа**
- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

Увозник и дистрибутер:
Марти Алко - Битола 047/203 615

Baxter

WHEN EARLY RECOVERY REALLY MATTERS

Дистрибутер за Македонија

FARMA TREJD

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Publisher
Department of Anaesthesia and Reanimation
Faculty of Medicine
"Ss. Cyril and Methodius" University
Skopje, R.N.Macedonia

Proofreading
Daniela Nacevska Stojcevska

CONTENT

ARTIFICIAL INTELLIGENCE AS A USEFUL TOOL FOR PRECISION MEDICINE IN CRITICAL CARE SETTINGS

Prof. Mirjana Shoholcheva, MD, PhD

Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, Macedonia

The question of whether a computer machine can think like a human can be answered by the application of artificial intelligence (AI) in many areas of human life whereby specific and precise data analysis are needed in shortest possible period of time. Biomedicine is one of these areas that can strongly benefit from employing AI. The application of different AI algorithms can predict, diagnose and treat various diseases with different therapeutic approaches. AI can understand complex situations, simulate human thinking and reasoning, and can solve complex problems. With all the possibilities that AI provides, it assembles it as an inseparable part of precision medicine. Precision medicine focuses on the identification of therapeutic strategies that are effective for a group of patients based on similar unifying characteristics, something that is more challenging than tailoring care for each individual that personalized medicine encompasses. For better individualizing the delivery of therapies and improving care for patients, precision medicine research includes the creation of large richly phenotyped networks of clinical, imaging and multianalyte data. AI supports the implementation of novel trial designs, including adaptive designs, and embedding trial procedures in the electronic health record, continued innovation in the data science and engineering methods required to identify heterogeneity of treatment effect, further development of the tools necessary for the real-time application of precision medicine approaches, as well as work to ensure that precision medicine strategies can be applied to different patients regardless of their race, ethnicity or socioeconomic status.

The relationship between AI, machine learning and deep learning (DL) is especially important in today's era of intelligent digital systems (1). AI implies any technique that enables computers to mimic human intelligence (e.g., logic, if-then rules, decision trees and machine learning). Subset of AI includes statistical algorithms that enable machines to improve at tasks with experience present learning from past experience or machine learning, while DL implies subset of machine learning using deep multilayered neural networks that can train themselves (self-learning ability) to perform tasks on vast amount of data (2).

The application of AI technology in clinical critical care practice is a particular challenge from the point of view of legal regulation and ethics. Of course, this also includes personal learning, standardization, but also techniques such as neural networks, random forests, and gradient boosting models as examples of "black box" techniques which are opposite of "white box" algorithms which are presented as logistic regression and decision trees. AI potential applications are in a variety of

preoperative (blood marker tumor screening, computer assisted radiological diagnosis, accurate prognostication etc.), intraoperative (malignant tissue identification, risk detection etc.) and postoperative (prediction of complications, tailored follow-up, prediction of recurrence, tailored therapeutics etc.) clinical care procedures (3).

These applications run through disease identification, disease evolution prediction, disease phenotyping, guiding the clinical decisions and implementation. Timely detection or prediction of disease enables clinicians to manage critically ill patients earlier than conventional strategy (4). For example, chronic heart failure (CHF) could be differentiated from other causes of lung disease using a machine learning model, such as: amounts of pulmonary edema secondary to the CHF could be quantified with semi-supervised machine learning, image segmentation and quantification of lesions by convolutional neural networks, a type of algorithm is used to detect COVID -19, or the presence of traumatic brain injury (TBI) on head computed tomography could be evaluated with higher accuracy than manual reading. Oftentimes, by finding the cause of the clinical deterioration, obtaining a more precise diagnosis is possible, which is a particular challenge in differential diagnosis. The prediction of disease evolution is very important in order to decrease the mortality rate. To predict hemodynamic decompensation intraoperatively or in the intensive care unit is a challenge that will help prevent late detection which in turn would lead to mortality (5,6). AI-driven models are used to predict the progression of COVID-19 by predicting hypoxia and respiratory distress as well as mortality of COVID-19 patients with different risk profiles. Cardiac arrest, sepsis and mortality after TBI have been also predicted so far, using different models (7,8). As far as disease phenotyping is concerned, AI could recognize different phenotypes or endotypes that could reflect influences from the critical state and hence open up the door to personalize management. Providing individualized solutions with using reinforcement learning (the algorithm in reinforcement learning is designed to detect numerous variables in a given state to build an action model), can help in guiding clinical decisions, and in that way AI impacts and contributes to generate personalized therapeutic solutions. Finally, the application of AI in critical care settings depends on the implementation and acceptance at the bedside, and in this way, it will be possible to redesign the current ICU in a new model, where it will be possible to react earlier to all potential deteriorations in patients, and of course it will also enable individual treatment based on generally accepted guidelines.

Recently, few publications process the application of AI in the real –life setting, but for it to come true, the model should be able to deliver important information in a timely manner, the feedback time should be extremely short, sometimes less than few minutes, and a real time AI model should be equipped with a very fast data pre-processing platform. It should be emphasized here that only few clinical studies have achieved real-time prediction.

Although AI is changing the picture in the clinical environment through all the advantages it has, it still has certain limitations or pitfalls in critical care settings. There are difficulties in overcoming the complexity of DL models and strong resistance to accept these models into daily

practice. DL has been criticized for being a "black box" that does not explain how the model generates outputs from given input. The large number of parameters involved, makes difficult for understanding how DL models analyze data and make decisions, so that's it why DL tools have to be more interpretable and applicable in clinical settings. Efforts must be made to make the explanation and interpretation of AI models as easy as possible.

There is a lack of adequate clinical experiments and trials in critical care settings. Current AI models in critical care have largely been generated using retrospective data, without external validation or prospective evaluation which imply that reproducibility of AI solutions is not guaranteed. The application of AI in critical care settings is not exempt from the ethical dilemmas, especially regarding data privacy and data sharing. De-identification and parallel/distributive computing can minimize data leakage and potentially speed up the multicenter validation process. And finally, the most important pitfall is that the human will be excluded from the care of the patient, which is of course unacceptable. The human remains a major part of patient care with monitoring and decision-making.

Recently, novel AI models and trial designs are introduced as Randomized Embedded Multifactorial Additive Platform for Community-Acquired Pneumonia (REMAP-CAP) which were initially developed to identify optimal treatment for community–acquired pneumonia and continued throughout the COVID-19 pandemic and the same contributed to improved survival among critically ill COVID-19 patients (9).

As a conclusion, AI is suitable for recognizing hidden disease patterns among the extremely heterogeneous clinical datasets, provides useful solutions in disease detection, phenotyping, and prediction that might alter the course of critical diseases,

and may also lead to optimal, individualized treatment strategies when multiple treatment options exist. A recommendation arising from all abovementioned is that the concept of AI has to be accepted in clinical practice with all its advantages and parts that require better development. Hereby, above all, it means standardization and data sharing, a model that will ensure data reliability, real-time application and quality control.

It is certain that the application of AI in critical care settings will represent a real revolution in the new approach to critical patients. Through proper employment of AI advantages, precision medicine may soon become a worldwide reality.

References:

1. Wainberg M, et al. Deep learning in biomedicine. Nat Biotechnol. 2018;36(9): 829–38. DOI: 10.1038/nbt.4233.
2. Akkus, et al. Artificial Intelligence (AI)-Empowered Echocardiography Interpretation: A State-of-the-Art Review. J. Clin. Med. 2021, 10, 1391. ttps://doi.org/10.3390/jcm10071391.
3. Busnatu Ș, et al. Clinical Applications of Artificial Intelligence-An Updated Overview. J Clin Med. 2022 Apr 18;11(8):2265. doi: 10.3390/jcm11082265
4. Yoon et al. Artificial Intelligence in Critical Care Medicine. Critical Care (2022) 26:75. doi: 10.1186/s13054-022-03915-3.
5. Joosten A, et al. Computer-assisted individualized hemodynamic management reduces intraoperative hypotension in intermediate- and high-risk surgery: a randomized controlled trial. Anesthesiology. 2021; 135:258–72. doi: 10.1097/ALN.0000000000003807.
6. Yoon JH, et al. Predicting tachycardia as a surrogate for instability in the intensive care unit. J Clin Monit Comput. 2019; 33:973–85. doi: 10.1007/s10877-019-00277-0. Epub 2019 Feb 14.
7. Bartkowiak B, et al. Validating the electronic cardiac arrest risk triage (eCART) score for risk stratification of surgical inpatients in the postoperative setting: retrospective cohort study. Ann Surg. 2019; 269:1059–63. doi: 10.1097/SLA.0000000000002665.
8. Nemati S, et al. An interpretable machine learning model for accurate prediction of sepsis in the ICU. Crit Care Med. 2018; 46:547–53. Doi: 10.1097/CCM.0000000000002936.
9. Angus DC et al. The REMAP-CAP (randomized embed- ded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design. Ann Am Thorac Soc. 2020; 17:879–91. doi: 10.1513/AnnalsATS.202003-192SD.

THE EFFECT OF ESMOLOL ON CARDIAC RECOVERY AFTER CARDIOPULMONARY BYPASS IN PATIENTS WITH CORONARY ARTERY DISEASE

Kostadinovska-Jordanoska B[1], Nikolic A[1], Stefanovski I[1], Radoeski A[1], Bedzeti F[1], Bislimovski D[1]

[1] Department of Cardiac Surgery, Acibadem Sistina Hospital, Skopje, North Macedonia

ABSTRACT

Introduction: Esmolol is a cardio-selective beta-blocker (BB) with an ultra-short-acting half-life of about 9 minutes due to esterase hydrolysis, which allows its negative inotropic effect to rapidly cease after the infusion is reduced or stopped. Because of these characteristics, this beta-1 selective adrenergic blocker is the drug of the first choice for use as an adjuvant to cardioplegia in patients in whom the possible side effects (hypotension, bradycardia, heart failure) of the longer-acting BBs administered would be avoided in the intraoperative period.

Aim: The aim of this study was to determine whether the application of a fast-acting beta-1 selective adrenergic blocker - esmolol immediately before CABG and as an adjunct to cardioplegia itself, would provide additional myocardial protection, faster cardiac recovery after cardiopulmonary bypass and would reduce the occurrence of heart rhythm disturbance in the perioperative and postoperative period.

Material and Methods: This prospective, randomized, controlled study included 50 patients aged 40-80 years with coronary artery disease that according to the recommendations of the professional associations, refers to revascularization with CABG. Patients were randomized into two groups according to whether they received esmolol beta1-selective adrenergic blocker or placebo.

Results: The incidence of spontaneous re-beat, recovery time (time from initiation of reperfusion to establishment of cardiac rhythm), atrial and ventricular fibrillation, and the need for temporary pacemakers were reduced with the use of esmolol. **Conclusion:** Myocardial cardio-protection with esmolol given as an adjunct before and during cardioplegia in patients with coronary artery disease has a positive effect on cardiac recovery after cardiopulmonary bypass.

Key Words: cardiac surgery, cardiopulmonary bypass, coronary artery disease, esmolol, heart rhythm.

Introduction

Beta-(β)-adrenergic blockers (BBs) have the ability to reduce the degree of myocardial injury during ischemia and reperfusion, but the most BBs have prolonged (hours) negative inotropic and chronotropic effects, thus possessing positive properties significant for preoperative and postoperative period, but this limits their use during cardiac surgery (1,2,3). Esmolol is an ultra-

short-acting BB that represents a cardio-selective BB, with a half-life of about 9 minutes due to esterase hydrolysis, which allows its negative inotropic effect to be rapidly terminated after the infusion is reduced or stopped (4,5). For this reason, is more suitable for use in acute situations such as cardiac surgery. Esmolol can be used to induce "appropriate cardiosurgical conditions", which manifests as a significant slowing of the heart rate (6).

Esmolol also reduces the metabolic demands of the myocardium before and during cardioplegic arrest reducing ischemia-reperfusion injury. If given before aortic cross clamping, esmolol reaches the coronary microcirculation and provides cardio-protection before the administration of cardioplegia itself (7). In addition, if added to the cardioplegic solution, esmolol may provide additional protection by reducing myocardial activity (8,9,10). A meta-analysis of randomized trials showed a significant reduction in the rate of perioperative myocardial ischemia and arrhythmias after CABG when esmolol was administered during cardiac surgery, without an increased need for inotropic support (11). In 2003, Scorsin et al., investigated the protective effect of esmolol during continuous retrograde cardioplegia. The result of the study was a reduced consumption and demand of the myocardium for oxygen, and thus a reduced ischemia-reperfusion injury (12). In 2011, Sun et al., investigated the effect of esmolol as an adjuvant to cardioplegia on cardiac recovery after CABG (13). There were results of reduced occurrence of ventricular arrhythmias, shortened time to automatic heart rhythm establishment, reduced occurrence of ventricular fibrillation after establishment of heart rhythm and shortened reperfusion time. In two experimental studies, Fannelop et al. – 2008, Dahle et al. – 2015, the use of esmolol in cardioplegia improved left ventricular function in the postoperative period (14, 15).

Figure 1. *Role of esmolol as a beta1-blocker (Adapted from Scorsin et al. 2003 (12)).*

Because of these properties, this beta-1 selective adrenergic blocker is the drug of the first choice for use as an adjuvant to cardioplegia in patients in whom the possible side effects (hypotension, bradycardia, heart failure) of the longer-acting BBs given would be avoided in the intraoperative period (16).

The aim of this study was to determine whether the application of a fast-acting beta-1 selective adrenergic blocker - esmolol immediately before CABG and as an adjunct to cardioplegia itself would provide additional myocardial protection, faster cardiac recovery after cardiopulmonary bypass and would reduce the occurrence of the heart rate disturbance in the perioperative and postoperative period.

Material and Methods
Study Design, Specimens and Methods

Material

In this prospective, randomized, controlled study, 50 patients aged 40-80 years with coronary artery disease, which according to the recommendations of the professional associations refer to revascularization with CABG were included (17). All patients met the criteria for inclusion in the study and had signed the informed written consent for their participation in the study which was previously explained to them in detail. Patients were grouped into two randomized groups according to whether they received esmolol beta1-selective adrenergic blocker or placebo. A computer-generated list of random numbers was used for appropriate randomization of patients. Participants were assigned a progressive randomization number that was written on a sealed, numbered, opaque envelope containing information about patient allocation (esmolol or placebo).

Methods

According to the protocol for the inclusion of esmolol:

The first dose of esmolol (1mg/kg in 10mg/ml solution) was administered through a central venous catheter after cannulation of the aorta i.e., immediately before clamping the aorta. The second dose of esmolol (2mg/kg in a 10mg/ml solution) was given along with antegrade cold blood cardioplegia. The maximum dose of esmolol given before aortic clamping was 100mg, while the maximum dose of esmolol given with cardioplegia was 200mg. The control group of subjects received a placebo (saline solution) in the same volume. In all patients, cardiac recovery after cardiopulmonary bypass was monitored on the basis of the following parameters: (1) the rate of spontaneous cardiac re-beating (spontaneous re-beating without ventricular fibrillation or temporary pacemaker); (2) recovery time (time from the start of reperfusion to establishment of cardiac rhythm); (3) atrial fibrillation during reperfusion; (4) ventricular fibrillation during reperfusion; (5) heart rate after establishment of cardiac rhythm; (6) heart rate after 10 min. from establishing a heart rhythm; (7) need for a temporary pacemaker. Also, in all patients, the following were monitored: (8) duration of aortic cross clamp, (9) duration of cardiopulmonary bypass and (10) duration of reperfusion (period from aortic declamping to weaning of cardiopulmonary bypass).

Statistical Analysis

Categorical parameters were summarized as percentages and continuous parameters as a mean ± standard deviation. The difference between groups was tested using Pearson's Chi-square test for categorical variables and Mann-Whitney nonparametric tests for continuous variables. Correlation has been made using Pearson or Spearman analysis. All data analysis was performed using SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois, USA), and $p \leq 0.05$ was considered as statistically significant.

Results

The comparison of the two groups with and without esmolol showed that patients in the placebo group were non-significantly older than those in the esmolol group (P=0.392). All patients had a normal body mass index on average. NYHA class was significantly higher in the placebo group, 3.52±0.51, than in the esmolol group, 3.19±0.40, (P=0.018). The CCS class was 3.55±0.51 in the placebo group and 3.19±0.40 in the esmolol group (P=0.009). The EuroScore score was significantly higher in the placebo group, 6.37±5.01 than in the esmolol group, 3.91±2.09, (P=0.040). The STS score was non-significantly higher in the placebo group, 2.90±3.10 than in the esmolol group, 1.82±1.35, (P=0.144). (Table 1)

Table 1. *Basal values of the examined patients.*

Parameters	All patients (n=50)	Esmolol n=21	Placebo n=29	p
Age (years)	65.58±8.99	64.29±8.19	66.52±9.56	0.392
Gender Men /Women (n//%)	36/72 (14/28)	17/4 (81.0/19.0)	19/10 (72.9/27.1)	0.239
BMI (kg/m2)	27.79±4.88	26.92±5.08	28.42±4.72	0.289
NYHA	3.38±0.49	3.19±0.40	3.52±0.51	0.018
CCS class	3.40±0.49	3.19±0.40	3.55±0.51	0.009
EuroSCORE	5.33±4.20	3.91±2.09	6.37±5.01	0.040
STS score	2.45±2.55	1.82±1.35	2.90±3.10	0.144

CCS=Canadian Cardiovascular Society; NYHA=New York Heart Association; EuroSCORE=European system for cardiac operative risk evaluation; STS score= Society of Thoracic Surgeons score.

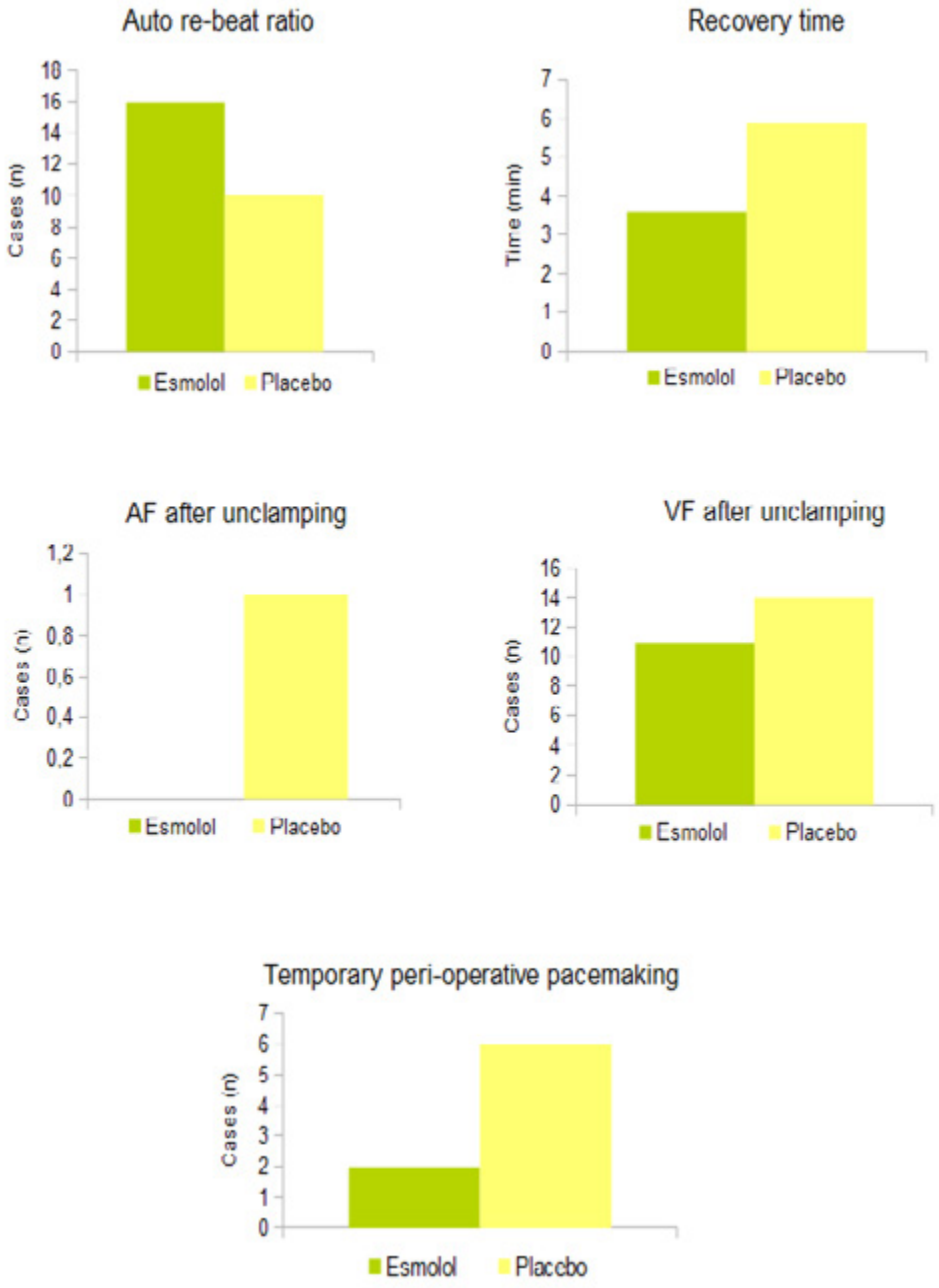
Table 2. *Cardiac recovery parameters after cardiopulmonary bypass.*

Parameters	All patients (n=50)	Esmolol n=21	Placebo n=29	p
Recovery time (min)	5.01±6.39	3.60±2.21	5.89±7.94	0.385
Auto re-beat ratio (n/%)	26/52.0	16/76.2	10/34.4	0.245
VF after declamping (n/%)	25/50.0	11/52.4	14/48.3	0.500
AF after declamping (n/%)	1/2	0	1/3.5	0.563
HR after re-beat (bmp)	62.04±20.59	67.43±18.69	58.14±21.32	0.087
HR 10 min after re-beat (bmp)	78.70±15.49	79.67±15.33	78.00±15.83	0.829
Aortic-cross clamping time (min)	41.70±10.52	40.71±10.36	42.41±10.75	0.437
Bypass time (min)	71.06±16.55	70.33±16.34	71.59±16.0	0.867
Temporary peri-op PM (n/%)	8/16	2/9.5	6/20.7	0.255
Reperfusion time (min)	25.98±8.72	25.90±6.81	26.03±9.99	0.959

These values are obtained only if the recovery time of those with spontaneous recovery is taken into account, those without spontaneity are not taken into account.

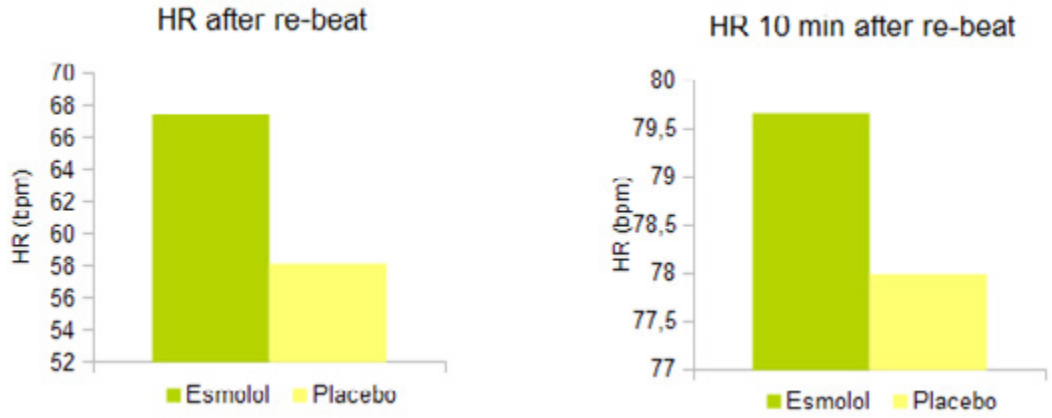
Following the esmolol treatment, the heart underwent re-beat automatically in 16 patients, as compared to 10 patients in placebo group (P=0.405). The recovery time was 3.60±2.21 minutes compared to 5.89±7.94 in placebo group (P=0.385). Ventricular fibrillation after declamping happened in 11 cases in esmolol group and 14 patients in placebo group (P=0.500). Atrial fibrillation was found in 1 case in placebo group and none in esmolol group (P=0.563). Two patients of the esmolol group, compared to eight patients in placebo group required temporary pacemaking (P=0.255). (Figure 2, Table 2).

Figure 2. *The heart recovery data after unclamping.*



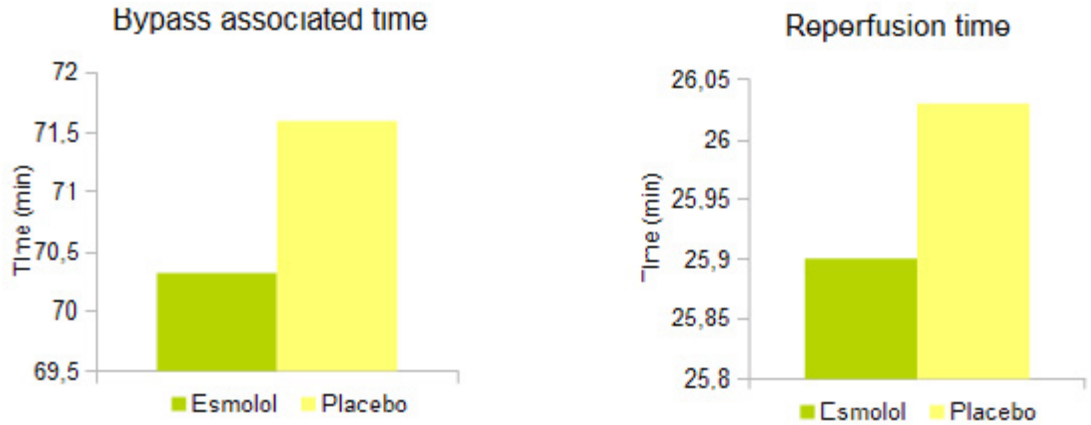
The heart rate after steady re-beat was 67.43±18.69 in the esmolol group compared to 58.14±21.32 in the control group (P=0.087). The heart rate after successful re-beat 10 minutes later was 79.67±15.33 in esmolol group, but 78.00±15.83 in placebo group (P=0.829). (Figure 3, Table 2).

Figure 3. *Heart rate after declamping.*



The aortic-cross clamping time was 40.71±10.36 in the esmolol group and 42.41±10.75 in the control group (P=0.437). The bypass time was 70.33±16.34 in esmolol group and 71.59±16.0 in placebo group (P=0.867). The reperfusion time was 25.90±6.81 minutes in the esmolol group, compared to 26.03±9.99 in the placebo group (P=0.959). (Figure 4, Table 2).

Figure 4. *Bypass associated time and reperfusion time.*



Discussion

The use of a fast-acting beta1-selective adrenergic blocker esmolol intravenously in the period immediately before clamping the aorta and together with the cardioplegic solution, is based on the data that esmolol reduces oxygen consumption of the myocardium by blocking beta-1 adrenergic receptors. Its basic characteristics such as the short T1/2 of 9.2 minutes and

its breakdown in the body through erythrocyte esterase, make it quite suitable for the protection of the heart muscle in the perioperative period without unwanted hemodynamic effects such as: hypotension, bradycardia and low blood pressure syndrome (low-cardiac output syndrome).

In our study, although we did not find statistically significant differences due to the limited number of patients included, we still identified that esmolol increases the automatic heart rate (spontaneous heart rate without ventricular fibrillation or temporary pacemaker), decreases the recovery time (time from initiation of reperfusion until cardiac rhythm is established), reduces the incidence of atrial and ventricular fibrillation after primary re-beating and participates in maintaining a balance between oxygen delivery to the myocardium and oxygen consumption without prolonging bypass time. On the contrary, treatment with esmolol according to the intended protocol shortens the recovery time and reduces the need for a temporary pacemaker to maintain the target heart rate after cardiopulmonary bypass.

Conclusion

Cardio-protection of the myocardium with esmolol, given as an adjunct before and during cardioplegia in patients with coronary artery disease, has a positive effect on cardiac recovery after cardiopulmonary bypass.

References

1. Hans J. Geissler, Karen L. Davis, Glen A. Laine et al. Myocardial protection with high-dose b-blockade in acute myocardial ischemia. *European Journal of Cardio-Thoracic Surgery.* 2000;63–70.
2. Brinkman W, Herbert MA, O'Brien S et al. Preoperative β-blocker use in coronary artery bypass grafting surgery: national database analysis. *JAMA Intern Med.* 2014;174(8):1320-7.
3. Blessberger H, Lewis SR, Pritchard MW, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2019;9(9):CD013438.
4. Oliver E, Mayor F Jr, D'Ocon P. Beta-blockers: Historical Perspective and Mechanisms of Action. *Rev Esp Cardiol (Engl Ed).* 2019;72(10):853-862.
5. Loscalzo J, editors. Harrison's Cardiovascular Medicine, 3e. McGraw Hill; 2016.
6. Blessberger H, Kammler J, Steinwender C. Perioperative use of β-blockers in cardiac and noncardiac surgery. *JAMA.* 2015;313(20):2070-1.
7. Fujii M, Chambers DJ. Cardioprotection with esmolol cardioplegia: efficacy as a blood-based solution. *Eur J Cardiothorac Surg.* 2013;43(3):619-27.
8. Neustein SM, Bronheim DS, Lasker S. Esmolol and intraoperative myocardial ischemia: a double-blind study. *J Cardiothorac Vasc Anesth.* 1994; 8: 273–277.
9. Rinne T, Harmoinen A, Kaukinen S. Esmolol cardioplegia in unstable coronary revascularisation patients. A randomised clinical trial. *Acta Anaesthesiol Scand.* 2000; 44: 727–232.

10. Cork RC, Kramer TH, Dreischmeier B et al. The effect of esmolol given during cardiopulmonary bypass. *Anesth Analg.* 1995; 80: 28–40.
11. Devereaux PJ, Yang H, Yusuf S et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008; 371: 1839–1847.
12. Scorsin M, Mebazaa A, Al Attar N et al. Efficacy of esmolol as a myocardial protective agent during continuous retrograde blood cardioplegia. J Thorac Cardiovasc Surg. 2003;125(5):1022-9.
13. Sun J, Ding Z, Qian Y. Effect of short-acting beta blocker on the cardiac recovery after cardiopulmonary bypass. *J Cardiothorac Surg.* 2011; 6:99.
14. Fannelop T, Dahle GO, Matre K et al. Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. *Eur J Cardiothorac Surg.* 2008;33(1):9-17.
15. Dahle GO, Salminen PR, Moen CA et al. Esmolol added in repeated, cold, oxygenated blood cardioplegia improves myocardial function after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2015;29(3):684-93.
16. Zangrillo A, Bignami E, Noè B et al. Esmolol in Cardiac Surgery: A Randomized Controlled Trial. *J Cardiothorac Vasc Anesth.* 2021;35(4):1106-1114.
17. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2018; 00:1-96.

FERRITIN LEVELS AS A MARKER OF DISEASE SEVERITY IN PATIENTS WITH COVID-19

Dimitrov I[1] , Sazdov D[1]

[1] Clinical Hospital Acibadem Skopje, Republic of North Macedonia, Department of Anesthesia and Intensive Care Medicine

ABSTRACT

Introduction:

The cytokine storm is a dysregulated immune response to the **SARS-CoV-2 virus,** that resembles the one seen in severe forms of flu. Inflammatory markers like TNF-α, IL-6, IL-8, IL-12, are being released in excessive amounts during disease progression which can lead to development of Acute Respiratory Distress Syndrome (ARDS), and multiorgan failure (MOF). Different studies have reported association between the levels of serum ferritin, d-dimers, lactate dehydrogenase (LDH), and interleukin-6 (IL-6) with disease severity and mortality.

Hiperferritinemia, associated with inflammation caused by the **SARS-CoV-2 virus** is frequently seen in patients that need ICU admission and with mortality. So far in Macedonia there aren't enough studies that report the prognostic value of ferritin for development of severe form of COVID-19 disease. The purpose of this study is to evaluate the association of ferritin levels with the development of cytokine storm and progression to severe forms of COVID-19 disease.

Goal:

To evaluate the role of ferritin as prognostic biomarker for disease progression in severe forms of

COVID-19 disease.

Material and Methods:

56 male and female SARS-CoV-2 positive patients admitted to the COVID center in Clinical hospital Acibadem from Skopje from January to December 2021were included in this case control study. Patients were divided in two groups. Group 1 with 28 SARS-CoV-2 positive patients with severe form of the disease in need of High flow oxygen therapy (HFO), noninvasive (NIV) and invasive mechanical ventilation (IMV) and have received tocilizumab, and Group 2 with 28 SARS-CoV-2 positive patients with non-severe form of COVID-19 infection only on oxygen support with oxygen flow bellow 15L/min.

Results:

The study included 56 SARS-CoV-2 positive patients between 25 and 83 years of age. The median age was 59.9 ± 11.8 years with 71.4% (40) male and 28.6% (16) female patients. Ferritin values on admission and at the three follow ups were significantly higher in the severe group compared to the non-severe (p=0.016), and (p=0.00063, p=0.000079 p=0.0017, accordingly).

Conclusion:

In this study, we found that ferritin is an independent predictor of disease severity and increased mortality in SARS-CoV-2 positive patients. The goal is to predict and prevent deteriorations such as the Cytokine storm, and to enable an adequate medical treatment in SARS-CoV-2 positive patients.

Key Words: COVID 19, cytokine storm, ferritin.

Introduction

Ferritin is a universal intracellular protein involved in iron storing and releasing in a controlled manner. It is produced in almost all living organisms including bacteria, algae, plants and animals. In humans it acts as a buffer between iron deficiency and iron overload (1). Serum ferritin has been long studied as a marker of iron metabolism; however, it also has a role as biomarker of inflammation as demonstrated by previous studies (2).

The novel coronavirus (SARS-CoV-2) infection is associated with high morbidity and mortality, especially among those with underlying health conditions. It is caused by a novel enveloped RNA virus, and can result in severe pneumonia (3). Several complications can worsen the patient's condition. One of the most severe complications seen in COVID-19 patients is the cytokine storm syndrome (CSS) (4). Inflammatory markers TNF- α, IL-6, IL-8, IL-12, are released in excessive amounts during disease progression. These biomarkers interact with the proteins from the complement and coagulation system, and can induce the development of disseminated intravascular coagulation, Acute Respiratory Distress Syndrome, hemophagocytic lymphohistiocytosis and multiorgan failure (5). Different studies and meta-analysis show that levels of serum ferritin, d dimers, lactate dehydrogenase (LDH), and interleukin-6 (IL-6) are higher in patients with disease progression and increase the risk of mortality (6-8).

The most of these studies show significant elevation in serum ferritin and other biomarkers in COVID-19 infected patients, yet they fail to identify an optimal serum cutoff level that can reliably predict the development of CSS resulting in acute lung injury with the need of ventilatory support and in-hospital mortality. According to Eloseily et al., an elevated ferritin value should alert clinicians to additional diagnostic work-up, so that therapeutic approaches can be considered without significant delay. Early institution of treatment for CSS has been proven to lead to better patient outcomes (9).

Goals

- To evaluate the association between higher levels of ferritin and disease severity in patients on HFO, NIV and IMV that have received tocilizumab;
- To determine the prognostic value of ferritin in determining disease progression and outcome;
- To determine a cut off value for ferritin that can help in management of patients with higher risk for disease progression and negative outcome.

Material and Methods:

Study Population

This was a Case-Control study that included 56 SARS-CoV-2 positive patients admitted in the COVID center in Clinical hospital Acibadem from January 2021 to December 2021. Adult patients from 25 to 83 years were divided in two groups 28 each:

1. The CASE group included patients with severe and critical COVID-19 disease who have SpO2 <94% on oxygen support, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50% and patients who have respiratory failure, septic shock, and/or multiple organ dysfunction who need HFO therapy, NIV and IMV.
2. (CONTROL) Patients with non-severe form of COVID-19 who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO2) ≥94% with oxygen support lower than 15L/min.

During hospital admission, baseline demographics, medical history, admission symptoms and exploratory findings were registered. We've collected treatment information and need for intensive care or HFO or mechanical ventilatory support.

Laboratory Analysis

Ferritin levels were measured from blood samples taken from patients on the day of admission and every 3 to 4 days or on request of the ordinarius according to the patient's condition. Patients were followed for up to 30 days or till all-cause death events. Blood samples were taken by the nurse from a venipuncture cite opposite of the infusion line or from a central venous catheter. Ferritin values are given in **ng/ml**, in the referent range of **22-322.**

Results

The study included 56 SARS-CoV-2 positive patients between 25 and 83 years of age. 71.4% (40) of the patients were male and 28.6% (16) of the patients were female. The median age was 59.9 ± 11.8 years.

Table 1. *Patients distribution according to gender and age.*

variable	
gender **n (%)**	
female	16 (28.57)
male	40 (71.43)
age **(mean ± SD) (min-max)**	(59.9 ± 11.8) (25 – 83)

Male and female patients were equally distributed among both groups. 28.6% (8) patients with severe and non-severe disease were females and 71.4% (20) patients were males accordingly.

Table 2. *Disease severity and gender*.

gender	Disease severity	
	Non-severe **n (%)**	severe **n (%)**
female	8 (28.57)	8 (28.57)
male	20 (71.43)	20 (71.43)

There wasn't a statistically significant difference in patients' age between groups (p=0.1). Patients in the severe group were older having an average age of 62.5 ± 10.9 and patients in the non-severe group 57.5 ± 12.3.

Table 3. *Disease severity and age.*

Age/years	Disease severity		**p-level**
	non-severe	severe	
mean ± SD	57.5 ± 12.3	62.5 ± 10.9	t=1.62 p=0.11 ns

t(Student t-test)

Ferritin values on admission and at the three follow ups were significantly higher in the severe group compared to the non-severe (p=0.016), and (p=0.00063, p=0.000079 p=0.0017, accordingly).

Median values of ferritin on admission were 1106.85ng/ml and 541.95ng/ml, in the severe and non-severe group accordingly and 1359.75ng/ml and 632.9ng/ml, at the last control measurement.

Table 4. *Disease severity and mean ferritin values*.

	Disease severity				**p-level**
		n	mean ± SD	median (IQR)	
ferritin 1	non-severe	28	752.89 ± 724.3	541.95(224.25 – 1123.45)	Z=2.4
	severe	28	1962.37 ± 3744.3	1106.85(490.65 – 1727.05)	*p=0.016
ferritin 2	non-severe	28	791.98 ± 706.3	641.8(237.95 – 1165.25)	Z=3.42
	severe	28	1744.54 ± 2029.5	1309.3(759.05 – 2051.3)	***p=0.00063
ferritin 3	non-severe	23	789.42 ± 741.2	656.5(194 – 1101)	Z=3.95
	severe	28	3656.20 ± 6660.5	1555.15(954.95 – 2130.3)	***p=0.000079
ferritin 4	non-severe	9	619.66 ± 403.2	632.9(603 – 736.2)	Z=3.13
	severe	20	1484.52 ± 972.0	1359.75(871.95 – 1715.8)	**p=0.0017

Z (Mann-Whitney U Test); *p<0.05, **p<0.01, ***p<0.0001

Higher levels of ferritin on admission were more frequently measured in patients with severe 89.3% (25) than in patients with no-severe disease 64.3% (18), p=0.027.

On the first follow up 96.4% (27) patients with severe disease and 71.4% (20) patients with non-severe disease had elevated levels of ferritin; on the second follow up 96.4% (27) patients in the severe group and 73.9% (17) in the non-severe group had elevated values of ferritin. On the last follow up all of the patients in the severe group had elevated values of ferritin and 77.8% (7) patients in the non-severe group were with elevated levels of ferritin. Statistical analysis has shown that the higher values of ferritin were statistically more frequently seen in patients with severe form of COVID-19 disease at the follow ups (p=0.029, p=0.037, accordingly).

Table 5. *Distribution of elevated and normal values of ferritin.*

		Disease severity			**p-level**
		n	Non-severe **n (%)**	severe **n (%)**	
ferritin 1	normal	13	10 (35.71)	3 (10.71)	X^2=4.91
	elevated	43	18 (64.29)	25 (89.29)	*p=0.027
ferritin 2	normal	9	8 (28.57)	1 (3.57)	Y X^2=4.76
	elevated	47	20 (71.43)	27 (96.43)	*p=0.029
ferritin 3	normal	7	6 (26.09)	1 (3.57)	Fisher exact, two-tailed
	elevated	44	17 (73.91)	27 (96.43)	*p=0.037
ferritin 4	normal	2	2 (22.22)	0	Fisher exact, two-tailed
	elevated	27	7 (77.78)	20 (100)	p=0.089 ns

In order to evaluate the contribution of ferritin for development of severe forms of COVID-19, binary logistic regression was performed. Results showed that patients with serum ferritin levels higher than 322ng/ml had 4.6 times significantly higher risk for development of severe form of disease than patients with values lower than 322ng/ml (OR=4.63 95%CI 1.113-19.257).

Table 6. *Logistic regression analysis.*

variable	B	S.E.	Wald	Sig.	Exp(B)	95% C.I. for EXP(B)	
						Lower	Upper
ferritin	1.532	0.727	4.440	0.035	4.630	1.113	19.257
constant	-1.204	0.658	3.345	0.067	0.30		

ROC analysis was used to determine the discriminatory capabilities of serum ferritin levels in distinguishing severe from non-severe forms of disease. For this test a ROC curve was constructed to show the sensitivity and specificity of every result of the test.

The area under the curve (AUC=0.687), for the values of serum ferritin shows that it has satisfactory power in distinguishing patients with non-severe from those with severe form of the disease with sensitivity of 58% and specificity of 71%.

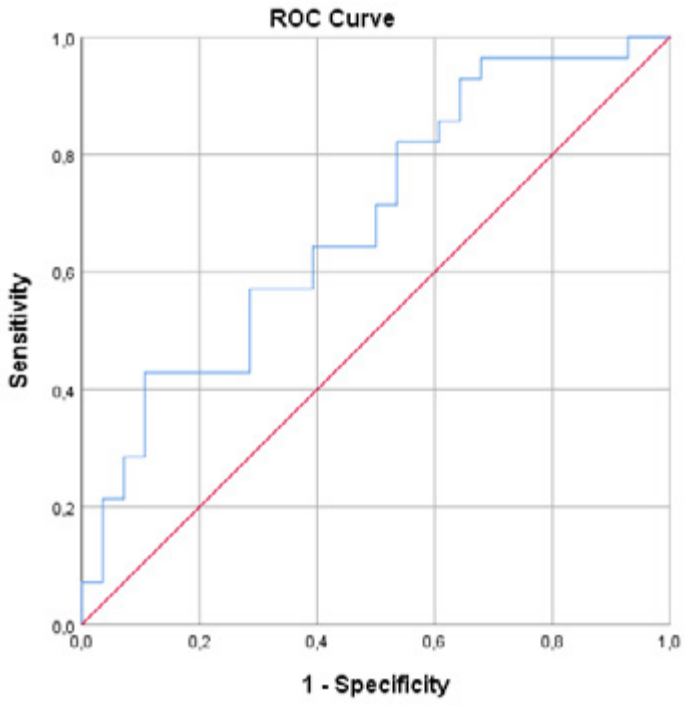


Table 7. AUC

Area	Std. Error	Asymptotic Sig	Asymptotic 95% confidence Interval	
			Lower	Upper
0.687	0.071	0.016	0.549	0.826

Discussion

In this Case-Control study we show that SARS-CoV-2 positive patients with severe form of the disease that require ICU admission and HFO, NIV or IMV have higher values of ferritin. Also, we demonstrate that the patients with higher values of ferritin have 4.6 times higher risk for development of more severe forms of the disease than patients with normal values of ferritin. In addition, we proved that ferritin as a serum marker has the capability to differentiate patients with severe from those with non-severe form of the disease.

Ferritin is a large protein (440kDa) present within the cytosol and also within the mitochondria of the cell. It can capture up to 4500 atoms of iron (10).

Cytosolic ferritin is composed of a light (L ferritin) and heavy (H ferritin) subunits (11). The ratio of H to L subunits varies depending on the tissue type and the developmental stage of the cell, and can be modified in inflammatory and infectious conditions (10). It has a pivotal role in cellular iron homeostasis. That is why its synthesis is tightly regulated , from DNA regulation via the promoter, to interactions with numerous iron regulatory proteins in the process of mRNA translation ; and finally, to a diverse set of signaling pathways and several proinflammatory

cytokines including TNF α, Interleukin 1, Interleukin 6, Interferon γ that affect ferritin content within cells (12-14). Iron homeostasis has a very important role in maintaining host's immune defense and inflammatory response. Both iron deficiency and/or overload can cause cellular and organ dysfunction (15).

Recent studies show that hypoferremia is an independent risk factor for hypoxic respiratory failure and death in COVID-19 patients (16,17). The overload of intracellular iron, especially in macrophages, causes cell and tissue damage, through the reactive oxygen species (ROS) catalyzed by iron. In addition, iron overload may trigger a form of non-apoptotic cell death termed ferroptosis (18). Serum ferritin concentration has been proven to reflect the individual's iron storage status. Studies have also found that increased serum ferritin levels are also associated with adverse outcomes (19-21). Elevated serum ferritin levels may suggest not only the presence of an iron overload state, but are also marker of inflammatory, autoimmune, infectious or malignant conditions (22,23). Extremely high levels can be found in patients with macrophage activation syndrome (MAS), adult-onset still disease (AOSD), catastrophic anti-phospholipid syndrome (cAPS) and sepsis (23-25). These four conditions were identified by Shoenfeld et al., and were put under the term "hyperferritinemic syndrome" (23). But high levels of ferritin have been also found in patients with severe forms of COVID-19. Ferritin has been characterized as an acute phase protein and as a mediator of immune dysregulation in severe COVID-19 (21). So, ferritin may be a marker of the inflammation and an active factor in the "cytokine storm" that is the mechanism for development of severe COVID-19. Complex feedback mechanisms between ferritin and cytokines may exist. Cytokines can induce ferritin expression, but also ferritin can induce the expression of pro- and anti-inflammatory cytokines as well. That's why some authors have included COVID-19 with pulmonary involvement within the spectrum of hyperferritinemic syndrome (26). These findings fit with the concept of hyperinflammation in COVID-19, and since hyperferritinemia has been associated with inflammatory states in SARS-CoV-2 infection, it is plausible that ferritin may be a useful parameter to predict disease severity and the extent of the cytokine storm.

There are several studies that evaluate the prognostic value of ferritin and its role in the development of cytokine storm syndrome and severe forms of COVID-19. Results from these studies are in line with the results in our study.

Deng, F. et al., in their study, classified the patients in three groups according to the disease severity as moderate, severe and critical and compared the values of ferritin between them (27). In their study, statistical analysis of the results showed that ferritin values in the severe and critical group of patients was 2.3-4.6 times higher compared to the patients in the moderate group. Also, the median level of ferritin in patients that died was 3.4 times higher than in those that survived.

Dahan S.et al, also evaluated the association between ferritin levels and disease severity in SARS-CoV-2 positive patients (28). They divided the patients in three groups as light, moderate and severe. Significantly higher levels of ferritin were seen in patients with severe

form of COVID-19 compared to those with moderate and light disease (P = 0.006 and 0.005, accordingly). The median value of ferritin in the severe group was (2817.6ng/ml) compared to those with non-severe form (708.6ng/ml) for p = 0.02.

So, the authors concluded as in our study, that higher levels of ferritin were indeed associated with disease severity in SARS-CoV-2 positive patients.

In the case control study by Ahmed, Sibtain et al., similar to our study, patients are divided into severe and non-severe group and survivors and non-survivors (29). They found statistically significant difference between the two categories of the disease severity and survival for the values of ferritin. Binary logistical regression analysis showed that ferritin is an independent predictor for all-cause mortality with AUC of 0.69 from the ROC analysis.

Maghfirah AI et al. in their study from 2022 included 63 SARS CoV-2 positive patients and divided them as mild moderate and severe. They found statistically significant correlation between ferritin values and disease severity ($p<0.001$). They carried out a Receive Operator Characteristic (ROC) curve analysis to determine whether ferritin could be used as a predictor of severity. Based on the Area Under Curve (AUC) value of ferritin 0.767 ($p<0.001$), they concluded that ferritin can be used as a predictor of the severity of COVID-19. They found a cut-off ferritin value at mild-moderate patients of 153.89ng/mL, and cut-off ferritin at mortality was 1145.54ng/mL (30).

The results from our study show that according to the AUC value ferritin has the capability to discriminate patients with non-severe and severe forms of the disease with a sensitivity of 58% and specificity of 71%. The cut off value for ferritin in our study between severe and non-severe of the disease is 322ng/ml.

Limiting Factors

The study has the following limitations: It is a unicentric study with a relatively small sample size. Although viral presence was confirmed mainly by polymerase chain reaction assay, false positives and false negatives could be present.

Conclusion

This case control study confirms ferritin is an independent predictor for disease severity and risk of mortality in SARS-CoV-2 positive patients. It can be used for timely management of these patients, their allocation to an intensive care unit, and early institution of treatment strategies such as tocilizumab in order to prevent disease progression and the cytokine storm syndrome.

References:

1. Casiday R, Frey R. "Iron Use and Storage in the Body: Ferritin and Molecular Representations". Department of Chemistry, Washington University St. Louis.
2. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014 Apr;6(4):748-73.
3. Huang C., Wang Y., Li X., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497–506.
4. Mehta P., McAuley D.F., Brown M., et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033–1034.
5. Mangalmurti, N. and Hunter, C. A. (2020) 'Primer Cytokine Storms: Understanding COVID-19', Immunity, 53(1), pp. 19–25. doi: 10.1016/j.immuni.2020.06.017.
6. Chen, Y. (2020) 'Increased Serum Levels of Hepcidin and Ferritin Are Associated with Severity of COVID-19', pp. 1–6. doi: 10.12659/MSM.926178.
7. Cheng, L. et al. (2020) 'Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis', (July), pp. 1–18. doi: 10.1002/jcla.23618.
8. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020 Dec;25(8):616-625. doi: 10.1080/1354750X.2020.1797880. Epub 2020 Nov 24. PMID: 32700561.
9. Eloseily E.M., Weiser P., Crayne C.B., et al. Benefit of anakinra in treating pediatric secondary hemophagocytic Lymphohistiocytosis. Arthritis Rheumatol. 2020; 72:326–334
10. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. Biochimica et biophysica acta (BBA)-bioenergetics. 1996 Jul 31;1275(3):161-203.
11. Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood. 2002 May 15;99(10):3505-16.
12. Arosio P, Levi S. Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. Biochimica et Biophysica Acta (BBA)-General Subjects. 2010 Aug 1;1800(8):783-92.
13. Hintze KJ, Theil EC. DNA and mRNA elements with complementary responses to hemin, antioxidant inducers, and iron control ferritin-L expression. Proceedings of the National Academy of Sciences. 2005 Oct 18;102(42):15048-52.
14. Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. cell. 2004 Apr 30;117(3):285-97.
15. Ganz T, Nemeth E. Iron homeostasis in host defense and inflammation. Nature Reviews Immunology. 2015 Aug;15(8):500-10.
16. Shah A, Frost JN, Aaron L, et al. Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19. Crit Care. (2020) 24:320. doi: 10.1186/s13054-020-03051-w.

17. Zhao K, Huang J, Dai D, et al. Serum iron level as a potential predictor of coronavirus disease 2019 severity and mortality: a retrospective study. Open Forum Infect Dis. (2020) 7: ofaa250. doi: 10.1093/ofid/ofaa250.

18. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell. (2017) 171:273–85. doi: 10.1016/j.cell.2017.09.021.

19. Lv Y, Chen L, Liang X, et al. Association between iron status and the risk of adverse outcomes in COVID-19. Clin Nutr. (2021) 40:3462–9. doi: 10.1016/j.clnu.2020.11.033.

20. Huang I, Pranata R, Lim MA, et al. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. (2020) 14:1753466620937175. doi: 10.1177/1753466620937175.

21. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. (2020) 25:616–25. doi: 10.1080/1354750X.2020.1797880.

22. Agmon-Levin N, Rosário C, Katz BP, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). Lupus. 2013 Nov;22(13):1327-35.

23. Rosário, C., Zandman-Goddard, G., Meyron-Holtz, E.G. et al. The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 11, 185 (2013).

24. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood, The Journal of the American Society of Hematology. 2011 Oct 27;118(17):4577-84.

25. Bishara R, Braun-Moscovici Y, Dagan A, et al. Severe hyperferritinemia—a clue for severe hepatitis in a patient with adult-onset Still's disease. Clinical rheumatology. 2016 Mar;35(3):795-800.

26. McGonagle, D. et al. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun. Rev. 19(6), 102537 (2020).

27. Deng, F. et al. (2020) Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19, doi: 10.1016/j.medcli.2020.11.030.

28. Dahan S, Segal G, Katz I, et al. Ferritin as a Marker of Severity in COVID-19 Patients: A Fatal Correlation. Isr Med Assoc J. 2020 Aug;22(8):494-500. PMID: 33236582.

29. Ahmed, Sibtain et al. "Evaluation of serum ferritin for prediction of severity and mortality in COVID-19- A cross sectional study." Annals of medicine and surgery (2012) vol. 63 (2021): 102163. doi: 10.1016/j.amsu.2021.02.009.

30. Maghfirah AI, Esa T, Widaningsih Y,et al. Correlation of Serum Ferritin Levels and COVID-19 Severity in Makassar. Journal of Microbiology and Immunology. 2022 Jun 6;4(1):1-5.

CURRENT EVIDENCE OF TREATMENT WITH TUMOR TREATING FIELDS (TTF) IN PATIENTS WITH GLIOBLASTOMA AS A FOURTH MODALITY TREATMENT OPTION

Bojovska-Trajanovska V[1], Stojkovski I[1,2], Ivanova M[1], Djundeva J[1,2], Petkovska G[1,2], Hadzi-Manceva A[1]

1. University Clinic of Radiotherapy and Oncology, Skopje, R.N. Macedonia
2. Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, R.N. Macedonia

ABSTRACT

Background: High-grade glial tumors (HGGTs) are the most common malignant tumors that occur in the central nervous system; they form about 40% of all primary brain tumors. The group of high-grade glial tumors includes: Anaplastic astrocytoma (AA), Anaplastic Oligodendroglioma (AO) as well as Glioblastoma (GBM).

Tumor Treating Fields (TTFs) itself is a completely non-invasive and innovative approach, and because of the specific frequency which it uses, it has a selective anticancer or antimitotic effect on malignant cells.

Methods: A systematic search was conducted in PubMed in database and the most relevant articles were selected which are forming scientific evidence for application of this type of treatment in clinical setting.

Results: In the absence of meta-analysis, the most relevant articles were selected and a combination of evidence has been extracted to systematically organize this article. Positive studies with clinical benefits have been selected for further analysis.

Conclusion: As a result of several clinical and preclinical researches, the inclusion of the TTF (Tumor Treating Fields) treatment modality to the earlier traditional three modality treatment for patients with glioblastoma multiforme, is considered to become a standardized treatment, i.e., according to the novel approach, four modalities are used for newly diagnosed or recurrent patients with GBM modality treatment, i.e., cocktail-based therapy. And it's considered a valuable option for this type of solid tumors, so-called "cold" tumors.

Key Words: Alternating electric fields, Glioblastoma, systematic review systematic review, Tumor-Treating Fields

Introduction. Overview and "Traditional" Treatment Options

According to data from the World Health Organization (WHO), the incidence of High-Grade Gliomas (HGGs) is 5 patients per 100,000 population and approximately 80% of all HGG (High Grade Gliomas) are Glioblastomas (GBM). The incidence is thought to be higher in the white race, than in the black race, and it increases with age. By its nature, glioblastoma rarely metastasizes to other distant organs, the most likely due to the blood-brain barrier, but it overwhelms the surrounding tissue. Regarding the gender affectation, it is considered that the incidence is higher in men than in women, occurring around the sixth and seventh decade of life. GBM is an extremely aggressive tumor, and precisely because of this, the average survival is significantly short. Less than half of the patients, i.e., around 45%, survive the first year of diagnosis, and only 16% survive the second year (1,2).

Rapid multidisciplinary and multimodal treatment is always used in the treatment of glioblastoma because this affects overall survival. For the reason of its aggressiveness, GBM can be fatal in less than 6 months if multimodality treatment is not implemented at once. GBM can occur in any part of the brain hemispheres in adults, but in the most of the cases, it occurs in the frontal and temporal lobes of the brain. Direct causes and factors that influence the occurrence of this disease are still unknown (3,4).

It is thought that some of the factors that can affect the occurrence of GBM are the impaired immune response, earlier irradiation of the brain and reduced susceptibility to allergies. In addition to these reasons, several hereditary syndromes that include the occurrence of other types of carcinomas are also included as risk factors for the occurrence of GBM, such as Li-Fraumeni syndrome and Lynch syndrome. Prognostically, despite the rapid treatment approach and the application of the first-line therapy, GBM continues to be a disease with an extremely poor prognosis (4, 5).

The recurrence of the disease in the most of the patients occurs in the same previously treated place, regardless of which treatment modality was initially applied. Patients with GBM have a median survival of 14-16 months, with a five-year survival rate of less than 5% (1).

Surgery as the main modality aims to remove as much of the tumor tissue as possible, but without affecting the normal surrounding brain tissue, which is needed further to continue normal neurological and cognitive life functions. Considering the very nature of the disease, it is practically impossible to remove the tumor lesion in its entirety, because there are migrating and infiltrative tumor cells that invade the surrounding brain tissue. Surgery is important because it achieves a significant reduction in the size of the tumor mass, because of which overall survival is extended, and according to some studies and statistics, thanks to surgical treatment, the quality of life is also improved (3-5).

Radiotherapy plays a vital role in the treatment of GBMs. Its task is to destroy residual tumor cells, which could not be removed by surgical treatment and which infiltrate the surrounding brain tissue. Convectional, external beam radiotherapy delivers a dose of radiation to the tumor zone, as well as to the margin that covers the surrounding infiltrating cells (3,4).

With the radiotherapy treatment in standard fractionation, that is, multiple fractions with an identical dose per fraction, a treatment is carried out that can include from 10 to 30 fractions in total. Usually, single dose of radiation is performed during the day, and the same is repeated every day - a total of 5 days a week. Radiotherapy treatment as part of the modalities has been shown in many studies to prolong the life of patients compared to performing only operative treatment (3,4).

Chemotherapy is included as a third modality in the treatment of GBMs. Today, the main place in this treatment is occupied by the alkylating agent Temozolomide. As a standard in the treatment, the drug is included during radiotherapy - when it is received concurrently with the radiation, followed by the implementation of an added adjuvant treatment of additional 6 cycles-over a period of 6 months, when the administered dose is received over a period of 5 consecutive days, whereby the cycle repeats every 28 days (about 4 weeks), counting from the first day of prescribing the therapy (3,4).

Despite the extensive treatment comprising of a three-modality arrangement: surgical, concurrent radio-chemotherapy, followed by adjuvant chemotherapy with temozolomide, all these methods however, unfortunately, showed no significant improvements in the overall and median survival of patients with GBMs - it remains unchanged. That is, an average of 15 months, and 4% are considered to survive 5 years or more (4-7).

Patients with glioblastoma multiforme are considered incurable. The treatments implemented so far, especially when it comes to recurrent disease, have not shown much benefit and effectiveness in terms of survival. The search for new more successful options, targeted treatments, is constantly ongoing. A new treatment possibility, which after a long time joined as an added treatment for patients with glioblastoma multiforme, is the application of tumor treating fields (TTFs) (7,8).

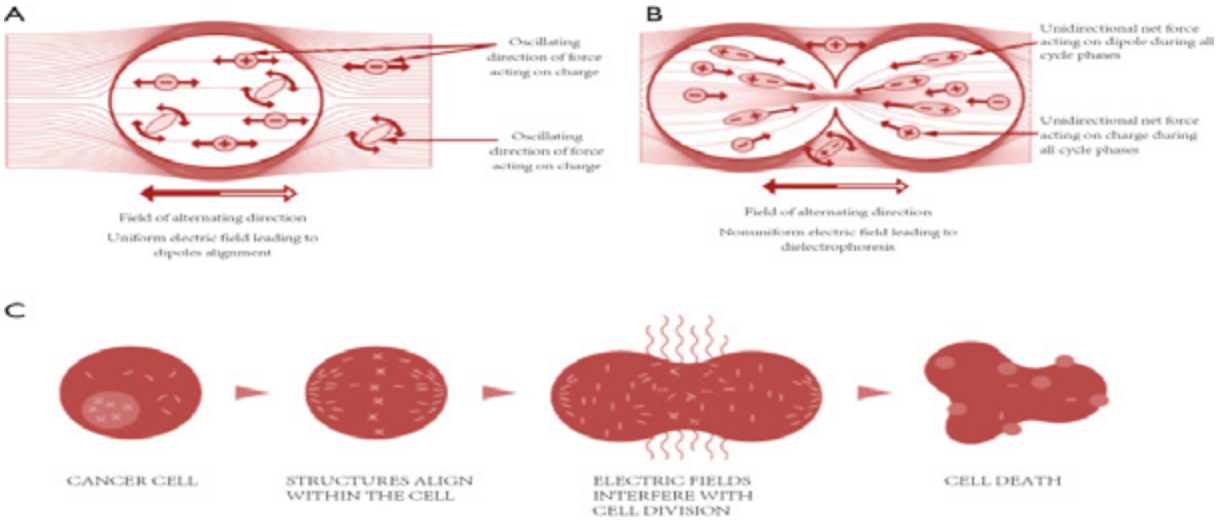
The principle of this treatment modality is fulfilled by the local effect of electric fields, which refer to the proliferative, i.e., mitotic activity of the malignant tumor. As a result of this treatment choice, cell replication is disrupted - which can be slowed down or completely skipped, after which apoptosis occurs. This effect is caused by the disruption in the formation of the mitotic spindle, and the later blocking of metaphase and anaphase of the cell cycle (7,8).

Tumor treating fields are specialized devices that are placed locoregionally, near the tumor itself, i.e., in the proper anatomical location. It uses low-intensity, medium-frequency alternating-current electric fields conducted through noninvasive transducer arrays. A series of preclinical studies and researches have shown that TTFs have an antiproliferative, i.e., antimitotic effect in several types of tumors. TTFs selectively disrupt, slowing down further cell division (1).

These alternating electric fields have a frequency range of 100-300kHz and a field intensity of 1-3V/cm. With the use of specialized ceramic electrodes, Transducer arrays that are adhered to the very skin of the patient's scalp, tumor-specific frequencies are used - which in the treatment of glioblastomas amount to 200kHz. According to the findings obtained from the phase III clinical trials, which are in favor of prolonging the average survival by 4.9 months, while there is no disturbance in the quality of life and with a significantly low percentage of side effects, this

new treatment modality has been approved, as the fourth adjunctive treatment in patients with newly diagnosed or recurrent glioblastoma (2).

Figure 1. *Mechanisms of action of TTF in and around quiescent (A) and dividing (B) cells*



. (A) Dipole alignment: the electric field is uniform inside quiescent cells and the oscillating electric forces result only in "vibration" of ions and dipoles; (B) dielectrophoresis: the non-uniform field within dividing cells induces forces pushing all dipoles toward the furrow; (C) TTF disrupts spindle formation, inhibits the division of tumor cells, and eventually leads to cell death. Adopted from the website of Novocure™ (https://www.novocure.com/)

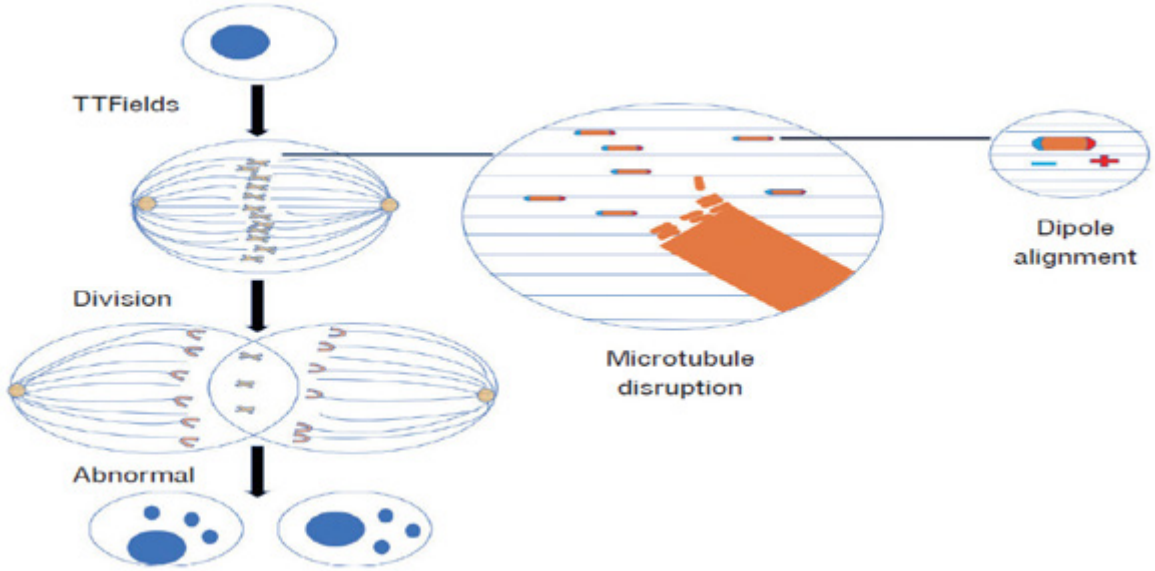
Principles and Biophysical Actions of TTFs

As a result of the frequency produced by TTFs, they affect a large part of the macromolecules and other organelles that are responsible for life processes and for the mitotic activity of dividing cells. What happens is the delayed spindle formation i.e., dipole alignment and dielectrophoresis - these are the two principles, basic physical principles that occur at the subcellular level, and as such result in characteristic effects on the further cycle of the malignant cell (1,2).

The separation of the molecule into positive and negative charge refers to a dipole. Each charged molecule will oscillate to align itself properly parallel to the direction of the electric force vector to which it is exposed, under a uniform alternating electric field. These organelles are with the now disrupted function, that handle cytokinesis and mitosis by the application of localized electric fields. The geometry of the treated organ, the dielectric properties of the tissue and the distance between the arrays of transducers applied to the patient's skin are some of the parameters that dictate the arrangement of the fields. Exactly because of these parameters TTFields are nonuniformly distributed within the treated region (3).

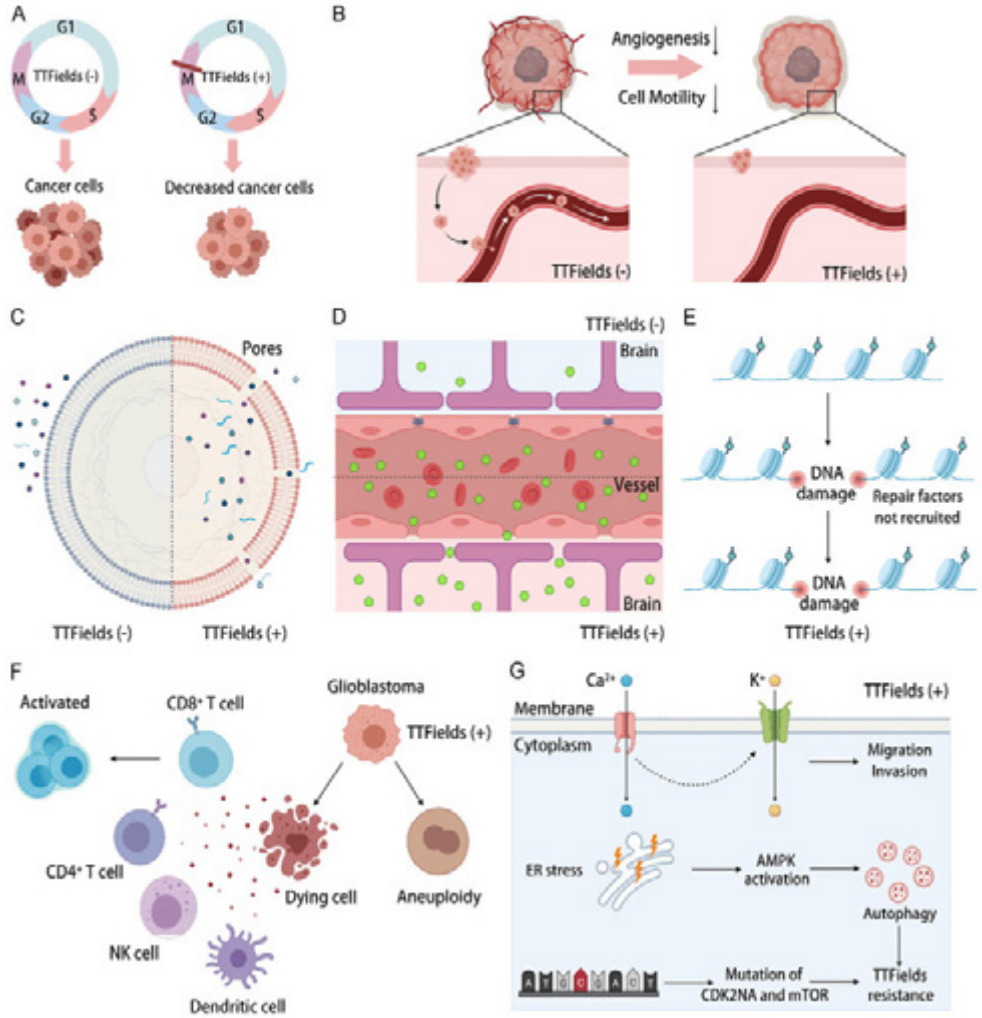
These devices can also be used in deeply found lesions, since the distance from the lesion to the array does not cause weakening of the fields. During the entire treatment TTFs-constantly, continuously deliver a fixed frequency, because electric fields have no half-life (1,2).

Figure 2. *The alteration of the mitotic spindle during mitosis by TTFields that results in death.*



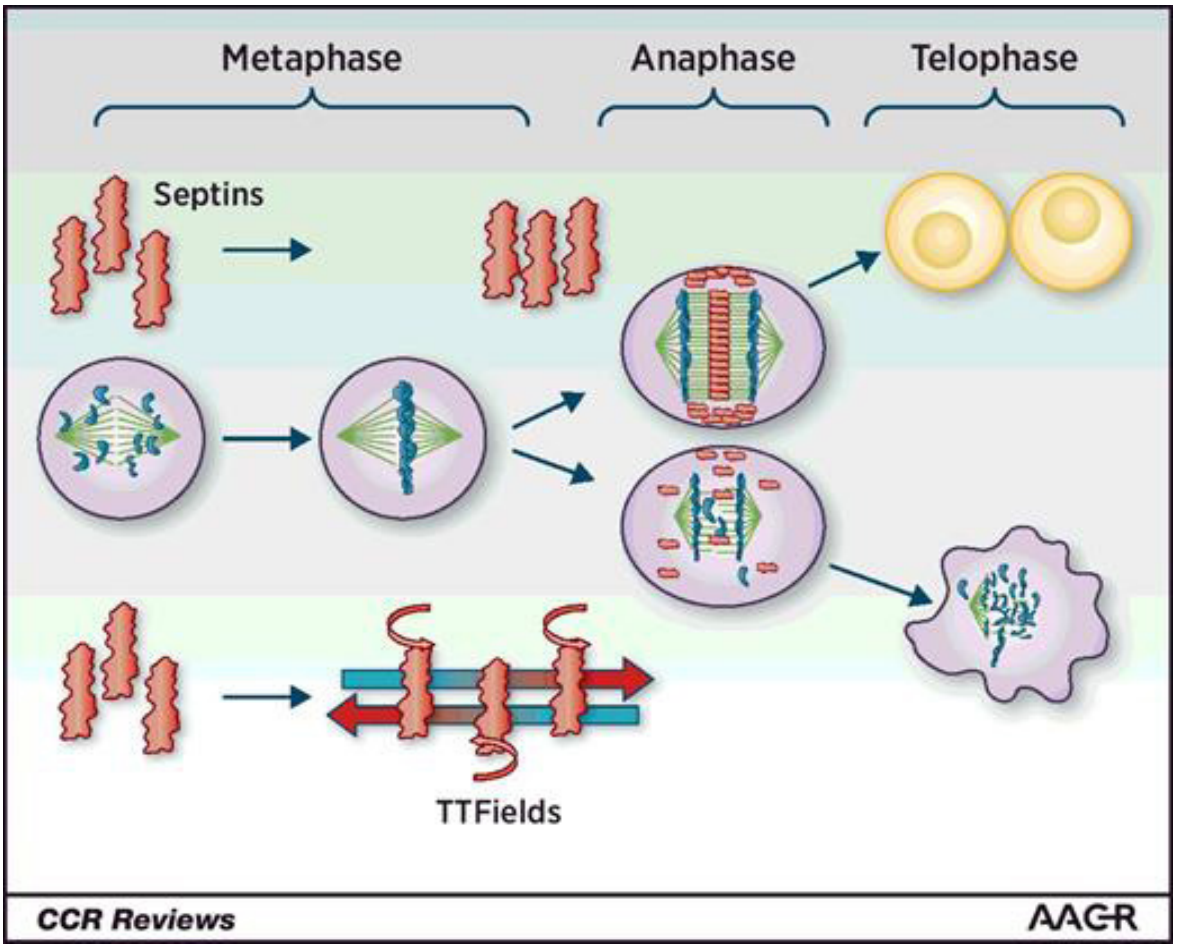
TTFields: treatment method called tumor treating fields. Adopted from Zhang C, Du J, Xu W, Huang H, Gao L. The Value of Tumor Treating Fields in Glioblastoma. J Korean Neurosurg Soc.

Figure 3. *Mechanisms of TTFields.*



Summary of existing and potential mechanisms that have been discovered and proposed in recent years. A. Generation of cell cycle-specific effects; B. Reduction of cancer cell motility and angiogenesis; C. Increase in cancer cell membrane permeability; D. Increase in blood-brain barrier (BBB) permeability; E. Delay in DNA damage repair; F. Regulation of the anticancer immune response; G. Induction of resistance to TTFields.
Wang M, Zhang C, Wang X, et al. Tumor-treating fields (TTFields)-based cocktail therapy: a novel blueprint for glioblastoma treatment. American Journal of Cancer Research. 2021 ;11(4):1069-1086.

Figure 4. *Model for TTFields leading to mitotic disruption.*



During mitosis, the Septin 2, 6, 7 complex is recruited to the Anaphase spindle midline and the cytokinetic cleavage furrow by Anillin, where it self-assembles into a fibrous lattice due to lateral interactions between parallel Septin filaments. By inducing rotational movement about the long axes of the parallel fibers, TTFields can inhibit the propagation of lattice formation by disrupting the ability of individual fibers to bind each other. In the absence of proper Septin function, contractile elements of the cytokinetic furrow are not restrained within the equatorial midline of the cell resulting in ectopic furrow malfunction that leads to violent membrane contractions at the onset of anaphase followed by aberrant mitotic exit. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. Clin Cancer Res. 2018 Jan 15;24(2):266-275. doi: 10.1158/1078-0432.CCR-17-1117. Epub 2017 Aug 1. PMID: 28765323.

Cellular effects of TTFs

The actual biological effects and impact at the cellular level are unknown and are currently being investigated and ongoing. Medium-frequency TTFields (100-300kHz), like alternating electric fields, were originally thought to have no effect on cells. The membrane depolarization of low-frequency fields (below 1kHz) and the heating effect of high-frequency fields (above

1MHz) are frequency-dependent biological effects that are mutually independent in alternating electric fields (2,9).

By cutting the normal random movement of tubulin subunits in the cytoplasm during metaphase, TTFields disrupt the normal process of polymerization of microtubules that form the mitotic spindle. This, in turn, leads to prolonged mitosis, metaphase arrest and ultimately cell death (1,2).

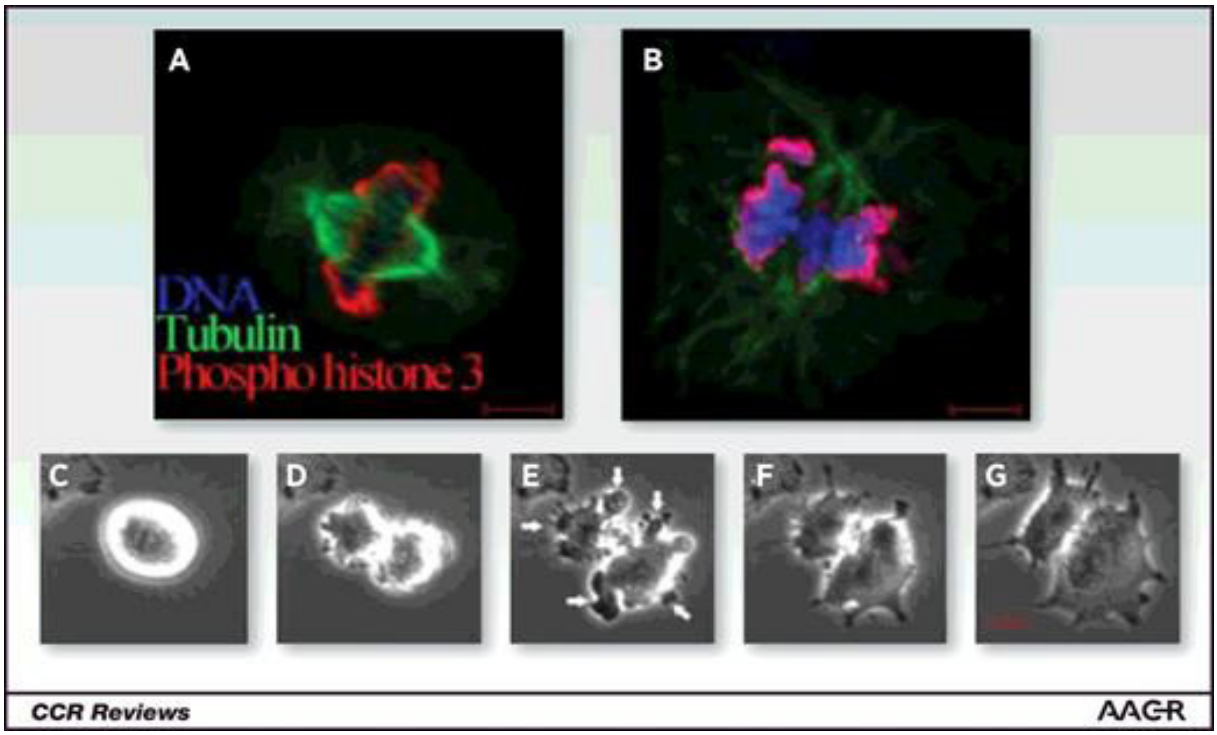
TTFs affect metaphase, anaphase and telophase phase in mitosis, resulting in apoptosis and cell cycle arrest in the body. Under the influence of frequencies from TTFs-, the formation of the mitotic spindle and the process of tubulin polymerization are limited. This event occurs during metaphase. The resulting changes lead to irregular segregation of chromosomes and caspase-dependent apoptosis of daughter cells. On the other hand, the defect of the septin protein complexes, which are influenced by TTFs, leads to a failure to stabilize the contractile apparatus, which causes aberrant mitotic exit to occur in anaphase. Abnormal chromosome segregation leading to aneuploidy in daughter cells or violent cytoplasmic blebs, are effects that occur towards the end of telophase, after which clonogenic potential is later reduced (1, 2).

Some molecules that are responsive to electric fields (large biological molecules such as certain proteins) are dipolar particles. Dipolar particles will move toward when placed within a nonuniform electric field under the area of a higher intensity field. Under exposure to TTFields, during cytokinesis, two daughter cells present an hourglass-like cell morphology and form an intracellular electric field with a higher furrow density. Polar macromolecules and organelles are moved to the narrow neck and separated from the newly formed daughter's daughters, which we call dielectrophoresis, under the influence of the force of the non-uniform field (2,7).

Some membrane-penetrating indicators, such as ethidium D, dextran-FITC and 5-aminolevulinic (5-ALA), were found to increase the effect of TTFs of their uptake in the malignant GBM cells, but not in the normal cell lines. TTFields increase intracellular drug concentration and have the potential to treat drug-resistant cancer cells that overexpress ABC transporters, also the application of preoperative TTFields may help to delineate cancer boundaries and improve the surgical excision of GBM (2,9).

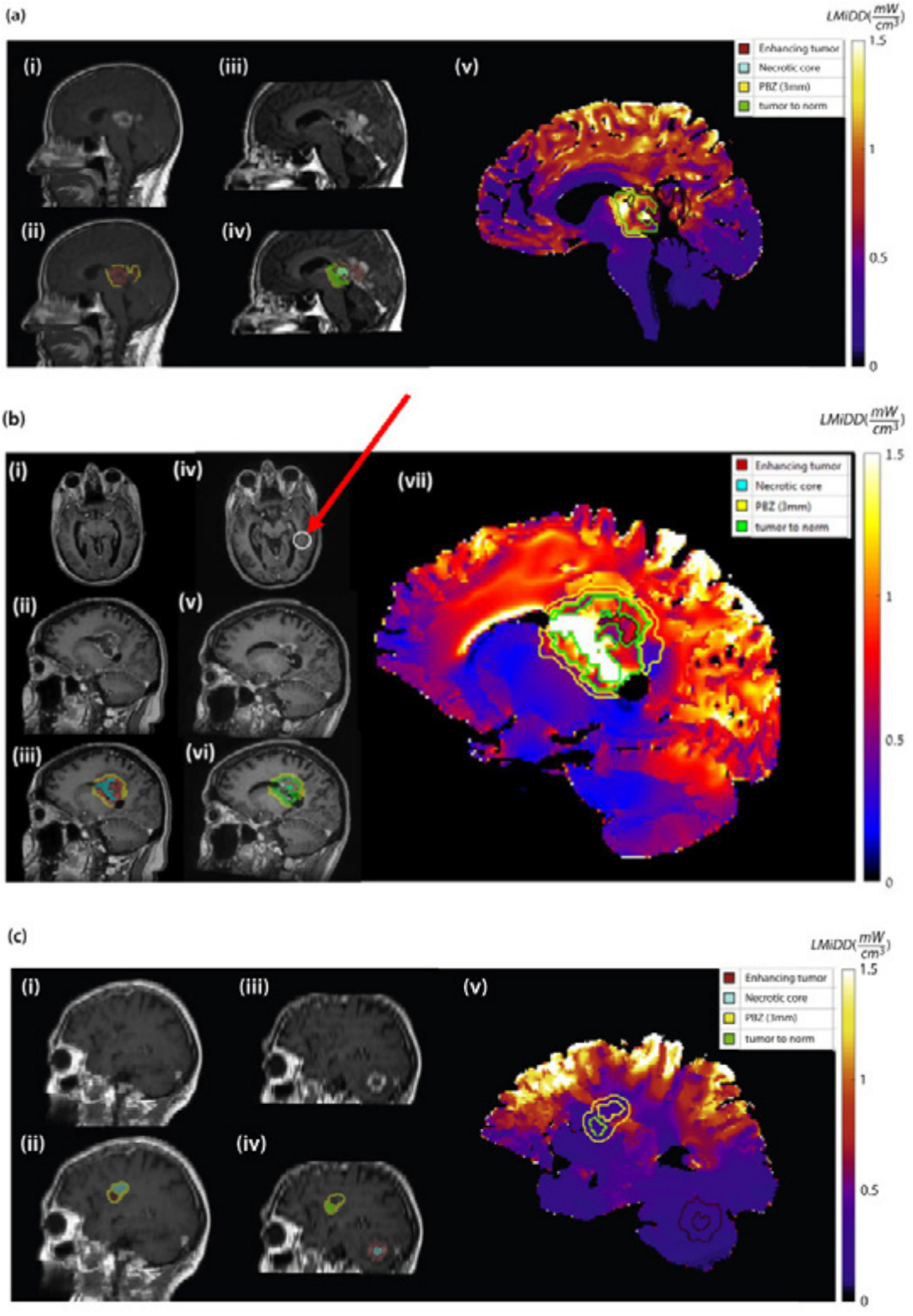
As a result of a unique action, TTFs directly affects the permeability of the blood-brain barrier, as well as the permeability of the cell membrane of malignant cells. Thanks to these changes, the penetration of various therapeutic agents that are needed to enter the intracranial malignant GBM cells increases. Such a synergistic effect can increase and improve the effect of applied anticoagulant agents (4).

Figure 5. *TTFields affect normal spindle formation during metaphase.*



Control cell (A), TTFields-treated cell (B). A and B are stained with phosphohistone 3 (marker for mitotic cells). C–G, Time-lapse of treated cell showing membrane blebbing (arrows) during telophase. Red bar in G corresponds to 10mm. 2015 IEEE. Reprinted, with permission, from Wenger, C., et al. Modeling Tumor Treating Fields (TTFields) application in single cells during metaphase and telophase. Picture is adopted from Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. Clin Cancer Res. 2018 Jan 15;24(2):266-275. doi: 10.1158/1078-0432.CCR-17-1117. Epub 2017 Aug 1. PMID: 28765323.

Figure 6. *Representative TTFields distribution dose maps.*



(a) Patient with both regression and local progression. (i) Baseline MRI. (ii) Baseline MRI with segmented baseline volumes: GTV (Gross Tumor Volume) (red) and 3mm PBZ around baseline tumor (yellow). (iii) Progression MRI. (iv) Progression MRI with segmented volumes: tumor to tumor (red), necrotic core (cyan), tumor to norm (green) and norm to norm (yellow). (v) TTFields dose density map with volumes contours overlaid. (b) Patient showed distant progression (marked with a white circle in the axial slice) and local regression. (i and ii) Baseline MRI. (iii) Baseline MRI with segmented baseline volumes: GTV (red), necrotic core (cyan) and 3mm PBZ around baseline tumor (yellow). (iv and v) Progression MRI. (vi) Progression MRI with seg-

mented volumes: tumor to tumor (red), necrotic core (cyan), norm to norm (yellow), and tumor to norm (green). (vii) TTFields dose density map with volumes contours overlaid. (c) Patient with infratentorial progression. (i) Baseline MRI. (ii) Baseline MRI with segmented baseline volumes: GTV (red), resection cavity (cyan), and 3 mm PBZ around baseline tumor (yellow). (iii) Progression MRI. (iv) Progression MRI with segmented volumes: tumor to norm (green), norm to norm (yellow), normal to tumor (red), and necrotic core (cyan). (v) TTFields dose density map with volumes contours overlaid. The image is adopted from Glas M, Ballo MT, Bomzon Z, Urman N, Levi S, Lavy-Shahaf G, Jeyapalan S, Sio TT, DeRose PM, Misch M, Taillibert S, Ram Z, Hottinger AF, Easaw J, Kim CY, Mohan S, Stupp R. The Impact of Tumor Treating Fields on Glioblastoma Progression Patterns.

Methods of Application, Clinical Practice and Devices

Through unique transducer arrays, which are attached to the patient's clean and dry skin, the right frequency is delivered from the TT fields to the affected region. The field-generator (NovoTTF System, Novocure Ltd.) may be connected to a portable battery (total weight 1.2kg) and is intended for continuous, home use (3).

The strings of the transducer, in patients with GBM, are placed on the head, while it is recommended to shave the skin of the scalp every 2-3 days, to achieve minimal resistance between the surfaces. The device must be constantly connected to the patient. According to the results of the conducted clinical trials, it was seen that the median average survival is significantly higher in patients who wore their device longer than 18 hours a day. That is why it is recommended that patients regularly keep their device with a full battery and active, and wear it for at least 18 hours, with those exceptions that are needed to perform certain physiological activities (3).

The placement of the treatment field, i.e., the transducer, has an individualized approach. For this purpose, a diagnostic MRI of the brain with contrast is used. This approach determines and specifies the exact location of the lesion, which increases the intensity of the field in the affected zone (3). To obtain an exact and precise plan through which the treatment will be carried out, the doctor who will lead the treatment uses treatment planning software (NovoTAL, Novocure Ltd.) which allows him cranial morphometric geometry. Through this software, the precise location of the tumor is obtained, and thus the personalized configuration of the transducer arrays is obtained (3).

Figure 7.

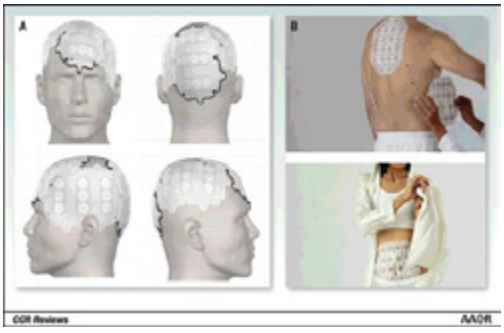


Figure 8.

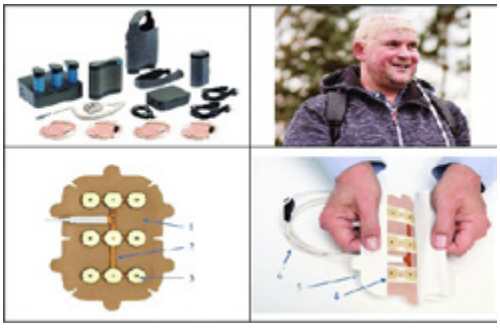


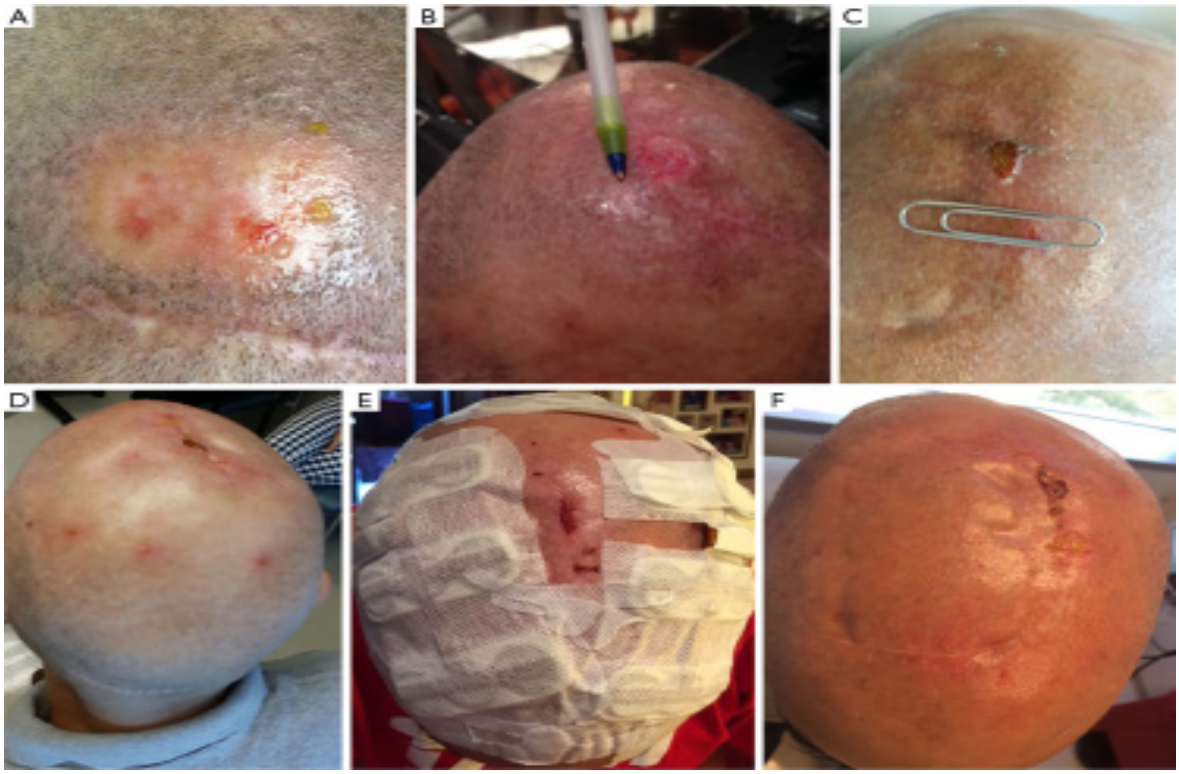
Figure 7. Placement of arrays on patient's shaved scalp. An array map used as guidance for best placement of transducer arrays based on tumor size and location. B. Transducer arrays attached to the device, Optune, are placed on patient's body, for lung cancer (top) and ovarian cancer (bottom). Image is adopted from Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. Clin Cancer Res. 2018 Jan 15;24(2):266-275

Figure 8. The Tumor Treating Fields (TTFields) device and transducer arrays. Top left panel: second generation (Gen 2) battery-operated field generator device, portable battery packs, plug-in power supply, tan transducer arrays, connection cables and box, and carrying case. Top right panel: Shows a patient* with glioblastoma during therapy, wearing the tan transducer arrays on his scalp. Bottom panels: 1. A hypoallergenic cover tape holds tan arrays in place on the scalp. 2. Transducer arrays deliver low intensity, intermediate frequency (200kHz) alternating electric fields and check the temperature of the scalp. 3. Conductive hydrogel layers (top) ensure separation between the arrays and skin, and the ceramic disks (beneath) send TTField. 4. Mid-pads mechanically stabilize the gel over the arrays. 5. An overlapping liner covers the gel and cover tape. 6. A cable connects array to the connection box. The image is adopted from Lacouture ME, Anadkat MJ, Ballo MT, Iwamoto F, Jeyapalan SA, La Rocca RV, Schwartz M, Serventi JN, Glas M. Prevention and Management of Dermatologic Adverse Events Associated with Tumor Treating Fields in Patients with Glioblastoma.

Adverse Effects and Toxicity Profile

TTF therapy is a unique modality, according to the method of application, the mechanism of implementation of the treatment itself and the typical localized effect, and almost does not give more serious side effects. Among the most common side effects, according to the very wearing of the product, are those that affect the skin. Including irritant contact dermatitis, mild to moderate allergic dermatitis, folliculitis and in rare cases erosions. No high-grade systemic toxicity has been related to TTFs. The occurrence of side effects of this type is between 16-43%. It must be emphasized that the rate of occurrence of side effects was more represented in patients with recurrence. It is considered that the average time in which the appearance of side effects would be expected ranges between 2 to 6 weeks from the start of treatment. Treatment options for side effects depend on the presenting event. Corticosteroid creams, isolation of the affected skin surface, local and oral antibiotics in more severe conditions are generally used (1,18, 21).

Figure 9. *Skin toxicities occurred due to TTF therapy from one patient who was enrolled in the EF-14 trial.*



All images are from the same patient with different scalp lesions at various times during his TTF treatment course. (A) Example of scalp rash with ulcer, 512 days after TTF initiation; (B) accidental scalp skin tear while array was removed, initial stage, 184

days after TTF initiation; (C) improved scalp skin tear after avoiding any contact of the area, 188 days after TTF initiation; (D) scalp skin tear is resolved and multiple contact dermatitis rash visible, 462 days after TTF initiation; (E) TTF array placement avoiding skin wound, 370 days after TTF initiation; (F) scalp scab and healed scalp skin tear and rashes, 462 days after TTF initiation. TTF, tumor treating fields; TMZ, temozolomide; GBM, glioblastoma; BEV, bevacizumab. Image is adopted from Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. Chin Clin Oncol. 2017 Aug;6(4):41. doi:

The Future of TTFs and the Technologies that Follow

To expand its range of use and further include this treatment modality in other types of solid tumors and in many other locations, is the future of TTFs (Tumor Treating Fields) as a unique treatment choice. In many solid tumors, TTFs are in the phase of preclinical studies. Attempts to implement this treatment modality have particularly attracted attention in the treatment of mesotheliomas and small cell lung cancer. Other sites that are in the phase of preclinical research are: gastric, cervical, breast, colorectal, renal, urinary transitional cell, hepatocellular and malignant melanoma (3). Despite all efforts and treatments, patients with glioblastoma multiforme, due to their extremely aggressive nature, experience disease progression and death, despite treatment with TTFs. Therefore, to increase the efficiency of this new treatment modality, both in patients with GBMs and other localizations, it is necessary to deepen and continue further clinical research (3).

Conclusion

Since 2005, despite all efforts and all kinds of attempts, there have been insignificant advancements in GBM therapy. Despite tries to escalate the dose or increase fractions of radiation treatment, many years in researching the effect of targeted molecular inhibitors, researching the effect of immunotherapy, have not shown any benefit in increasing survival (10,11).

A series of studies and clinical trials show the effect of the TTF modality. During the analysis of the EF11 and EF14 studies, positive effects were especially seen in patients with recurrent disease where the application of TTF was prescribed as an alternative to chemotherapy treatment; while in patients with newly diagnosed disease, the TTF modality was prescribed as an adjuvant treatment. What particularly stands out and is interesting is the data obtained from the EF14 study, in which there is an improvement in the median survival time in those patients treated with the TTF modality (20.9) months, compared to the group of patients treated with TMZ (16.4) months (10,11).

In the treatment of malignant tumors, TTF is included as an additional unique non-invasive new therapeutic modality. What makes this treatment modality unique is the selective destruction of malignant cells, which have a high proliferative index (1).

Another additional benefit of this treatment modality is that unlike systemic therapy, i.e., chemotherapy, the delivery of the TTF effect is localized; that is, targeted at the level of the tumor lesion itself, which significantly reduces the likelihood of developing systemic side effects. It is necessary to point out that, depending on the type of malignant tumor, the best required frequency can be modified and adjusted, which will supply the maximum antimitotic, that is, anticancer effect (3).

As a result of several clinical and preclinical researches, the inclusion of the TTF treatment modality to the earlier traditional three modality treatment for patients with glioblastoma multiforme is considered to become a standardized treatment, i.e., according to the novel approach, four modalities are used for newly diagnosed or recurrent patients with GBM modality treatment, i.e., cocktail-based therapy. This approach of joint treatments is the best strategy for solid, so-called "cold" tumors (4).

REFERENCES

1. Simon JE, Prabhu VC, Barton K, et al. Synergistic Therapies for Recurrent Malignant Gliomas. World Neurosurg. 2020 Jan; 133:237-239.
2. Batash R, Asna N, Schaffer P, et al. Glioblastoma Multiforme, Diagnosis and Treatment; Recent Literature Review. Curr Med Chem. 2017;24(27):3002-3009.
3. Chen W, Wang Y, Zhao B, et al. Optimal Therapies for Recurrent Glioblastoma: A Bayesian Network Meta-Analysis. Front Oncol. 2021 Mar 29; 11:641878
4. Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. Chin Clin Oncol. 2017 Aug;6(4):41.
5. Zhang I, Knisely JP. Tumor-Treating Fields-A Fundamental Change in Locoregional Management for Glioblastoma. JAMA Oncol. 2016 Jun 1;2(6):813-4. doi: 10.1001/jamaoncol.2016.0081. PMID: 26986446
6. Krigers A, Pinggera D, Demetz M, et al. The Routine Application of Tumor-Treating Fields in the Treatment of Glioblastoma WHO° IV. Front Neurol. 2022 Jun 16; 13:900377. doi: 10.3389/fneur.2022.900377. PMID: 35785334; PMCID: PMC9243748.
7. Mun EJ, Babiker HM, Weinberg U,et al. Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. Clin Cancer Res. 2018 Jan 15;24(2):266-275. doi: 10.1158/1078-0432.CCR-17-1117. Epub 2017 Aug 1. PMID: 28765323.
8. Kessler AF, Frömbling GE, Gross F, et al. Effects of tumor treating fields (TTFields) on glioblastoma cells are augmented by mitotic checkpoint inhibition. Cell Death Discov. 2018 Jul 16; 4:12.
9. Wang M, Zhang C, Wang X, et al. Tumor-treating fields (TTFields)-based cocktail therapy: a novel blueprint for glioblastoma treatment. Am J Cancer Res.
10. Lacouture ME, Anadkat MJ, Ballo MT, et al. Prevention and Management of Dermatologic Adverse Events Associated with Tumor Treating Fields in Patients With Glioblastoma. Front Oncol. 2020 Jul 28; 10:1045. doi: 10.3389/fonc.2020.01045.
11. Lukas RV, Ratermann KL, Wong ET, et al. Skin toxicities associated with tumor treating fields: case based review. J Neurooncol. 2017 Dec;135(3):593-599.
12. Zhang C, Du J, Xu W, et al. The Value of Tumor Treating Fields in Glioblastoma. J Korean Neurosurg Soc. 2020 Nov;63(6):681-688. doi:
13. Fabian, Denise et al. "Treatment of Glioblastoma (GBM) with the Addition of Tumor-Treating Fields (TTF): A Review." Cancers vol. 11,2 174. 2 Feb. 2019, doi:10.3390/cancers11020174.

14. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48(14):2192–202.

15. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy with Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA. 2015 Dec 15;314(23):2535-4316. Davies AM, Weinberg U, Palti Y.

16. Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci. 2013 Jul; 1291:86-95.

17. Rominiyi O, Vanderlinden A, Clenton SJ, et al. Tumour treating fields therapy for glioblastoma: current advances and future directions. Br J Cancer. 2021 Feb;124(4):697-709. doi: 10.1038/s41416-020-01136-5. Epub 2020 Nov 4. Erratum in: Br J Cancer. 2021 Aug;125(4):623. PMID: 33144698; PMCID: PMC7884384.

18. Glas M, Ballo MT, Bomzon Z, et al. The Impact of Tumor Treating Fields on Glioblastoma Progression Patterns.

19. Optimal treatment strategy for adult patients with newly diagnosedglioblastoma: a systematic review and network meta-analysis Lei Jin1& Shenquan Guo1& Xin Zhang1, et al. Neurosurgical Review.

20. Optimal treatment strategy for adult patients with newly diagnosedglioblastoma: a systematic review and network meta-analysis Lei Jin1& Shenquan Guo1& Xin Zhang1, et al. Neurosurgical Review.

21. Yalman D, Koylu M, Kayabasi C, et al. Effect Of Tumor Treating Fields And Radiotherapy Combination On Brain Tumor And Normal Brain Cell Lines. Int J Radiat Oncol. 2020 Nov 1;108(3):e509.

ORIGINAL ARTICLE *UDK: 616-007.53:572.087.1]-057.874*

COMPARISON OF ANTHROPOMETRIC CHARACTERISTICS AND MOTOR SKILLS BETWEEN STUDENTS WITH POOR LORDOTIC POSTURE AND STUDENTS WITH NORMAL BODY STATUS

Chokuzovska A

Higher Medical School, Bitola, Republic of North Macedonia

ABSTRACT

On two subsamples, 50 male students with lordotic poor posture and 50 male students with normal body status aged 7 years, 13 anthropometric manifest variables and 14 motor manifest variables have been applied. The results were processed with the basic statistical parameters, separately for the anthropometric manifest variables and separately for the motor manifest variables. The obtained results of the research showed that no statistically significant difference has been determined in the anthropometric space between the two groups of respondents. The motor domain showed that the groups differed from each other at the 0.05 level. The biggest contribution to that difference was shown by three motor tests. According to the results of the research, it has been established that complexes of exercises can be programmed in a preventive and corrective sense for students with poor lordotic posture in order to improve their motor skills.

Key Words: anthropometric measures, basic descriptive statistical parameters, lordotic poor posture, motor tests, normal posture, students.

INTRODUCTION

With the development of science and technology, we have witnessed a change in the lifestyle and overall life contents. Achievements that directly facilitate our work at the workplace, transportation from home to work, the organization of free time, the way of relaxation, rest and recovery, affect certain changes of our locomotor apparatus, especially the physical status.

Computerization and automation in all spheres nowadays lead to reduced movement, i.e. hypokinesia, which is one of the primary prerequisites for the occurrence of poor posture, and thus spinal disorders. In addition, bad habits, incorrect body posture, incorrect sitting, inadequacy of school desks, school chairs and the excessive weight of the school bag, affect the appearance of various forms and a growing number of postural disorders.

The correct postural position takes its place less and less in children's daily activities. Improper sitting, standing, inadequate sleeping mattresses, various forms of movement activities, as well as certain endogenous factors, systematically act on the spinal column causing

loads that often exceed the tolerance zone of the soft tissues of the spine, not realizing a greater load, but with cumulative action through repetition and long-term positions and movements, tissues experience certain deformations in terms of their morphology and function. There is a shortening or weakening of certain muscles, which by itself leads to muscle imbalance, which is the main reason for the appearance and development of bad postures, that is, body deformities.

The main motive for carrying out this research is the need to determine if there is a difference between the prevalence of poor body postures among the first-grade students, a young age at which preventive and corrective action can be taken.

The results that will be obtained from this research and the procedures that will be applied in it, can represent a modest contribution for undertaking further researches with similar research objectives, with larger samples of different age and gender of respondents, by treating more types of bad body postures, with the application of similar and other multivariate statistical methods, for processing data from such surveys.

METHODS

The population from which the sample is drawn is defined as the population of elementary school students (the first grade), who are approximately chronologically 7 years old. Any male student could enter the sample. The number of students who participated in the research is 100.

The following anthropometric measures were used to determine the manifest and latent anthropometric dimensions:

1. Body height,
2. Length of a leg,
3. Length of an arm,
4. Shoulder width,
5. Pelvic width,
6. Hip width,
7. Body weight,
8. Average chest circumference,
9. Circumference of the outstretched upper arm,
10. Upper thigh circumference,
11. Skin fold on the upper arm,
12. Leather fold on the back,
13. Abdominal skin fold.

The following tests were used to determine the manifest and estimate the latent motor dimensions:

1. Tests for estimating the factor-explosive force,
2. Tests for assessing the balance factor (balancing),
3. Tests for estimating the factor-frequency of the movements,
4. Tests for assessing the coordination factor,
5. Tests for assessing the flexibility factor,
6. Tests for assessing the factor - general strength.

The measurements were performed in the morning hours in the physical education classrooms, and lasted for three weeks (10 students each day). After the group of 2-3 students entered the gym, barefoot and only in sports jerseys, the anthropometric points on the spine of each of them are marked with a demography. Then, the spinal curvature in the sagittal plane was measured for each subject individually from a standing position in a normal upright body position with the help of the spinal mouse.

The basic descriptive statistical parameters were calculated.

RESULTS AND DISCUSSION

Table 1. *Basic statistical parameters of anthropometric measures for the group of students with normal body posture.*

Variables	Mean	Min.	Max.	SD.	Std. Err	Skew.	Kurt.	KS.	p
AMT	27,87	17,00	53,70	6,77	0,96	1,63	3,65	1,026	0,243
AVT	126,86	113,40	139,40	6,20	0,88	-0,13	-0,25	0,552	0,921
ADN	69,68	60,50	77,80	4,07	0,58	0,02	-0,27	0,584	0,885
ADR	53,15	46,60	58,50	2,51	0,36	-0,24	0,52	0,672	0,757
ABR	29,34	25,30	33,60	1,65	0,23	0,24	0,38	0,431	0,992
ASKA	21,05	18,00	25,50	1,66	0,23	0,66	0,38	0,883	0,416
ASKO	22,04	18,20	28,00	1,81	0,26	0,80	1,43	0,801	0,543
AOGN	60,26	50,50	84,20	5,73	0,81	1,86	5,38	1,039	0,231
AOIN	17,47	13,60	26,20	2,54	0,36	1,54	2,25	1,796	**0,003**
AON	33,60	26,00	45,20	4,12	0,58	0,89	0,94	1,042	0,227
ANN	11,02	5,00	36,00	5,71	0,81	2,56	8,13	1,448	**0,30**
ANG	9,95	2,60	36,40	7,30	1,03	2,30	5,51	1,779	**0,004**
ANS	10,44	2,80	38,00	7,93	1,12	1,99	4,10	1,568	**0,015**

The results in Table 1, which present the results for the group of subjects with normal body posture, range within the usual values of the anthropometric measures that refer to the treated age of this research. In fact, they are similar, and this applies to all calculated basic statistical parameters (Mean, Minimum, Maximum, Std.Dev., Std.Err., Skewness and Kurtosis).

It can be seen that out of all 13 anthropometric measures in the group of respondents with normal body posture, only 4 anthropometric measures differ statistically significantly from the normal distribution of their results.

Those variables are "Shoulder Width" (ABR) with a value of the Kolmogorov-Smirnov test, 1.751 and a value of the statistical significance of the difference 0.004; "Back skinfold" (ANG) with a Kolmogorov-Smirnov test value of 1.524 and a statistical significance value of the difference of 0.019; "Abdominal skin fold" with a Kolmogorov-Smirnov test value of 1.410 and a statistical significance value of the difference of 0.037. One of these variables "Shoulder Width" (ABR)

is statistically significantly different at the 0.01 level. This means that this variable deviates the most from the normal distribution of its results.

Table 2. *Basic statistical parameters of the anthropometric measures for the group of students with lordotic poor posture.*

Variables	Mean	Min.	Max.	SD	Std.Err	Skew.	Kurt.	KS	p
AMT	25,71	17,90	45,70	6,47	0,92	1,35	1,74	1,144	0,146
AVT	123,58	106,20	140,30	6,69	0,95	0,31	0,99	0,702	0,708
ADN	66,55	51,60	78,50	4,80	0,68	-0,21	1,38	0,589	0,878
ADR	51,65	44,50	59,00	2,95	0,42	-0,09	0,20	0,658	0,904
ABR	28,42	25,10	50,10	3,53	0,50	4,87	29,66	1,751	**0,004**
ASKA	20,55	17,70	24,20	1,58	0,22	0,61	0,23	0,975	0,298
ASKO	21,30	15,00	25,80	1,95	0,28	-0,08	1,59	0,986	0,286
AOGN	58,32	51,80	78,00	5,61	0,79	1,73	3,28	1,225	0,099
AOIN	16,87	13,00	24,20	2,45	0,35	0,99	0,80	0,871	0,434
AON	33,46	26,20	45,00	4,19	0,59	0,73	0,35	0,677	0,748
ANN	10,65	5,20	28,20	4,53	0,64	1,61	3,49	1,314	0,053
ANG	8,73	4,20	25,00	4,52	0,64	1,52	2,41	1,524	**0,019**
ANS	9,80	3,40	22,20	6,23	0,88	0,83	0,76	1,410	**0,037**

The results in Table 2, which present the results for the group of respondents with poor lordotic posture, are within the usual values of the anthropometric measures that refer to the treated age of this research. In fact, they are similar, and this applies to all calculated basic statistical parameters (Mean, Minimum, Std.Dev., Std.Err., Skewness and Kurtosis).

It can be seen that out of all 13 applied anthropometric measures in the group of respondents with lordotic poor posture, only 3 anthropometric measures statistically significantly differ from the normal distribution of their results.

Those variables are "Shoulder Width" (ABR) with a Kolmogorov-Smirnov test value of 1.751 and a value of statistical significance of the difference of 0.004; "Back skin fold" (ANG) with a Kolmogorov-Smirnov value of 1.524 and a statistical significance value of the difference of 0.019; "Abdominal Skinfold" (ANS) with a Kolmogorov-Smirnov test value of 1.410 and a statistical significance value of the difference of 0.037. One of these variables "Shoulder Width" (ABR) is statistically significantly different at the 0.01 level. It means that this variable deviates the most from the normal distribution of the results.

Table 3. *Basic statistical parameters of motor tests for the group of students with normal body posture.*

Variables	Mean	Min.	Max.	SD	Std.Err.	Skew.	Kurt.	KS	p
MT20M	4,96	3,97	6,78	0,06	0,09	0,33	-0,52	0,755	0,618
MSVMD	178,86	158,00	193,00	8,84	1,25	-0,12	-0,52	0,486	0,972
MSDM	103,00	65,00	140,00	17,99	2,54	-0,07	-0,80	0,903	0,389
MFM	2,22	1,00	3,40	0,57	0,08	0,23	-0,54	0,826	0,502
MPZO	3,81	1,20	14,20	2,19	0,31	2,41	9,36	1,087	0,188
MPOO	2,77	1,00	9,40	1,59	2,23	2,21	6,09	1,318	0,062
MTARP	17,82	13,00	23,00	2,80	2,40	0,30	-1,15	1,096	0,181
MTAPN	15,66	4,00	20,00	2,60	0,37	-1,56	7,20	1,130	0,156
MON	32,27	25,62	43,60	3,49	0,50	0,60	0,92	0,580	0,889
MPK	36,02	23,00	52,00	5,90	0,83	-0,23	0,24	0,802	0,541
MPPL	21,32	3,00	55,00	10,23	1,45	1,77	3,89	1,377	0,045
Variables	Mean	Min.	Max.	SD	Std.Err	Skew.	Kurt.	KS	p
MHISS	22,41	14,64	37,04	5,50	0,78	0,96	0,61	0,855	0,458
MIGF	16,07	6,70	26,70	4,28	0,61	0,13	-0,05	0,499	0,965
MIKF	3,94	1,50	6,80	1,33	0,19	0,31	-0,66	0,609	0,853

The results in Table 3, which present the results for the group of respondents with normal body posture, range in the usual values of the motor tests related to the treated age of this research. In fact, they are similar and this applies to all calculated basic statistical parameters (Mean, Minimum, Maximum, Std.Dev., Std.Err., Skewness and Kurtosis).

It is visible that of all 14 applied motor tests in the group of subjects with normal body posture, it does not differ statistically significantly, that is, it does not deviate from the normal distribution of its results.

Table 4. *Basic statistical parameters of the motor tests for the group of students with lordotic poor posture.*

Variables	Mean	Min.	Max.	SD	Std.Err	Skew.	Kurt.	KS	p
MT20M	5,13	4,06	7,28	0,59	0,08	1,18	2,43	0,901	0,391
MSVMD	172,88	141,00	194,00	10,01	1,42	-0,13	1,10	0,816	0,518
MSDM	102,50	55,00	135,00	18,22	2,58	-0,52	-0,23	0,887	0,411
MFM	1,98	1,10	3,50	0,46	0,07	0,54	1,42	0,963	0,312
MPZO	5,07	1,40	11,60	2,86	0,40	0,79	-0,40	1,037	0,232
MPOO	2,76	0,90	6,60	1,45	0,20	1,16	0,55	1,376	0,045
MTARP	18,00	11,00	30,00	3,70	0,52	0,81	1,22	1,035	0,234
MTAPN	16,24	11,00	25,00	2,96	0,42	0,88	1,72	0,980	0,292
MON	32,79	25,55	42,53	3,62	0,51	0,53	0.64	0,862	0,447
Variables	Mean	Min.	Max.	SD	Std.Err	Skew.	Kurt.	KS	p
MPK	36,58	19,00	50,00	6,27	0,89	-0,45	0,68	0,994	0,227

MPPL	19,42	10,00	70,00	9,66	1,37	3,70	16,91	1,801	**0,003**
MHISS	22,14	13,18	30,72	3,99	0,56	-0,12	-0,27	0,474	0,978
MIGF	13,36	3,00	24,70	4,35	0,62	0,23	0,41	0,876	0,427
MIKF	2,82	1,00	5,40	1,29	0,18	0,36	-1,01	0,751	0,625

The results in Table 4, which presents the results for the group of subjects with lordotic poor posture, range in the usual values of the motor tests that refer to the treated age of this. In fact, they are similar and this applies to all calculated basic statistical parameters (Mean, Minimum, Maximum, Std.Dev., Std.Err., Skewness and Kurtosis).

It can be seen that out of all 14 applied motor tests in the group of subjects with lordotic poor posture, only one motor test statistically significantly differs from the normal distribution of its results.

That variable is "Preslope to Floor" (MPPL) with a Kolmogorov-Smirnov test value of 1.801 and a statistical significance value of the difference of 0.003. They are statistically significantly different at the 0.01 level. This means that this variable deviates the most from the normal distribution of its results.

CONCLUSION

Based on the obtained research results, it is possible to draw several conclusions. Among them are the following:

1. The basic statistical indicators for the values of the anthropometric variables for the group of respondents with normal body posture are similar to the other group.
2. The respondents in whom lordotic poor posture was determined in this research are characterized by values of the basic statistical parameters, that are to a certain extent compatible with the values of the respondents that have been analyzed in some researches from different researches carried out in our environment and in other regions.
3. The two groups of subjects in the results of all the treated motor tests, whereby the motor abilities are estimated, differ statistically significantly at the level of 0.01, and the possibility of being ranked at that level in some tests has been determined.
4. The best results in the MICF and MIGF tests for assessing static strength were achieved by subjects with normal body posture, and subjects with poor lordotic posture were in the second place.
5. It would be especially desirable and necessary to apply preventive and corrective exercise complexes with special dosing methods to children from the youngest age in primary schools.

REFERENCES:

1. Bogdanovic, Z., Marković, Zh.I. Konicanin, A. (2011). Kyphotic posture in relation to computer use and gender. Research in kinesiology, 39(2), 235-239.
2. Bogdanovic, Z., Marković, Zh.I. Kahrović, I. (2011). Participation of parents in sports recreation and the presence of lordotic posture in children. Activities in physical education and sport, 1(1), 17-22.
3. Berrgyman, F., Pynsent, P., Fairbank, J. (2008). A new system for measuring three-dimensional back shape in scoliosis. Eur Spine J. 17(5), 663-72.
4. Filipovic, V. and Ciliga, D. (2010). Postural adaptation from idiopathic adolescent scoliosis. Kinesiology, 42(1), 16-27.
5. Madic, D. (2006). Relations of motor and postural status of children of preschool age in Vojvodina. In zbornikuradova: Interdisciplinary scientific conferences with international university, Novi Sad, 2006, "Anthropological status and physical activity of children, youth and adults". , (pp. 185-191). Novi Sad: Faculty of Sports and Physical Education.
6. Tomasevic, V. (1984). Prevention of postural disorders of the spine in children of preschool age. (Unpublished doctoral dissertation, University of Belgrade) Belgrade: Faculty of Physical Culture in Belgrade.
7. Shukov, J. (1989). Correction of kyphotic bad posture with the help of adequate complex exercises in elementary school students. Physical Culture, 17(1-2)7-12.
8. Shukov, J. (1976). Correction of lordotic bad posture with the help of adequate complex exercises. Physical Culture, 15(1-2), 11-17.

RECURRENT PREECLAMPSIA IN THE SAME PATIENT

Todorovska I, Samardziski I, Livrinova V, Simeonova Krstevska S, Dabeski D, Kondova Topuzovska I

University Clinic for Gynecology and Obstetrics, Vodnjanska st. 17, Skopje 1000

ABSTRACT

Introduction: Preeclampsia is a complex disease that occurs in 5-7% of the entire population. Preeclampsia is an important cause of maternal and perinatal mortality. The etiology of preeclampsia is unknown, but recent research suggests that these disorders originate in the placenta and are characterized by extensive maternal endothelial dysfunction. This leads to inadequate blood supplementation and oxidative stress. Placental factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble receptor for vascular endothelial growth factor (VEGF), are released into the maternal circulation, where they stimulate the inflammatory response and endothelial dysfunction.

Objective: To demonstrate the possibility of preventing severe preeclampsia in the same patient by determining the ratio of angiogenic factors sFlt-1/ PLGF. With early detection of angiogenic factors, the patient is monitored more closely when the growth of angiogenic factors begins without clinical manifest symptoms and timely termination of pregnancy in the interest of the patient's health.

Case Report: Monitor the clinical form of preeclampsia in a patient in her two pregnancies. In the first pregnancy, the patient develops the most severe form of preeclampsia (Eclampsia and HELLP Syndrome) at 29.1 weeks gestation.

The postpartum patient is in serious condition with a stay in the Intensive Care Unit. During the first pregnancy, in 2014, angiogenic factors were not examined.

In the second pregnancy, 2020/ 2021, in the second trimester (in the 24th week of gestation), the angiogenic factors are started to be examined. Along with the ultrasound examination and measurement of the mean arterial pressure, the danger of developing severe preeclampsia is detected early in pregnancy and with careful monitoring of the patient it ends in time before the patient's health is seriously endangered.

Conclusion: Preeclampsia is a unique health condition that occurs only in pregnancy and that can seriously endanger the health of both mother and fetus. With the development of medicine, many tests are being developed that try to diagnose the occurrence of preeclampsia very early. Recent studies of angiogenic factors and the correlation between sFlt-1/ PLGF have been shown to be sensitive in predicting preeclampsia, as well as in patient's case studies.

Key Words: angiogenic factors, monitoring, preeclampsia, prematurity.

Introduction

Preeclampsia is a complex disease that occurs in 5-7% of the entire population. However, geographical, social and racial differences affect the incidence of the outbreak. In some populations the incidence is three times higher. Preeclampsia is associated with a fivefold increase in mortality in developing countries (1,2).

Preeclampsia is an important cause of maternal and perinatal mortality (2).

The etiology of preeclampsia is unknown, but recent research suggests that these disorders originate in the placenta and are characterized by extensive maternal endothelial dysfunction.

The main causes of the pathogenesis of preeclampsia are hypoperfusion, hypoxia, ischemia. They lead to the release of inflammatory factors from the placenta into the maternal circulation. These factors cause maternal endothelial dysfunction and systemic symptoms of preeclampsia (3,4).

It is presented clinically in the second half of the pregnancy and is defined as an increase in blood pressure (above 140/90mmHg twice in a period of 6 hours) and proteinuria (> 300mg/ dl/ 24h) after the twentieth week of gestation in previously normotensive patients (5). It is often associated with the occurrence of cardiovascular disease, obesity, renal impairment and diabetes in adults.

Multiple risk factors increase the risk of developing preeclampsia such as obesity, insulin resistance and hyperlipidemia. They stimulate the release of inflammatory cytokines and together with oxidative stress, lead to endothelial dysfunction. Although the etiology is unknown, the major pathophysiological factor is endothelial dysfunction.

Factors causing endothelial dysfunction include: poor placental vascular remodeling and placental ischemia, oxidative stress, excessive inflammation, imbalance of antigenic factors, and loss of endogenous protective regulators.

Placental factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble receptor for vascular endothelial growth factor (VEGF) are released into the maternal circulation, where they stimulate the inflammatory response and endothelial dysfunction (5,7,8).

Preeclampsia can also develop in patients with normal placenta and are prone to systemic inflammation, such as patients with chronic cardiovascular disease or diabetes (5).

Eclampsia is a rare, but very serious complication when high blood pressure causes seizures during pregnancy. Seizures are a period of impaired brain activity that can manifest with stiff eyes, impaired consciousness and convulsions, and can occur in a coma, in the period after 20 weeks of gestation until the period of the puerperium (10,11).

HELLP Syndrome is a disorder of the liver and blood that can be fatal if left untreated. It is an acronym for three major abnormalities in laboratory tests: Hemolysis, EL-elevated Liver enzymes, LP-low platelet count (hemolysis, enlarged liver enzymes, and thrombocytopenia) (5,7,9).

Hemolysis results in anemia, which results in less oxygen being carried throughout the body. Elevated liver enzymes indicate impaired liver function. Decreased platelet levels lead to an increased risk of excessive bleeding. It occurs in less than 1% of pregnancies, but can be life-threatening for both mother and baby (10,11).

Purpose

To show the possibility of preventing a severe form of preeclampsia in the same patient, by determining the ratio of angiogenic factors sFlt-1/ PLGF. With early detection of angiogenic factors, the patient is monitored more closely and more closely when the growth of angiogenic factors begins without clinical manifest symptoms and termination of pregnancy in the interest of the patient's health.

Case Report:

In this paper we describe a patient who in both pregnancies, very early, in a small gestational week develops a clinical picture of severe preeclampsia.

The first pregnancy is in 2014. She was hospitalized at the University Clinic for Gynecology and Obstetrics in 29.1 AD. with a diagnosis of hypertension in pregnancy and signs of preterm delivery.

The patient was hospitalized at the clinic due to hypertension (140/90mmHg) which at first appeared a few days before hospitalization, but without subjective complaints.

From laboratory tests there is a deviation in uric acid which was increased (584umol/L), increased LDH value (432.1U/L), qualitative value of proteinuria +++, and quantitatively 1.9g/L and mild hypoproteinemia.

Fetal lung maturation with amp. Flosteron 14mg/24h/ II doses. In the next two days the patient was in stable condition without subjective complaints. Consecutive nephrologist called due to increase in blood pressure (up to 180/120mmHg) and ophthalmologist on 15.07.2014. Nephrological findings: Increased dose of antihypertensive and a second introduction. Th: tabl. Methyldopa 4x500mg; tabl. Cordipin R 2x20 mg and vigilant monitoring. Ophthalmic findings: Fundus hypertonicus gr. I / II.

Laboratory findings from 15.07.2014: Uric acid 499umol/L; LDH 640.6U/L. Other findings in reference values.

At 1 pm on 15.07.2014, the patient was found in bed, in a supine position, in a cramped body position. The patient was transferred to the Intensive Care Unit where anticonvulsant therapy was prescribed (sol. MgSO4 4g IV, then 1.5g/h) and antihypertensive therapy.

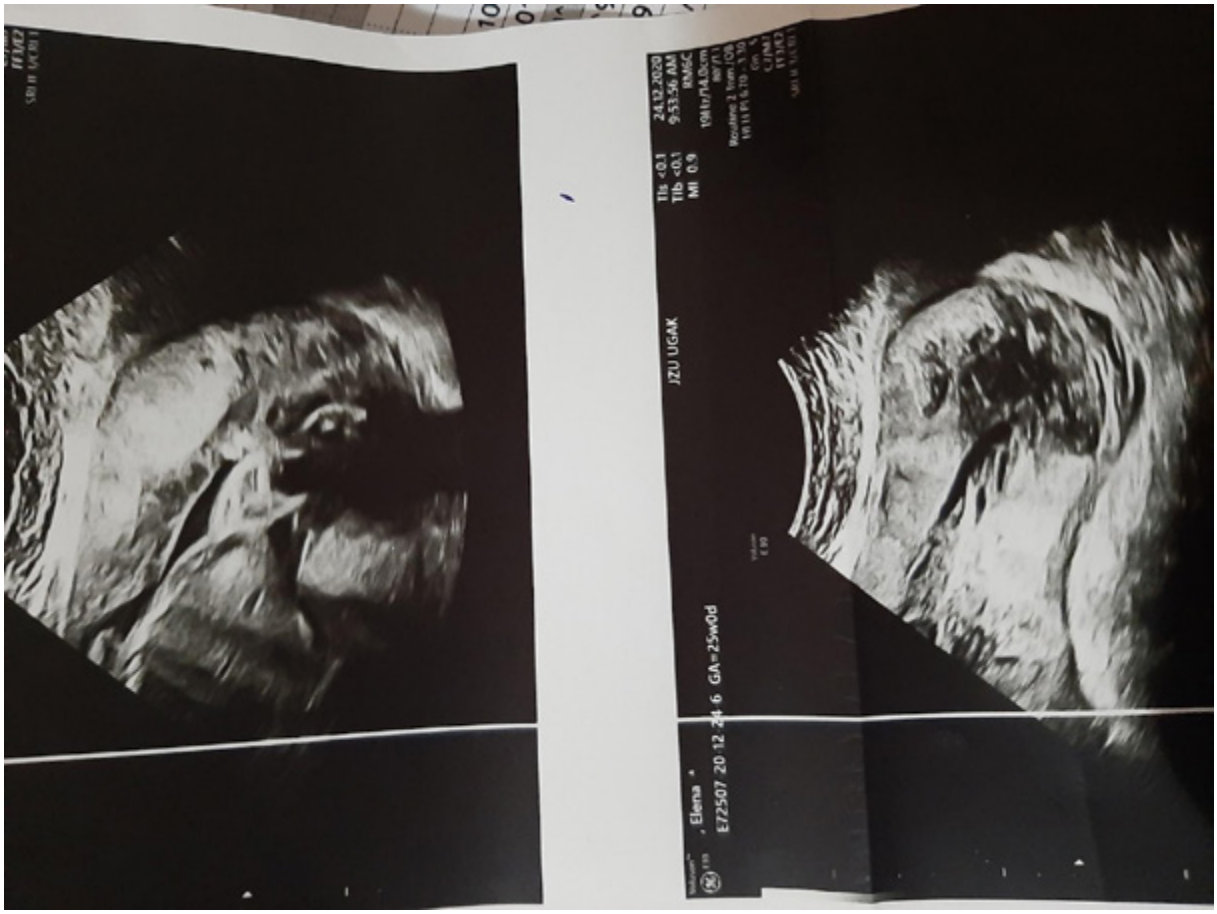
The patient after the eclamptic attack at the Department of Pathological Pregnancy is not conscious, placed airway. TA at 140/85mmHg, but later until blood pressure rises to 180/130mmHg. Ordinary amp. Embrantyl a 10mg/ IV on three occasions, amp. Enap 1.25mg/IV, tabl. CordipinR 2x20mg and tabl. Methyldopa 4x500mg. Magnesia maintained above 2mmol/L. She is sedentary all the time.

On 16.07.2014, the morning laboratory with signs for HELLP Sy. Hgb=121g/L; Plt=37x109, Uric acid 523umol/L; CRP=47.5mg/L; LDH=2258.4U/L; AST=507.8U/L; ALT=319.1U/L. Due to the deterioration of the clinical picture and laboratory tests, it was decided to terminate the pregnancy with an emergency caesarean section. A live male preterm was obtained with RT-M=1040g/33cm and AS=4/5. The operational flow went smoothly. Postoperatively, the condition gradually stabilizes.

Postoperatively prescribed antihypertensive therapy (tabl. Methyldopa 4x500mg; tabl. Cordipin R 2x20mg, tabl. Vasoflex 2x5mg), bronchodilator (amp. Aminophylline 2x125mg/ iv), anticonvulsant (MgSO4 1.5, 2x40mg), diuretic (amp. Lasix 3x10mg/ iv), corticosteroid (amp. Dexamethason 2x8mg), antianemic, dual antibiotic (amp. Lendacin 2g/24h/ iv; solEfloran 3x0,5L/ iv), then ampotemral 2x (amp. Syntocinon 3x10ie/ iv) and replacement therapy (14 fresh frozen plasmas, 3 x Albumin 20% 50ml, 10 doses of cryoprecipitate). On 20.07.2014, fourth postoperative day platelets increased by 129x109, and uric acid and LDH decreased (UA=443umol/L, LDH=799U/L).

The patient in a much-improved condition was discharged from the clinic on 24.07.2014, on the eighth postoperative day. The premature newborn after 53 days of stay at the Department of Intensive Care and Therapy for premature babies was registered on 07.09.2014 with weight of 1840g.

On December 3, 2020, she reappears at the Clinic for Gynecology and Obstetrics, in the 22nd gestational week of pregnancy for screening in the second trimester. The patient in stable general condition, with regulated blood pressure using tabl. Methyldopa 2x250mg. From the first trimester of pregnancy (12 weeks of gestation), a family gynecologist has prescribed tabl. cardiopirin a 100mg, knowing the severe clinical picture of the previous pregnancy. The ultrasound examination showed that the fetus lags behind in growth for a week and that the placenta is inhomogeneous and with calcifications.



Due to the predisposition for the occurrence of preeclampsia, the patient is called for 2 weeks for examination of angiogenic factors and ultrasound control.

Angiogenic factors play an important role in the pathogenesis of preeclampsia. Increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), with decreased placental growth factor (PLGF), are the first predictors of preeclampsia. The correlation between sFlt1 / PLGF should be determined. If the ratio is <38 it excludes preeclampsia for a week. If the ratio is> 38, it confirms preeclampsia within 4 weeks. If it is over 85, it is confirmed preeclampsia and its further management should be considered.

The control determined that the patient is in 24 weeks of gestation, and the fetus is 2 weeks behind in growth, the placenta is inhomogeneous, and the umbilical artery Doppler is a tidy, present notch on the uterine artery. The ratio of angiogenic factors is 338.

From the laboratory analyzes there is a weak presence of protein in the urine, increased value of CRP=15.4mg/L and partially activated partial time 22.2. The patient begins anticoagulant therapy with amp. Clexane 1x40mg. TA=130/75mmHg.

The patient is still in stable condition and is scheduled for re-examination after 1 week.

On 24.12.2020 the ratio of angiogenic factors is 473.55; Ultrasound finding: The patient is at 25 weeks gestation. The fetus lags behind in growth by 2 weeks (fetal weight 492g), neat fetal movements, absent flow in umbilical artery Doppler diastole, acute proteinuria, and CRP value remain the same. Blood pressure with the prescribed therapy in reference values.

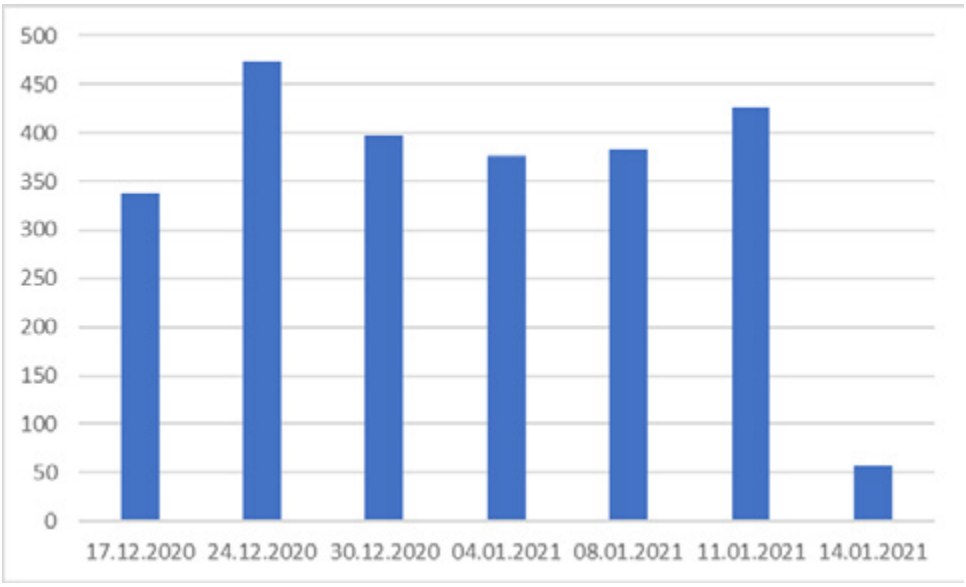
Next week on 30.12.2020 the ratio of angiogenic factors is 397.67, the value of CRP=13.0mg/L, there is proteinuria of 500mg/ 24 hours, ultrasound delay of fetal growth 3 weeks, absent flow in the diastole of the umbilical artery, inhomogeneous plant, normal amount of amniotic fluid. The patient has no subjective complaints, is normotensive and a recommendation is given for careful monitoring of the condition and at the first sign to immediately call our hospital for hospitalization.

On 04.01.2021 the patient was hospitalized in the Department of Peripartum Intensive Care at the Clinic for Gynecology and Obstetrics with Dg: Graviditas ml VII (26gn Preeclampsia recurrence, Pr. Caudae, IUGR, AEDF, St. post SC aa VI, Insuffit) due to slight deterioration of laboratory tests and persistence of a high ratio of angiogenic factors. The value of the ratio of angiogenic factors is 375.8; proteinuria 800mg/ 24 hours, CRP value=23mg/L, impaired hemostasis factors (activated partial time 18.7, D-dimers 17002) despite prescribed anticoagulant therapy. After hospitalization, therapy for fetal lung maturation (amp. Flosteron 14mg/ 24h/ II doses), anticonvulsant therapy (sol. MgSO4 1g/h), antihypertensive therapy (tabl. Methyldopa 4x250mg) and anticoagulant therapy (ampoxx) C therapy are included.

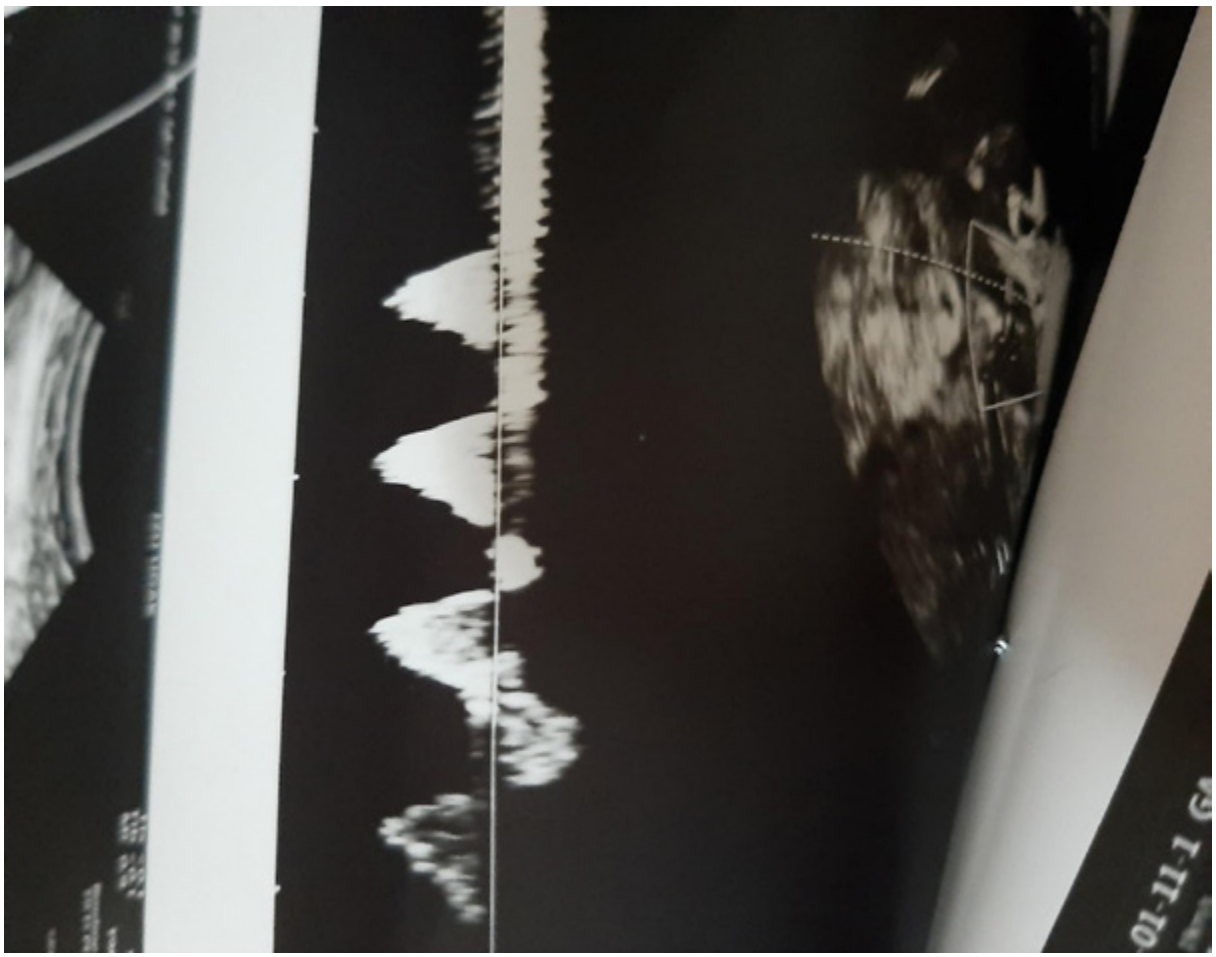
In the following days, the patient's condition is monitored.

On January 8, 2021, the ratio of angiogenic factors is 382.67. Blood pressure ranges up to 145/90mmHg.

On 11.01.2021 due to deterioration of both the clinical picture and laboratory parameters (angiogenic factors 426,27) and the ultrasound finding (reverse flow of the umbilical artery flow), the factors of hemostasis with the same values of the activated partial time, but with reduced D-dimers - 1866, decided to terminate the pregnancy.



Dynamics of the movement of the values of angiogenic factors.



Reverse flow of a.umbilicalis

On January 12, 2021, a live male fetus was delivered by caesarean section with RTM=520g/ 28cm and AS=7/7. Operative and postoperative course in order. The second postoperative day has a significant decrease in angiogenic factors = 56.66. It is substituted with 1 fresh frozen plasma. Hemostasis factors postoperatively were in reference values.

Unfortunately, on the ninth postoperative day, exitus letalis occurred in the newborn.

The mother was discharged the fourth postoperative day in good general condition.

From here we can see the significance of the prediction of preeclampsia. In the second pregnancy, with the early detection of the correlation of angiogenic factors, the risk of preeclampsia can be detected in time, the patient should be hospitalized and the pregnancy should be completed before the patient develops the most severe form of preeclampsia. The postoperative course of the second pregnancy was shorter and easier than the first.

Discussion

Preeclampsia is a serious disorder of unknown etiology. The patient, who is normotensive outside of pregnancy, develops preeclampsia in pregnancy. The only cure for preeclampsia is childbirth. It is difficult to estimate the ideal time to give birth - not to endanger the mother, and not to take the fetus out of the mother's womb too soon. Therefore, the tests that are done allow us to diagnose preeclampsia in time and to avoid the most severe complications such as Eclampsia and HELLP Syndrome. The patient in the first pregnancy develops severe preeclampsia and HELLP Syndrome, and is in clinically a very severe condition. In the second pregnancy, which is closely monitored, the occurrence of preeclampsia is diagnosed in time and intervened (she gave birth) before the onset of eclampsia. The patient is in stable condition and leaves the clinic after a short hospitalization.

Angiogenic factors are useful in the diagnosis of preeclampsia when the symptoms are still uncharacteristic, atypical. They distinguish cases of preeclampsia from cases of hypertension caused by another etiology, as existing hypertension caused by renal impairment. The height of the angiogenic factors correlates with the severity of the clinical picture and allows us to prevent pregnancy complications such as intrauterine fetal growth retardation and placental abruption.

SFlt-1 levels rise very early with the onset of preeclampsia and intrauterine growth retardation, and PLGF levels are lower before the onset of symptoms. Ultrasound examination and the sFlt-1/ PLGF ratio proved to be a solid predictor of the occurrence of preeclampsia and the prevention of its severe complications (1,4).

Conclusion

Preeclampsia is a unique health condition that occurs only in pregnancy and that can seriously endanger the health of both mother and fetus. With the development of medicine, many tests are being developed that try to diagnose the occurrence of preeclampsia very early. Recent studies of angiogenic factors and the correlation between sFlt-1/ PLGF have been shown to be sensitive in predicting preeclampsia, as well as in patients' case studies.

Preeclampsia is a multisystem disorder, based on a cascade of immune events originating from an ischemic bed. Identification of inflammatory markers in the first trimester will contribute to a better understanding of the pathophysiology of preeclampsia and give us clinically valid screening procedures for better management of this disorder. Early identification of high-risk cases will offer the possibility of prophylactic therapy, which will improve the perinatal outcome.

In recent years, several pathogenetic mechanisms have been discovered that explain the occurrence of preeclampsia. But the initial developments are still not well known. It has recently been discovered that excessive circulation of antiangiogenic factors contributes to placental damage and maternal manifestations of preeclampsia. Further research in the pathophysiology of preeclampsia allows us to develop new possibilities in its treatment.

References:

1. De Jonge LL, Steegers EA, Ernst GD, et al. C-reactive protein levels, blood pressure and the risks of gestational hypertensive complications: the Generation R Study. J Hypertens. 2011; 29: 2413-2421.
2. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005; 330:565.
3. Esplin MS, Fausett MB, Fraser A, et al. Paternal and maternal components of the predisposition to preeclampsia. *N Engl J Med.* 2001; 344:867–872.
4. Forest JC, Charland M, Massé J, et al. Candidate biochemical markers for screening of pre-eclampsia in early pregnancy. Clin Chem Lab Med. 2012; 50: 973-984.
5. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ Res.* 2004; 95:884–891.
6. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet.* 2002; 359:1877–1890.
7. Baschat AA, Madger LS, Doyle LE. Prediction of preeclampsia utilizing the first trimester screening examination. Am J Obstet Gynecol. 2014;211:524. et al. e1-524.e7. [PubMed] [Google Scholar].
8. Cuffe JSM, Holland O, Salomon C, et al. Review: Placental derived biomarkers of pregnancy disorders. Placenta. 2017;54:104e110. [PubMed] [Google Scholar],
9. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066–1074. [PubMed] [Google Scholar],
10. Kinay T, Kucuk C, Kayikcioglu F, et al. Severe Preeclampsia versus HELLP Syndrome: Maternal and Perinatal Outcomes at <34 and ≥34Weeks Gestation,balkanmedj.2015 Oct 1,32(4):359-63.
11. Kocijančić Belovic D, Plešinac S, Dotlić J, et al. Hypertensive Disorders of Pregnancy, J Med Biochem 2019 Mar; 38(1): 71–82[PubMed] [Google Scholar] WHO. *World health report: make every mother and child count.* Geneva: WHO; 2005. p.63. [Google Scholar].

PULMONARY EMBOLISM IN A PATIENT WITH COVID-19 PNEUMONIA DESPITE SATISFYING ANTICOAGULATION STATUS

Jovanoski M[1,4], Boshev M[1,4], Marinkovikj Petrusevska S[3], Srceva Jovanovski M[2,4], Georgiev A[1,4], Damjanovska Lj[2,4]

[1]University Clinic of Cardiology, 1000 Skopje, Republic of North Macedonia
[2]University Clinic of Traumatology, Orthopedic Disease, Anesthesiology, Reanimation, and Intensive Care Medicine and Emergency Department, 1000 Skopje, Republic of North Macedonia
[3] Institute of Respiratory Diseases in Children – Kozle, 1000 Skopje, Republic of North Macedonia
[4]Faculty of Medicine, "Ss. Cyril and Methodius" University in Skopje, Republic of North Macedonia

ABSTRACT

Introduction: COVID-19 disease is a disease related to many complications, some of them are life threatening. Venous thromboembolism is one of the cardiovascular causes (the third in mortality in the group of cardiovascular diseases), which can lead to serious morbidity and even mortality.

Aim: To present the fact that a quality anticoagulation therapy is not always a 100 percent safe mechanism of dealing with VTE.

Case Report: This case report is about a patient which was presented with a clinical condition related to COVID-19 bilateral bronchopneumonia. As such, she was treated with all the necessary medications, but after a VTE occurred as one of the complications, we had to upgrade the doses of anticoagulation to a therapeutic status. The CT angiography showing lobar and subsegmental pulmonary embolism was the gold standard to confirm the diagnosis. The effect of the LWMH which was used for the VTE was controlled by measuring the anti-Xa blood level. A further correction of the doses and types of antibiotics had to be done because of medications related thrombocytopenia which made the condition even more difficult to fight with.

Conclusion: Using the antiXa as a tool to control the anticoagulation status in VTE patients can be a valuable thing to do. However, we must be always thorough in observing the clinical condition of the patient and be aware of the complications which can happen.

Key words: antiXa, bronchopneumonia, COVID-19, venous thromboembolism.

Introduction

Corona virus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical picture may vary, as 20% of the patients can be completely asymptomatic, with mild symptoms and some people may develop acute

respiratory distress syndrome (ARDS) precipitated by cytokine storm, with multi organ damage, septic shock and blood clots formation. Lungs and heart are the primary targets of this novel virus, but as we mentioned earlier, other vital organs can be affected leading to a vicious circle which can lead to other life-threatening complications and end up with death. As to 11th of November, 2022 we have had more than 640 million cases confirmed worldwide, all leading to a total of 6.6 million casualties up to now (1).

This virus has been linked with abnormalities in more coagulation parameters. Unfortunately, there is no sufficient information coming from the limited studies about the epidemiology and pathophysiologic mechanisms underlying COVID-19 associated venous thromboembolism. However, the clinical practice confirms a huge number of patients treated for COVID-19 associated pneumonia, having deep vein thrombosis or pulmonary thromboembolism. As we already know, every pneumonia can be one of the pathologies in which we have increased D-dimers, and the long hospitalization required for the treatment of it is one of the risk factors that can be associated with venous thromboembolism (VTE) as complications trough mechanisms like endothelial dysfunction caused by the inflammatory process, venous stasis during the hospital treatment, the hypoxia stimulation. Few articles have described the antiphospholipid antibodies, such as anticardiolipin antibodies, lupus anticoagulants, and anti–β_2-glycoprotein I antibodies as one of a possible pathomechanism. Clinical practice has shown us that the potency of coronavirus in causing hypercoagulable state is not benign at all in comparison to other pneumonias (1, 2). The approved anticoagulant treatment for these complications as for thromboprophylaxis, is heparin which among other anticoagulant effects has antiviral, anti-inflammatory and endothelial protective effects, especially the low molecular heparin, which can be associated with fewer medications related side effects. The anti-factor Xa assay is designed to measure plasma heparin levels and to monitor anticoagulant therapy. Its reference values are from 0.3-0.8 and 0.7-1.2IU/ml for preventive and therapeutic doses respectively (3). Lower values implicate insufficient anticoagulation treatment, while increased values can alarm us about being too aggressive with the LMWH therapy and force us to reduce the dosage.

CT angiography of the pulmonary arteries is the gold standard for diagnosing pulmonary embolism. The pulmonary window detected from the CT is another benefit which gives us deeper insight in describing the pulmonary consolidations and their distribution in the lungs.

Case Presentation

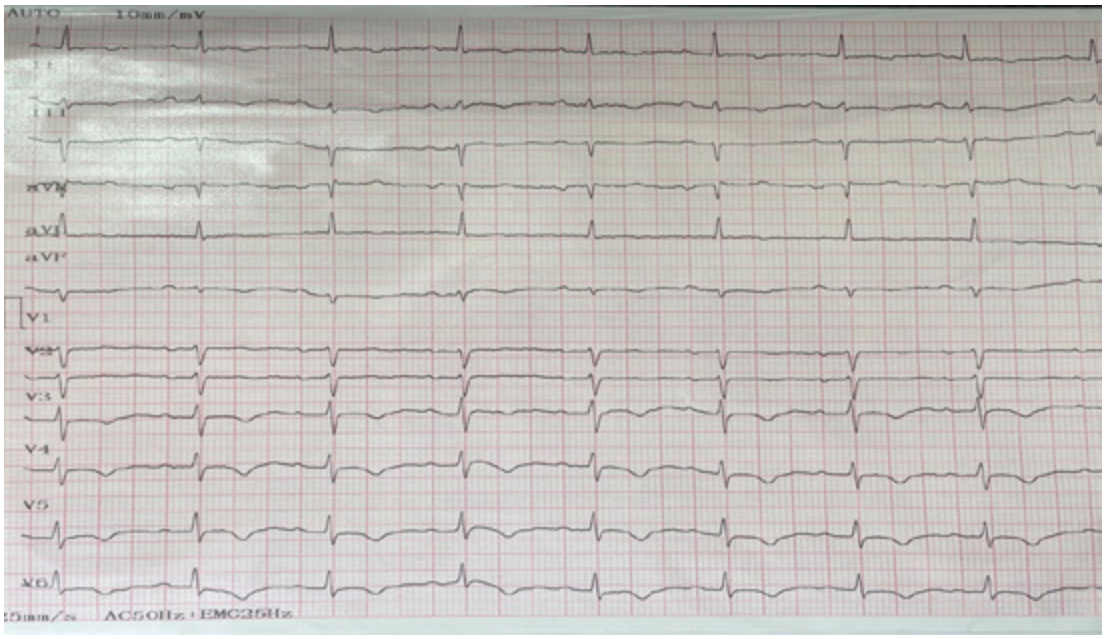
In this case we report a 73-years-old patient who was admitted in our COVID center with a symptom of fatigue and lightheadedness for the past week. Few days before the symptoms began, she was in a contact with a client who was diagnosed with SARS-CoV2 infection. Nasopharyngeal swab was taken 3 days after the symptoms, and it was also positive. She was recommended to see a specialist in infectious diseases, an examination which also included a chest radiography and laboratory analysis. Radiography of the chest showed bilateral consolidations typical for COVID-19 infection and a diagnosis of bronchopneumonia of both lungs was confirmed. Laboratory findings showed a normal differential blood count except for a slight decrease of the

platelets (around 140), slightly increased CRP (18) and LDH (289). Other findings were in the normal range, including electrolytes, urea, creatinine and liver enzymes, glycaemia, and protein status.

The patient was a non-smoker, nondrinker and she denied any allergies to food and medications. She was already on a medication for a high blood pressure (including a Ca antagonist and an ACE inhibitor), and besides the hypertension, she reported about having a deep vein thrombosis of the left inferior limb few years ago (at the time of the admission she was not taking any anticoagulation drugs). The first results of the hemostasis and D-dimers came in the normal range (300). An ECG on admission was with a sinus rhythm, with a heart rate of 70bpm, q wave with an inverted T wave in lead III. On auscultation of the lungs, we could hear crepitation in the basal and medium areas of both lungs. Hearts sounds, as well as the other part of the physical examination were normal. Her vital parameters showed a normal blood pressure and a normal heart rate, she was not febrile (body temperature around 36.8), and her blood saturation was 90% on room air. She was started with an intensive therapy with Meropenem 2grams, three times daily, Vankomycin 1gr twice daily and Vibramycin capsules 100mg twice daily. A preventive dosage of LMWH was given since she had a normal D-dimers level (she weighed 80 kilos, so enoxaparin 40mg twice daily was started). Other supportive therapy such as fluids, vitamins, gastroprotective therapy, probiotics, diuretics were started, and her antihypertensive therapy was continued. Since she was with a borderline saturation of 90%, with a shortness of breath and a bit dyspnoic, she was started on a high dose of methylprednisolone in addition to the medications mentioned above. The next day a convalescent plasma was given, and she was attached to a high flow level of oxygen with 15l/min. Laboratory analysis were performed once in 2-3 days.

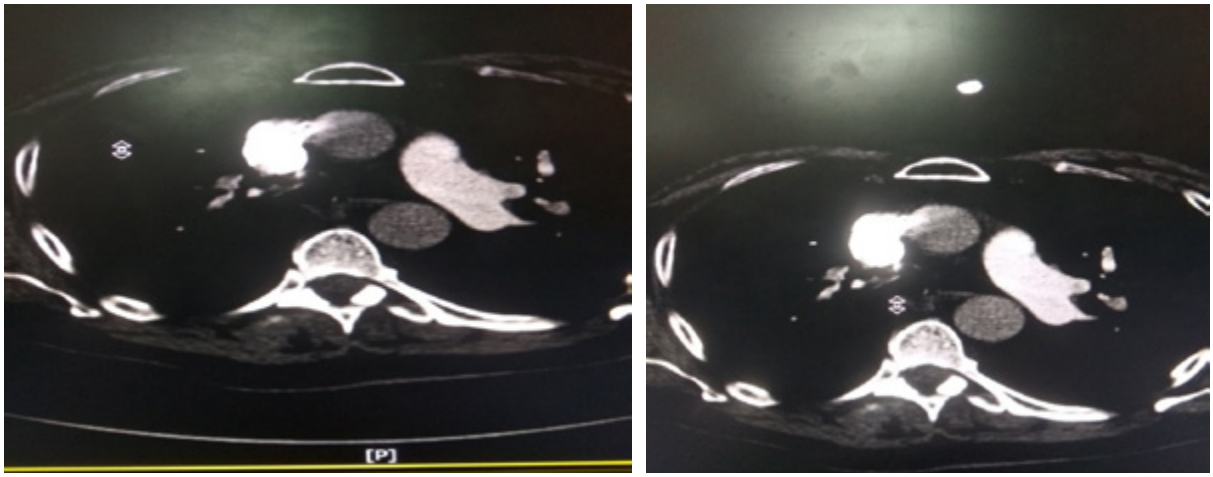
On the 6th day of the admission there was a rise in the C reactive protein (51) with a blood count with leukocytosis, neutrophilia and lymphopenia. We switched from the previous combination of antibiotics to Piperacillin/ Tazobactam a 4.5gr three times daily, a Linezolide 600mg twice daily and Fluconazole 150mg twice daily. We continued with careful reduction of corticosteroids. We did a hemostasis once in 2-3 days, and consulted transfusion medicine regarding the results, which showed a good satisfactory anticoagulation process with a slight increase in the d-dimers not going more than 1000. Considering that she had a history of deep vein thrombosis, we increased the level of LMWH to a therapeutic dosage of 80mg twice daily and continued with strict monitoring of the hemostasis. Anti Xa level was measured 8 days after the admission, it was 1.1, showing a good quality anticoagulation process. The repeated radiography of the lungs and heart was made with signs of improvement. At the 15th day after admission the patient reported that she had a chest pain. An ECG was made and there were typical inverted T waves in the right precordial leads with a heart rate around 75bpm (picture 1).

Picture 1. *ECG with typical strain pattern in the right precordial leads, pathognomonic for pulmonary embolism.*



We decided to make a CT angiography of the lungs with a protocol for pulmonary embolism. It discovered a defect in filling of both superior lobar arteries as for the segmental arteries. A diagnosis of lobar and segmental acute pulmonary embolism was confirmed (Picture 2, 3). A ground glass opacity in the periphery of both lungs was described with a dominant fibrotic component in the basal areas of both lungs plus multiple pulmonary infarct zones typical for COVID-19 pneumonia.

Picture 2, 3. *CT angiography showing defects in filling of the pulmonary arteries.*



Since we came up with a final diagnosis of pulmonary embolism, as a complication due to the corona virus pneumonia, we did an echocardiography to evaluate the heart dimensions and function. It was a normal echo finding, including the size and function of the right ventricle. At the same time, we did a blood sample for highly sensitive troponin, so we can estimate the

early mortality risk. It was in a normal range, so together with the normal dimension of the right ventricle we placed her in the group of intermediate low risk patients according to XXXcriteria. Doppler ultrasound of the lower limbs showed thrombus in the right popliteal vein (a knee operated few years ago) explaining the possible origin of the thromboembolism. Meanwhile the blood count showed a decrease in the level of platelets at around 80. She was already treated for more than 20 days with antibiotics such as meropenem, piperacillin/tazobactam and vankomycin which can cause thrombocytopenia and because of that we decided to stop them, put her only on clindamycin, three times daily, plus we continued with the LMWH therapy in therapeutic doses as an anticoagulant therapy which has HIT as side effect much less than the unfractionated heparin (UH).

The decision was made in consultation with a specialist in infectious disease, cardiologist and specialist in pulmonary medicine. The control blood count after a few days showed almost normal platelets (138). The patient denied any chest pain, difficulty breathing or other symptoms suggesting of worsening. D-dimers came in normal for the first time (370). After a whole month of hospital treatment, a control CT angiography of the pulmonary arteries was performed showing a resolution in the thrombus of the lobar and segmental arteries plus a doppler ultrasound of lower extremities with signs of resolution of the thrombus in the deep veins of the leg also. Few days before discharge the anti Xa level was 1. The patient was discharged after more than 30 days of treatment in a stable health condition with a NOAC (rivaroxaban) 20mg, once daily, in addition with the other therapy for the primary disease, with a recommendation for a regular follow up by a cardiologist and pulmonologist.

Discussion

Venous thromboembolism is the third most frequent acute cardiovascular syndrome after the myocardial infarction and stroke. It can be presented as either deep vein thrombosis or pulmonary embolism. As it can be seen in the article by Anderson Jr et al (1) there are many factors included in increasing the possibility of people being hospitalized because of a diagnosis of VTE. Our patient had some of them, such as prolonged bed stay >5 days, she had a pneumonia and she was overweight. The main factor contributing for the hypercoagulable state in our patient is COVID-19 associated pneumonia. The summary given by a cohort studies and case reports by Sakrand colleagues (2) explained the pathophysiology of COVID-19 hypercoagulable state as a major factor for pulmonary embolism and stated the importance of treatment with anticoagulation therapy, especially in critically ill patients. As we all know, every pneumonia by itself, including community acquired pneumonia and nosocomial pneumonia as well, is associated with an increased risk for PE and DVT because of the inflammation and necessary bedrest, which can last for a few weeks during the patients' recovery. Mei et al.in their study compared the rate of VTE in patients with COVID-19 pneumonia and in those with community acquired pneumonia in a hospital in Hubei, China and realized there is no significant difference between the 2 groups (4).

An effort has been made by Paparoupa et al. in order to find a predictive model for diagnosing a PE in patients hospitalized for pneumonia through a combination of laboratory parameters and clinical symptoms in a case control study of 100 patients in which they have failed in a way, but the study has urged us to keep looking for a clinically relevant symptoms and D-dimers values which can increase the suspicion for a possible PE in patients with pneumonia (5). The patient's weight (which was not extreme, but still around 80kg in our patient) is also an additional problem when it comes to blood cloths forming in these kind of patients. Plus, she had a history of deep vein thrombosis in the past due to the presence of varicose veins on both lower extremities. We couldn't have considered the previous knee surgery since it was long time ago (not during the last year), but already there were more than enough risk factors for us to consider if we should decide to go with preventive or therapeutic doses of anticoagulation therapy. That was of course before the complication of VTE occurred. At that time the therapeutic regimen was absolutely an imperative.

For the period of the hospital treatment, since day one a regular monitoring for D-dimers and hemostasis was performed, including the anti Xa level as a marker for a good anticoagulation effect while using LMWH. Although anti-factor Xa measurement maybe a little expensive marker for the follow up of the anticoagulation effect, Trunfio, and coworkers, with their retrospectively collected data from the Torino hospital, which included around 56 patients, (3) proposed it as a possible anticoagulation marker. They have set up the target range a little higher in SARS CoV2 patients to prevent or treat this disease and its complications. The coagulopathy and prothrombotic mechanisms induced by this virus leads to heparin resistance and decreased recovery of anti Xa activity. Their study showed that when using LMWH in a preventive and therapeutic cause, the target range should be 0.3–0.7 and 0.7–1.2 IU/mL respectively, in COVID-19 patients (3). The time between the last LMWH dose and measurement of this marker should be at least 4 hours apart, so we can have valid results. They have also showed that no complications in their patients (such as death, thromboembolic complications) happened in those who were in the desired range of anti Xa. The anti-factor Xa (anti- Xa) assay measures the direct inhibition of Xa factor by LMWH used in our scenario (6). In our patient it was measured twice, before and after the VTE event and it was always in the therapeutic desired range (1.1 and 1). Despite this, we had a thromboembolic event occurring. So, the question is, is it enough to have a quality anticoagulation effect measured by anti Xa level, hemostasis, and D-dimers in order not to worry about these kinds of complications? Guess not. But trying to make the most of it seems like a good idea. So, we continued with the treatment with enoxaparin 80mg twice daily alongside the other therapy.

The therapy also included three types of antibiotics in the most of the time of the hospitalization period. One of them, the antibiotic Tazocin is a mixture of two main ingredients, (piperacillin – belonging to a group of penicillin type antibiotics) plus tazobactam which prevents for the bacteria to deactivate the piperacillin. This combination is often used in treatment of infections such as urinary tract and skin infections, peritonitis, but also in patients with pneumonia. We use it frequently in our country, especially in patients with COVID-19

associated pneumonia plus a laboratory and clinical findings of bacterial superinfection. Our patient was switched to this antibiotic from the 6th day of the admission. She was almost two weeks on piperacillin/tazobactam combination, plus a linezolide 600mg twice daily. On the 20th day after admission, the blood count revealed decrease in platelets level and in a few days, they were down to 80. Few articles showed a correlation between the usage of Tazocin and reversible thrombocytopenia (7, 8).

Immune induced mechanism was also described in a case report by Hong Chen (7), in which IgM specific antibodies to piperacillin/ tazobactam tested positive, besides mechanisms like direct platelet number decreases and bone marrow suppression described in Chens article. A link, between the second antibiotic used in our patient Linezolid, and thrombocytopenia has been described in a retrospective study in Korea, which found a correlation between its use and the length of hospital treatment, confirming more cases with low platelets in patient treated for >7 days, as it was the case with our patient. A non-significant, but still the concomitant treatment with a piperacillin and tazobactam and heparin was mentioned in this study (9).

Another study also confirmed the possibility of patients being diagnosed with thrombocytopenia due to long Linezolide treatment for more than 7 days (10). Suppression of platelet release from mature megakaryocytes was given as a possible pathogenetic mechanism leading to thrombocytopenia in an animal study in Japan (11). Among the other antibiotic listed in this article, Vankomycin can also be the reason for platelets fall (12), but we only used it for less than a week, during the first week after admission, so we cannot prescribe as its side effect in this case. However, we should be aware about all the antibiotics we use in patients with pneumonia, especially when the laboratory findings show decrease in platelet number.

So, we decided to stop the treatment with both Tazocin and Linezolide in our patient, switching only to Clindamycin 600mg, three times per day. Platelets measured at the 23rd and 24th day of the admission (only 3 days after the therapy change) were rapidly increasing from 78 to 182 coming into a normal range. Since we were using LMWH in therapeutic doses for the treatment of the venous thromboembolism, we felt a lot safer with this level of platelets, as the risk for major bleedings additionally from possible heparin induced thrombocytopenia (HIT) gives us another reason to fear. HIT is defined by as a decrease in platelets to less than 50% or to less than 100x10/9/ L and positive HIT assay. As Martel and all. concluded in their meta-analysis (13), LMWH is way safer than UFH in form of inducing HIT. Although enoxaparin is much more expensive than UFH, due to the primary disease and the level of platelets, we decided to use the LMWH. Regarding the imaging methods used, the CT angiogram of the pulmonary arteries is the gold standard for the diagnosis of pulmonary embolism. It clearly discovered a defect in filling of both superior lobar arteries as for the segmental arteries. The question now was how to treat it. Should we consider fibrinolytic therapy or should we continue only with an anticoagulation therapy.

Table 1. *Platelets, D- dimmers and anti Xa values during hospitalization (year 2020).*

Date	27.11	28.11	01.12	02.12	10.12	15.12	16.12	17.12	18.12	22.12	28.12
Platelets	164	157	269	249	171	95	104	78	96	182	193
D dimers		300	915		975	798	692		252		283
Anti Xa			1.1								1

As a diagnosis was made, we further decided to classify the severity of pulmonary embolism and the risk of early death in outpatient according to the Guidelines for Pulmonary Embolism from 2019, written by the European Society of Cardiology (14). Our patient was hemodynamically stable, she had a normal blood pressure and was not in a cardiogenic shock. Still in order to stratify the risk of early death and evaluate the need for an eventual fibrinolytic therapy, we did an echocardiography looking for an increased size of the right ventricle which was normal and a blood measurement of high sensitive troponin I that was also normal.

One of the parameters in the evaluation process of the severity of PE and the risk of early death is the PESI score given in Table 7 with its modified versions as described by Tamizifar et al. (14,15). It was 1 in our patient because of the increased heart rate in correlation with the diagnose for PE. Finally, the normal echocardiography and normal right ventricle plus the negative troponin plus the sPESI score of 1, has classified our patient as being in an intermediate low risk group. We continued with the therapeutic dosage of enoxaparin (80mg twice daily since she was 80kg in body weight). After one month of hospitalization and 15 days after the diagnosis of PE, a control CT angiography of the pulmonary arteries was again performed with a complete resolution of the thrombus of the lobar and segmental arteries. The control Doppler ultrasound of the lower extremity also revealed a thrombus in resolution. In addition, the pulmonary window of the CT scan showed improvement of the primary process of pneumonia caused by COVID-19.

The patient was discharged in an improved health condition with a DOAC in addition to the other prescribed therapy. The oral treatment, rapid onset of action, minimal drug and food interactions, predictable pharmacokinetics, and lack of need for routine monitoring made it an excellent choice for further home treatment as studied by Eldredge et al. (16). The plan is to stay on rivaroxaban 20mg once daily for at least 3-6 months when it will be decided if a further anticoagulation therapy is needed. A lifelong therapy with OAC may be a reasonable solution since this was a second episode of a venous thromboembolism in the same patient.

Conclusion

Venous thromboembolism including PE is a common scenario in COVID-19 patients. Although finding a diagnosis of pulmonary embolism in a patient with pneumonia of any kind can be challenging, we should always raise the suspicion for VTE in COVID-19 patients and look thoroughly by evaluating the symptoms and analyzing the laboratory findings and use diagnostic tools that we have. The treatment with LMWH may be the safest treatment option in patients with COVID-19 and associated VTE and the anti Xa level can be a quality marker

for evaluating the anticoagulation process, but we should never rely just on it, because even a well anticoagulated patient shouldn't stop us from looking for a hypercoagulable complication in these patients. The variety of medications that we use while dealing with COVID-19 disease, should be carefully evaluated because of possible drug interactions, to provide a better treatment with less complications.

References:

1. Anderson, F. A., & Spencer, F. A. (2003). Risk factors for venous thromboembolism. Circulation, 107(SUPPL.23).https://doi.org/10.1161/01.CIR.0000078469.07362.E6.
2. Sakr, Y., Giovini, M., Leone, M., et al. (2020). Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. Ann. Intensive Care, 2020, 10:124.https://doi.org/10.1186/s13613-020-00741-0.
3. Trunfio, M., Salvador, E., Cabodi, D., et al. (2020). Anti-Xa monitoring improves low-molecular-weight heparin effectiveness in patients with SARS-CoV-2 infection. Thrombosis Research, 196(July), 432–434. https://doi.org/10.1016/j.thromres.2020.09.039.
4. Mei, F., Fan, J., Yuan, J., et al. (2020). Comparison of Venous Thromboembolism Risks between COVID-19 Pneumonia and Community-Acquired Pneumonia Patients. Arteriosclerosis, Thrombosis, and Vascular Biology, September,2332–2337.https://doi.org/10.1161/ATVBAHA.120.314779
5. Paparoupa, M., Spineli, L., Framke, T., et al. (2016). Pulmonary Embolism in Pneumonia: Still a Diagnostic Challenge? Results of a Case-Control Study in 100 Patients. Disease Markers, 2016.https://doi.org/10.1155/2016/8682506.
6. Newall, F. (2013). Anti-factor Xa (Anti-Xa) assay. Methods in Molecular Biology, 992, 265–272. https://doi.org/10.1007/978-1-62703-339-8-19.
7. Chen, H., Fan, Z., Guo, F., et al. (2016). Tazobactam and piperacillin-induced thrombocytopenia: A case report. Experimental and Therapeutic Medicine,11(4),1223–1226.https://doi.org/10.3892/etm.2016.3062.
8. Minh-Tri H. Nguyen, Pavneet Kaur, et al. The First Case Report of Tazobactam Induced Thrombocytopenia. Blood 2019; 134 (Supplement_1): 4897. doi: https://doi.org/10.1182/blood-2019-126227.
9. Choi, G. W., Lee, J. Y., Chang, M. J., et al. (2019). Risk factors for linezolid-induced thrombocytopenia in patients without haemato-oncologic diseases. Basic and Clinical Pharmacology and Toxicology, 124(2), 228–234. https://doi.org/10.1111/bcpt.13123.
10. Attassi, K., Hershberger, E., Alam, R., et al. (2002). Thrombocytopenia associated with linezolid therapy. Clinical Infectious Diseases, 34(5), 695–698. https://doi.org/10.1086/338403.
11. Tajima, M., Kato, Y., Matsumoto, J., et al. (2016). Linezolid-induced thrombocytopenia is caused by suppression of platelet production via phosphorylation of myosin light

chain 2. Biological and Pharmaceutical Bulletin, 39(11),1846–1851.https://doi.org/10.1248/bpb.b16-00427.

12. Bakchoul, T., & Marini, I. (2018). Drug-associated thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2018 Nov 30; 2018(1): 576–583. https://doi:10.1182/asheducation-2018.1.576.

13. Martel, N., Lee, J., & Wells, P. S. (2005). Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. Blood, 106(8), 2710–2715.https://doi.org/10.1182/blood-2005-04-1546

14. Konstantinides, S. V., Meyer, G., Bueno, H., et al. (2020). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS). European Heart Journal, 41(4), 543–603. https://doi.org/10.1093/eurheartj/ehz405.

15. Tamizifar B, Fereyduni F, Esfahani MA, et al. Comparing three clinical predictionrules for primarily predicting the 30-day mortality of patients with pulmonary embolism: The "Simplified Revised Geneva Score," the "Original PESI," andthe "Simplified PESI." AdvBiomedRes 2016;5:137. 10.4103/2277-9175.187372.

16. Eldredge, J. B., & Spyropoulos, A. C. (2018). Direct oral anticoagulants in the treatment of pulmonary embolism. Current Medical Research and Opinion, 34(1), 131–140. https://doi.org/10.1080/03007995.2017.1364227.

CARDIAC SURGERY IN PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Kostadinovska-Jordanoska B[1], Nikolic A[1], Stefanovski I[1], Slaveski D [1], Radoeski A[1], Bedzeti F[1], Bislimovski D[1]

[1] Department of Cardiac Surgery, Acibadem Sistina Hospital, Skopje, North Macedonia

ABSTRACT

This is a case report of 55-years old woman with heart valve disease diagnosed with chronic lymphocytic leukemia, requiring open heart surgery.

Chronic lymphocytic leukemia (CLL) is represented by the progressive accumulation of functionally incompetent monoclonal lymphocytes. CLL is the most common adult leukemia in the western world accounting for approximately seven percent of non-Hodgkin lymphomas. It is estimated that about 25-50% of the patients are asymptomatic at presentation.

Patients over the age of 50 and prolonged survival having a hematological disorder, means that more of them would require cardiac surgery treatment. Because of that, expanding the capacity of knowledge for such patients requiring cardiac surgery is essential.

The operative risk of patients with malignant hematologic disorders is increased, as this may include immune suppression, changes in blood viscosity, coagulation defects and bone marrow insufficiency. When these patients are scheduled for operative treatment, there must be cautious for infections in the postoperative period, bleeding and leukemic transformation. The effect of cardiopulmonary bypass (CPB) and inflammatory response in the body, combined with surgical trauma, provoke systemic inflammatory syndrome. But the interaction of this syndrome in these patients are still insufficient. Small data of retrospective studies report the uplifted risk of infections, bleeding, hemostatic system disorder and mortality.

Cardiac surgical experience in patients with hematological malignancies is still limited and detailed investigation is mandatory in decision making. Patients should be counseled on the increased risk of morbidities after cardiac surgery including immune modulation, bleeding, clotting and infection. Adequate medical treatment and long-term multidisciplinary follow up are crucial in prolonging survival.

Key Words: aortic stenosis, cardiac anesthesia, cardiac surgery, chronic lymphocytic leukemia, mitral regurgitation.

Introduction

Increased surgical experience and technological advances in cardiac surgery have encouraged surgeons to perform complex cardiac operations in patients with comorbidity

factors, with acceptable morbidity and mortality rates. Hematologic malignancies are diagnosed in all age groups, and chronic forms are predominantly seen in elderly population (1).

The operative risk of patients with malignant hematologic disorders is increased, as this may include immune suppression, changes in blood viscosity, coagulation defects and bone marrow insufficiency. When these patients are scheduled for operative treatment, there must be caution for infections in the postoperative period, bleeding and leukemic transformation. Cardiopulmonary bypass (CPB), because of their systemic inflammatory response and immune-suppressing effects, have the potential risk of increasing the hematological problems, leading to fatal or morbid complications (2).

Chronic lymphocytic leukemia is the most common type of leukemia in western countries, and outcomes of patients with CLL undergoing cardiac surgery are uncertain. Infectious complications occur in 63% of the patients with hematologic malignancy. Infections are reported to be the main life-limiting complications in CLL. A history of irradiation and chemotherapy predisposed to postoperative respiratory insufficiency, acute renal failure, and an impaired long-term survival (4).

Case Report

Our patient was 55-years old woman with history of primary Ewing sarcoma of left pubic bone who had underwent surgical resection 27 years earlier. Because of the secondary metastasis of the left lung, 6 cycles of chemotherapy and radiotherapy had been administered. One year ago, she had fatigue and swelling of the legs. She realized cardiac examination, including echocardiography, which revealed moderate aortic valve stenosis and regurgitation (Figure 1), severe mitral valve regurgitation (Figure 2) and moderate regurgitation with preserved left and right ventricular systolic and diastolic function. Medical therapy has been initiated, including beta-blocker, diuretics and angiotensin converting enzyme inhibitor. Because of symptoms persistence, one month later, she admitted to our cardiac surgery department for consultation and admission for cardiac surgery treatment.

The initial laboratory tests revealed leukocyte count 104.19 10^9/L, of which 97.12 10^9/L are lymphocytes (Table 1). The peripheral blood smear revealed smudge cells (Gumprecht shadows) indicative for chronic lymphocytic leukemia and rare prolymphocytes.

The patient underwent aortic valve replacement with mechanical valve 21mm and mitral valve replacement with mechanical valve 27mm with orderly postoperative course. In the intensive care unit, catecholamine support with adrenaline and vasopressor support with noradrenaline, and support with milrinone and levosimendan has been administered. In the second postoperative day because of pericardial effusion, she underwent subxiphoid drainage in operation room. She was extubated several hours later. Because of febrile episodes and increased inflammatory markers, double antibiotic therapy with meropenem and vancomycin, and antifungal therapy with fluconazole was administered. Hematologic specialist concluded no necessity for hematologic therapy for CLL. The echocardiography in the postoperative course

revealed proper function of the mechanical aortic and mitral valve. Because of pleural effusion the left and right pleural space were punctured.

The patient was discharged in the 19th postoperative day in stable general condition, with leukocyte count 46.25 10^9/L, of which 42.22 10^9/L are lymphocytes (Table 1). She realized regular heart and hematologic postoperative control examinations with stable condition.

Figure 1.

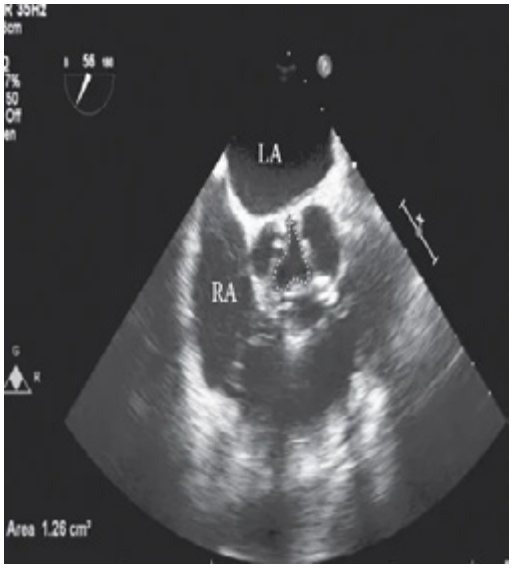


*Figure 1. Echocardiography revealing moderate aortic Stenosis, *LA=Left atrium, RA=Right atrium*

Figure 2.

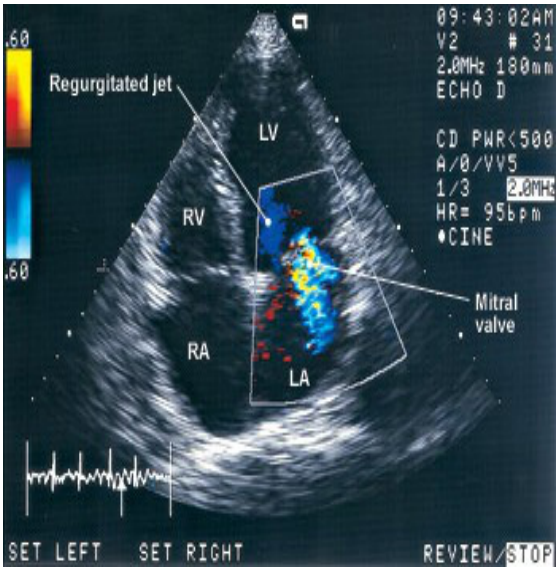


*Figure 2. Mitral valve regurgitation *LA=Left atrium, RA=Right atrium, LV=Left ventricle, RV=Right ventricle*

Table 1. *Evolution of the results of leukocyte and lymphocyte blood count in the preoperative and postoperative phase.*

	Admission	1st post-op	5th post-op	10th post-op	15th post-op	19th post-op
Leukocytes 10^9/L	104.19	76.84	102.09	108.95	50.02	46.25
Lymphocytes 10^9/L	97.12	63.91	88.61	96.03	45.42	42.22

Discussion

Results concerning cardiac surgery in hematological disorders and their treatment have not been examined completely yet. Data and evidence published in the world is still insufficient, and the results are announced by analyzing retrospective single-center studies with small number of cases. Recent advances in the medicine in the field of oncology and treatment strategies improve the outcome in hematological malignancies. Patients over the age of 50 and prolonged survival having a hematological disorder means more of them would require cardiac surgery treatment. Because of that, expanding the capacity of knowledge for such patients requiring cardiac surgery is essential (3).

The hemostatic system in the body and other organs are affected by hematological disorders and their treatment. Increased blood viscosity because of polycythemia can be found in myeloproliferative syndromes. Platelet dysfunction because of deficient glycoprotein IIb/IIIa complex can be found, including acquired von Willebrand syndrome. Pathologically, platelet morphology alteration and hyporesponsiveness are met. Syndromes of hypercoagulability and hyperviscosity can be met in malignant lymphomas resulting from acquired activated protein C resistance and monoclonal gammopathy. There must be serious caution because of impaired hemostatic system during cardiac surgery (5). The immune system is altered increasing the risk of infectious complications. In the data available, 63% of the patients experience infectious complications. In chronic lymphocytic leukemia (CLL), the main life-limiting illness are infections.

The effect of cardiopulmonary bypass (CPB) and inflammatory response in the body combined with surgical trauma provoke systemic inflammatory syndrome. But the interaction of this syndrome in these patients is still insufficient. Small data of retrospective studies report the uplifted risk of infections, bleeding, hemostatic system disorder and mortality (6).

Patients with hematological malignancies can undergo cardiac surgical intervention with allowable and acceptable results in the early postoperative period. The medical team must be careful in dealing with these patients in the intensive care unit in the postoperative period with focus on bleeding, infections and prolonged hospital stay. All staff involved, such as multidisciplinary follow-up by surgeon, anesthesiologist, hematology specialist, oncologist and cardiologist are essential in the optimal medical treatment and prolonged survival (7).

Conclusion

Cardiac surgery in patients with hematological disorder is found to have acceptable short and long-term morbidity and mortality. Optimal management requires multidisciplinary approach by surgeon, anesthesiologist, hematology specialist, oncologist and cardiologist.

References

1. Sommer SP, Lange V, Yildirim C, et al. Cardiac surgery and hematologic malignancies: a retrospective single-center analysis of 56 consecutive patients. Eur J Cardiothorac Surg. 2011 Jul;40(1):173-8.
2. Galea SA, Galea J. Urgent Coronary Artery Bypass Surgery in a Patient with Postinfarction Angina and Active Myelomonocytic Leukaemia. Case Rep Oncol. 2016 Nov 18;9(3):781-785.
3. Guler A, Sahin MA, Cingoz F, et al. Can cardiac surgery be performed safely on patients with haematological malignancies. Cardiovasc J Afr. 2012 May;23(4):194-6.
4. Nguyen A, Schaff HV, Arghami A, et al. Impact of Hematologic Malignancies on Outcome of Cardiac Surgery. Ann Thorac Surg. 2021 Apr;111(4):1278-1283.
5. Ghosh P, Carroll I, Kanhere A, et al. Cardiac operations in patients with low-grade small lymphocytic malignancies. J Thorac Cardiovasc Surg. 1999 Dec;118(6):1033-7.
6. Zhu Y, Toth AJ, Lowry AM, et al. Cardiac Surgery Outcomes in Patients with Chronic Lymphocytic Leukemia. Ann Thorac Surg. 2018 Apr;105(4):1182-1191.
7. Staab J, Cotter E, Kidd B, et al. Review and Update: Hematologic Malignancies and Adult Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020 Mar;34(3):759-771.
8. Chan J, Rosenfeldt F, Chaudhuri K, et al. Cardiac surgery in patients with a history of malignancy: increased complication rate but similar mortality. Heart Lung Circ. 2012 May;21(5):255-9.
9. Plumereau F, Pinaud F, Roch A, et al. Do patients with haematological malignancy who need cardiopulmonary bypass have a short-term higher mortality or a higher chance of disease progression? Interact Cardiovasc Thorac Surg. 2014 Sep;19(3):474-8.
10. Samuels LE, Kaufman MS, Morris RJ, et al. Open heart surgery in patients with chronic lymphocytic leukemia. Leuk Res. 1999 Jan;23(1):71-5.

ORIGINAL ARTICLE *UDK: 612.16.078:612.216*

CHANGES IN HEART RATE AND RELAXATION HEART RHYTHM COMPONENT AFTER CONDUCTED VENTILATION PROTOCOL (7171/6363)

Chokuzovska A,

Higher Medical School, Bitola, Republic of North Macedonia

ABSTRACT

The survey was conducted on five respondents through a composite survey containing four items. Sample indicators were heart rate and the relaxant component derived from heart rate variability. Indicators were continuously monitored (beat-to-beat) and recorded during the entire study with the Polar pulse tester. Phase 1 – Conscious and passive observation of breathing, Phase 2 - Complete and correct ventilation with rhythm 7171, Phase 3 - Complete and correct ventilation with rhythm 6363, and Phase 4 - Conscious and passive observation of breathing. The results were processed with the basic statistical parameters for the values of the heart rate and the relaxant component in the four phases of the ventilation protocol, the homogenization test of the variance of the heart rate and the relaxant component, as well as the Analysis of Variance of the values of the heart rate and the relaxant component in the four phases of the ventilation protocol. After the variance analysis, it can be determined that the difference in HR values shows a statistically significant difference, at the 0.00 level. The obtained results justify this research, which in the future should receive a more complex methodological approach.

Key Words: heart rate, relaxant component, ventilation.

INTRODUCTION

The largest number of heart rate researches so far, has been with the purpose of monitoring heart rate changes during more intense physical activities (when sympathetic activity dominates), as well as determining its values while rest (when parasympathetic activity dominates). There is a smaller number of studies on the reaction of this indicator during physical loads (or other experimental protocols) that cause changes in heart rate < 50% SF max.

One of such protocols that can induce a change in heart rate and the relaxant component derived from heart rate variability, is programmed ventilation. The change in the way of ventilation (depth, rhythm, retention of ventilation) causes changes in the tonicity of the components of the vegetative system. Inspiration speeds up the heart rate, and expiration slows it down.

Therefore, the aim of this paper was to analyze the heart rate response and the relaxant component derived from heart rate variability, after the ventilation protocol was implemented.

If this hypothesis is confirmed, it will mean that the activity of the parts of the autonomic nervous system (sympathetic and parasympathetic) can be toned with ventilation. For these possibilities, there is large amount of data from the literature, and smaller amount from the research environment.

PREVIOUS RESEARCHES

The relaxation component (Rlx, Relaxation rate) is an indicator that is based on and derived from the heart rate variability. The degree of heart rate variability is highly individual. It is the most variable when measured at rest or during daily activities that require little physical activity.

This problem was preceded by previous researchers (1,2,3,4,5,6)

The heart rate response is inversely proportional to the response to the relaxant component. An increase in the heart rate and a decrease in the relaxant component indicate greater sympathetic tone. Current stress causes an increase in the heart rate and a decrease in the relaxant component indicating greater sympathetic tonicity.

SUBJECT, OBJECTIVE AND HYPOTHESES OF THE RESEARCH

3.1. Subject of the research

The subject of the research is the heart rate and the relaxing component of the heart rhythm.

3.2. Aim of the research

The aim of the paper is to analyze the reaction of the heart rate and the relaxant component derived from the variability of the heart rate, after the ventilation protocol has been carried out.

3.3. Research hypotheses

X0: After implementing a ventilation protocol, the activity of parts of the autonomic nervous system can be toned,

X1: Significant changes in the heart rate values will be induced after a ventilation protocol is implemented.

X2: Significant changes in the values of the relaxant component will be induced after a ventilation protocol has been implemented.

Work Methods

The survey was conducted on five respondents through a composite survey containing four items. Sample indicators were heart rate and the relaxant component derived from heart rate variability. Indicators were continuously monitored (beat-to-beat) and recorded during the entire study with the Polar pulse tester.

Explanation of the phases

Body position during breathing

The subject sits in the Turkish sitting position (sukhasana), the back is straight, the palms are turned up and placed on the knees, the shoulders are relaxed, the head is directed forward, the eyes are closed, the facial muscles are relaxed with a gentle smile on it.

Phase 1 – Conscious and passive observation of breathing

Breathing takes place independently. The subject just consciously follows the melodious breathing i.e., the movement of the bladder wall forward (during inhalation) and the movement of the bladder wall backward (during exhalation). The subject is aware of the depth, rhythm and frequency of breathing.

Phase 2 - Complete and proper ventilation with rhythm 7171

Complete breathing means ventilation with all parts of the lungs (lower, middle and upper), both during inhalation and exhalation.

Correct ventilation is complete and takes place according to the principle of "filling and emptying the bucket with water": filling the bucket with water corresponds to inhalation, and emptying the bucket with water corresponds to exhalation.

Inhalation: The lower part of the lungs (diaphragm) is filled with air, then the middle part (chest, thoracic), and at the end of the upper part (sternoclavicular). Timed exhalation lasts while the subject counts to himself from 1 - 7.

Exhalation: Exhale with the upper part of the chest, then with the middle one and finally with the lower part of the chest. Timed exhalation lasts while the subject counts to himself from 1 - 7.

This phase is breathed with rhythm 7171. The numbers 7171 indicate the durations (rhythm) of the individual phases of the breathing cycle, namely: 7- inhalation, 1- pause to change the fingers that close the nostrils, 7 - exhalation and 1- pause to change on the fingers that close the nostrils.

One inhalation and one exhalation, together with two pauses in between, constitute one breathing cycle.

Phase 3- Complete and proper ventilation with rhythm 6363

Complete breathing means ventilation with all parts of the lungs (lower, middle and upper) both during inhalation and exhalation.

Correct ventilation is complete and takes place according to the principle of filling and emptying the bucket with water: filling the bucket with water corresponds to inhalation, and emptying the bucket with water corresponds to exhalation.

Inhalation:

The lower part of the lungs (diaphragm) is filled with air ,below the middle part (chest, thoracic),

and finally the upper part (sternoclavicular).

Time of the inhalation lasts while the subject counts to himself/herself from 1-6.

Exhalation:

Exhale with the upper part of the chest,

then with the middle one,

and finally with the lower part of the chest.

Time of the exhalation lasts while the subject counts to himself from 1-6.

This phase is breathed with rhythm 6363. The numbers 6363 indicate the durations (rhythm) of the individual phases of the breathing cycle, namely: 6 - inhalation, 3 - pause to change the fingers that close the nostrils, 6 - exhalation and 3 - pause to change on the fingers that close the nostrils.

The cycles are repeated until three minutes have passed.

The interruption of the cycles is indicated by means of a timer.

Phase 4 - Conscious and passive observation of breathing

Breathing takes place independently. The subject just consciously follows the melodious breathing i.e., the movement of the bladder wall forward (during inhalation) and the movement of the bladder wall backward (during exhalation). The subject is aware of the depth, rhythm and frequency of breathing.

A common note for all phases

The examinee breathes each phase of breathing for three minutes, which is regulated by a timer, which when the time expires gives a sound signal.

The first and fourth phases are identical.

RESULTS AND DISCUSSION

Table1: *Descriptive statistics for the values of the heart rate and the relaxant component in the four phases of the ventilation protocol.*

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
HR	1.00	1210	81.9818	10.85012	.31192	81.3699	82.5938	57.00	105.00
	2.00	1241	84.5713	12.26679	.34821	83.8882	85.2545	51.00	108.00
	3.00	1232	83.6648	10.95373	.31207	83.0525	84.2770	59.00	107.00
	4.00	1233	77.3585	9.69023	.27596	76.8171	77.8999	55.00	105.00
	Total	4916	81.8977	11.32553	.16153	81.5810	82.2144	51.00	108.00
RLX	1.00	1210	24.5455	6.82694	.19626	24.1604	24.9305	11.00	44.00
	2.00	1241	27.9726	7.41571	.21051	27.5596	28.3856	12.00	45.00
	3.00	1232	24.4334	4.23311	.12060	24.1968	24.6700	13.00	39.00
	4.00	1188	30.4579	7.33900	.21293	30.0402	30.8757	15.00	48.00
	Total	4871	26.8323	7.03727	.10083	26.6346	27.0299	11.00	48.00

According to the obtained data from the descriptive statistics in Table 1, it can be seen that in the heart rate variables, the arithmetic mean in the first phase is lower than the second and third phases, that is, it is the lowest in the fourth phase. This means that the values initially increase and then decrease. The standard deviations show that the distribution of the data is approximately normal in each phase, that is, the HR values in each phase are similar, namely,

they are quite homogeneous. The values of the standard deviations correspond to the arithmetic means, in fact, the highest standard deviation is in the second phase, then the first and third are similar and the smallest standard deviation is in the fourth phase. In other words, the largest arithmetic mean has the largest standard deviation and the smallest arithmetic mean has the smallest standard deviation. Standard errors are consistent with standard deviations and indicate that no major measurement errors were present. According to the minimum and maximum values, similar distances between the minimum and maximum results can be ascertained. The largest distance can be observed in the second phase, where the distance is 57.

We have a similar distribution of results with RLX. The arithmetic mean is the largest in the fourth phase and the smallest in the third phase. The standard deviations show an approximately normal distribution of the data in each of the phases just like HR. Standard errors are consistent with standard deviations and also indicate smaller measurement errors. Here, the greatest distance can be observed in the first phase.

Table 2.*Test for homogenization of variance of the heart rate and the relaxant component.*

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
HR	36.601	3	4912	.000
RLX	123.499	3	4867	.000

According to the obtained data from the variance homogenization test in Table 2, it can be concluded that both the heart rate and the relaxant component show a statistically significant difference between the groups of respondents.

Table 3. *Analysis of variance of the values of the heart rate and the relaxant component in the four phases of the ventilation protocol.*

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
HR	Between Groups	38131.890	3	12710.630	105.410	.000
	Within Groups	592303.6	4912	120.583		
	Total	630435.5	4915			
RLX	Between Groups	30647.460	3	10215.820	236.167	.000
	Within Groups	210530.5	4867	43.257		
	Total	241178.0	4870			

After the analysis of variance on tab. no. in Table 4, it can be determined that the difference in HR values between the groups is 38.9, within the groups it is 59.7 and they show a statistically significant difference at the level of 0.00.

T-test for heart rate and relaxant component by phases

Table 4. *T-test for large dependent values of the heart rate and the relaxant component in the four phases of the ventilation protocol.*

Multiple Comparisons

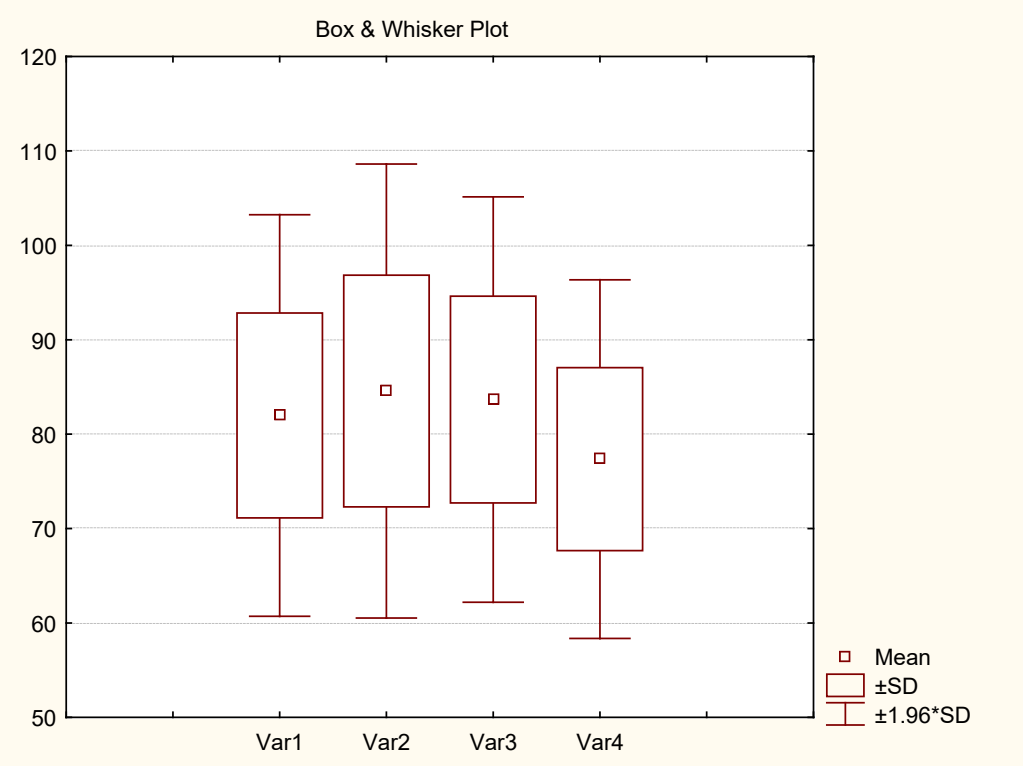
LSD

Dependent Variable	(I) VAR00001	(J) VAR00001	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
HR	1.00	2.00	-2.58950*	.44365	.000	-3.4592	-1.7198
		3.00	-1.68295*	.44444	.000	-2.5543	-.8116
		4.00	4.62334*	.44436	.000	3.7522	5.4945
	2.00	1.00	2.58950*	.44365	.000	1.7198	3.4592
		3.00	.90654*	.44164	.040	.0407	1.7723
		4.00	7.21284*	.44155	.000	6.3472	8.0785
	3.00	1.00	1.68295*	.44444	.000	.8116	2.5543
		2.00	-.90654*	.44164	.040	-1.7723	-.0407
		4.00	6.30630*	.44235	.000	5.4391	7.1735
	4.00	1.00	-4.62334*	.44436	.000	-5.4945	-3.7522
		2.00	-7.21284*	.44155	.000	-8.0785	-6.3472
		3.00	-6.30630*	.44235	.000	-7.1735	-5.4391
RLX	1.00	2.00	-3.42715*	.26572	.000	-3.9481	-2.9062
		3.00	.11201	.26620	.674	-.4099	.6339
		4.00	-5.91246*	.26863	.000	-6.4391	-5.3858
	2.00	1.00	3.42715*	.26572	.000	2.9062	3.9481
		3.00	3.53916*	.26451	.000	3.0206	4.0577
		4.00	-2.48531*	.26696	.000	-3.0087	-1.9619
	3.00	1.00	-.11201	.26620	.674	-.6339	.4099
		2.00	-3.53916*	.26451	.000	-4.0577	-3.0206
		4.00	-6.02447*	.26744	.000	-6.5488	-5.5002
	4.00	1.00	5.91246*	.26863	.000	5.3858	6.4391
		2.00	2.48531*	.26696	.000	1.9619	3.0087
		3.00	6.02447*	.26744	.000	5.5002	6.5488

*. The mean difference is significant at the .05 level.

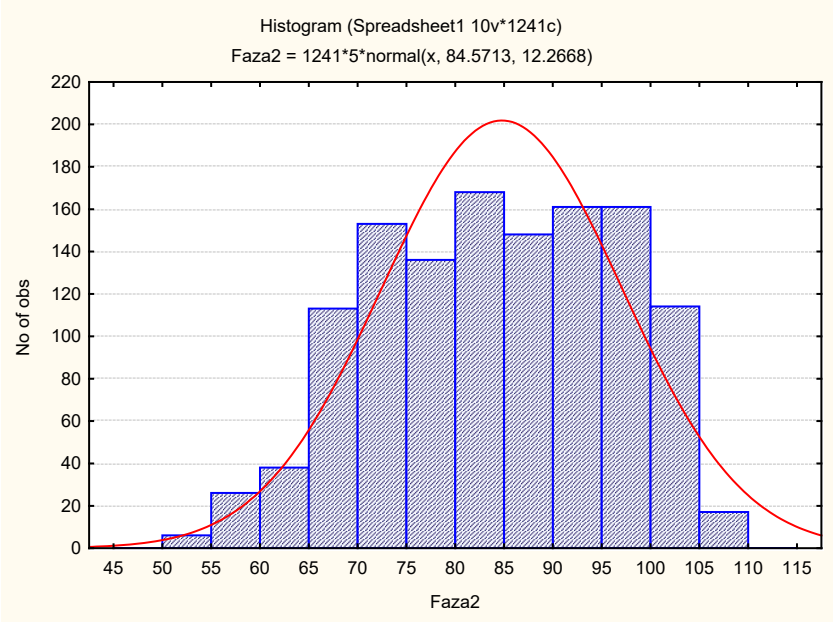
After performing the LSD test, followed by comparing the differences of the arithmetic means of HR data, it can be seen that there is a statistically significant difference between all phases of HR. While in RLX there is a statistically significant difference between all phases except between the first and the third phase.

Graph 1. *Graphic display of heart rate values in the four phases of the ventilation protocol.*

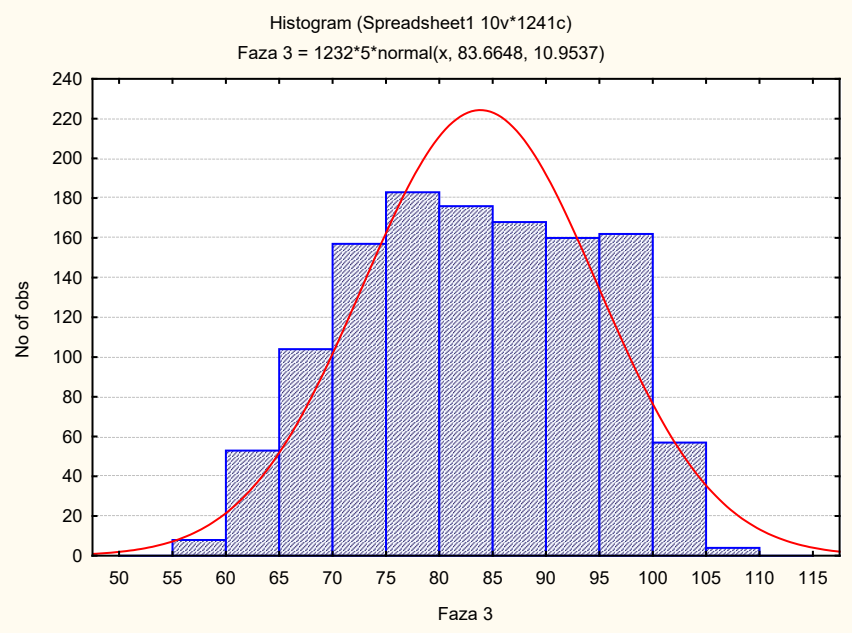


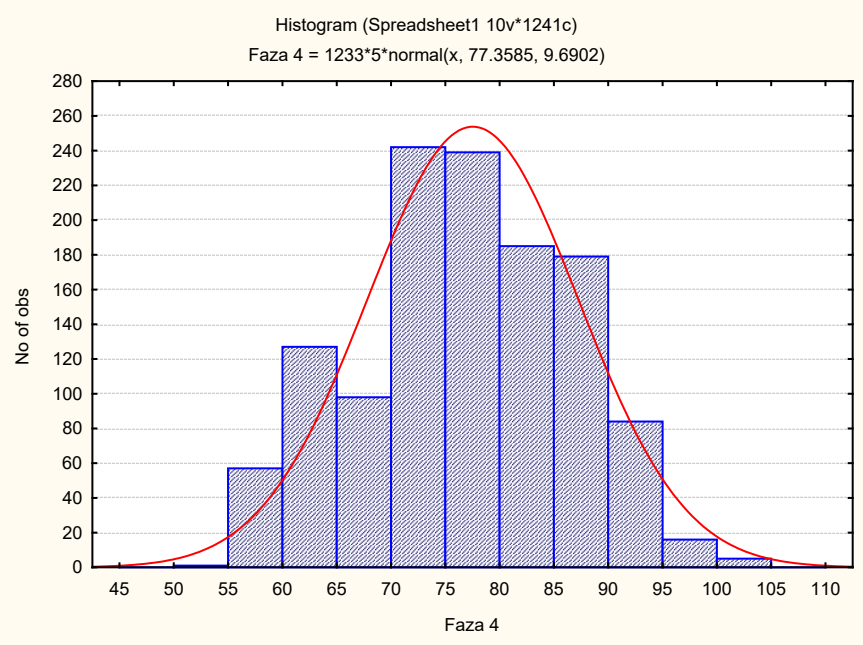
According to the obtained graphic presentation of the heart frequency, it can be seen that the arithmetic mean increases from the first to the second phase, and decreases from the third phase to the fourth phase.

Graph 2. *Histogram display of heart rate values in the four phases of the ventilation protocol.*



RLX in 1 zone N=1241, Mean=24.5455, Std. Dev.=6.82694, Min.=11, Max.=44.





From the heart rate histograms, it can be seen that the distribution of the data in the first and the fourth phase is similar, unlike the second and the third phase where we observe high values of the heart rate, so the distribution of the results by phase are as follows:

RLX in 1 zone N=1210, Mean=24.5455, Std.Dev.=6.82694, Min.=11, Max.=44

RLX in 1 zone N=1210, Mean=24.5455, Std.Dev.=6.82694, Min.=11, Max.=44

RLX in 1 zone N=1210, Mean=24.5455, Std.Dev.=6.82694, Min.=11, Max.=44

RLX in 1 zone N=1210, Mean=24.5455, Std.Dev.=6.82694, Min.=11, Max.=44

CONCLUSION

For the heart rate indicator, a significant difference was determined between the investigated phases. After performing the breathing protocols, the heart rate decreased from 81.98 beats per minute in the first phase and 77.35 beats in the fourth phase, thereby it can be concluded that these breathing protocols affect parasympathetic toning.

For the indicator of the relaxant component of the heart rate, a significant difference was also determined between the investigated phases. After performing the breathing protocols, the relaxant component decreased from 24.43 in the third phase and 30.45 in the fourth phase, which caused the toning of the parasympathetic part of the autonomic nervous system and increased heart rate variability that was investigated through this component. The obtained results justify this pilot research, which in the future should receive more complex methodological approach.

REFERENCES

1. Mihajlovski I. and Pop Petrovski V, (2007). Changes in heart rate and the relaxant component of heart rhythm after a ventilation protocol (7171/6363).
2. Pop Petrovski V. (1990). Reaction of heart rate and blood pressure code manopedalnog, pedomanalnog and centripetalnog sequence of training exercises. Master thesis. Belgrade: Faculty of Physical Culture.
3. Pop Petrovski V. (1991). Heart rate reactions during individual exercises of basic gymnastics, Specialist Paper, Sofia: National Sports Academy.
4. Pop Petrovski V, (2007). Changes in the heart rate and the relaxing component of the heart rhythm after the implementation of the prayer meditation technique (Praser, 3m. vpp). 11th Symposium on sports and physical education of young people.
5. Risteski Z. and Pop Petrovski V. (2009). Changes in the heart rate and the relaxing component of the heart rhythm after a ventilation protocol (6363 technique B).
6. Kotsev D. and Pop Petrovski V. (2009). Changes in heart rate and the relaxing component of heart rhythm after a ventilation protocol (6363/7171).

CAUSES OF ACUTE STRABISMUS

Gjoshevska Dashtevska E[1,2], Ivanova Cekov M[1], Pandilov S[1]

[1] *University Clinic for Eye Diseases, Skopje, Republic of North Macedonia,*
[2] *Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia*

ABSTRACT

Introduction: Acute strabismus is acute comitant esotropia, with an abrupt onset, a large angle of deviation, followed by diplopia. It occurs in three forms. The most of the cases have a normal neurological finding.

The etiology of acute strabismus associated with neurological symptomatology can be: malignant diseases, tumors, malformations, etc., which can appear months or even years after the appearance of diplopia.

Purpose: This paper aims to emphasize the importance of detailed investigations and long-term evaluation of patients with acute strabismus, due to the possibility of the existence of serious neurological abnormalities.

Materials and Methods: Medline and PubMed databases of medical publications were searched, entering key words: strabismus, acute strabismus and causes. More than 50 articles were obtained from the last 30 years, out of which 28 served to prepare this paper in which we present the most important insights from the literature, as well as our conclusions from the research in this branch of ophthalmology.

Conclusion: Acute strabismus is an emergency that requires careful investigation and a multidisciplinary approach. There is still no clear protocol for the evaluation of these patients. Before ruling out that it is benign decompensated strabismus, it is necessary to do: a detailed homo or heteroanamnesis, a clinical examination with monitoring of the most subtle neurological signs and symptoms that may indicate a neurological etiology, orthoptic examinations, a complete ophthalmological examination and neuroimaging.

Key Words: *acute, causes, strabismus.*

Introduction

Acute strabismus is a clinical puzzle that ophthalmologists face. Currently, there are no clear clinical guidelines on how to examine a patient with acute strabismus, whether to initially perform neuroimaging to rule out the small but serious risk of intracranial pathology, or to follow closely (1).

Acute strabismus is characterized by an acute onset of a relatively large angle of deviation, followed by diplopia.

In the evaluation of these patients who present to emergency ophthalmology departments, the primary concern is to rule out a potentially dangerous underlying condition that requires immediate intervention (1, 2).

Acute comitant esotropia is acute strabismus occurs in three forms. The most of the cases have a normal neurological finding (3-5).

On the other hand, various neurological diseases such as: tumors, congenital anomalies, malformations of blood vessels, etc. can be manifested by the appearance of acute strabismus. Clinically recognizable, such entities may appear months or even years after the onset of diplopia.

According to some authors, it is considered that one out of four children with acute strabismus who appear in the emergency department of ophthalmology has a neurological disease (2).

The presence of ptosis, papilledema, vomiting, gait disturbances, impaired consciousness, pupillary defects and involvement of multiple cranial nerves, should be considered as alarming signs (2).

Investigations of patients with this pathology should include: detailed anamnesis from the parents (beginning and course of symptoms, frequency of their appearance and presentation, past diseases and possible comorbidities, other symptoms and behavioral abnormalities), clinical examination (significantly different from that in benign entities such as chronic decompensated strabismus). A complete ophthalmic and motility examination should be performed promptly. Findings of incomitant, absence of sensory adaptations, variability in deviation and other concurrent paralysis, as well as systemic or neurological signs and symptoms, should be a signal for further laboratory tests and neurological imaging (3-5).

Of all neurological causes of acute strabismus, CNS malignancies appear as the most common cause, followed by inflammatory cranial neuropathies, cerebrovascular diseases, and demyelinating disorders. And the most common acute ocular motor neuropathy is sixth cranial nerve palsy (2, 3).

Materials and Methods

Medline and PubMed databases of medical publications were searched, entering key words: strabismus, acute strabismus and causes. More than 50 articles were obtained from the last 30 years, out of which 28 served to prepare this paper in which we present the most important insights from the literature, as well as our conclusions from the research in this branch of ophthalmology.

Causes of Acute Strabismus

Acute acquired comitant esotropia (AACE) is an uncommon presentation of esotropia that occurs in older children and adults. AACE is characterized by an acute onset of a relatively large angle of esotropia, along with diplopia and minimal refractive error (4, 5). It is not cyclical, although it can be intermittent.

AACE is classified into 3 types. Common to all 3 types is an acute onset with a relatively large angle of deviation, good binocular potential and no underlying neurological disease (6, 7).

Type 1 AACE (Swan type) occurs after eye occlusion or loss of vision in one eye, secondary to injury or disease (8, 9).

Type 2 AACE (Burian-Franceschetti type) is characterized by an acute onset of relatively large-angle comitant esotropia and diplopia. Refractive error is usually a minimal degree of hypermetropia.

Type 3 AACE (Bielschowsky type) is characterized by acute onset of esotropia in patients with uncorrected myopia of -5.00 diopters or more, possibly following physical or mental stress. Current research shows that these patients have good binocular function, which can be maintained with prisms (8-10).

Other causes of acute esotropia in adults include: sixth nerve palsy, age-related distance esotropia, divergence palsy, decompensated accommodative esotropia, decompensated monofixation syndrome, restrictive strabismus, secondary esotropia, sensory strabismus, ocular myasthenia gravis, diseases of the small brain, brainstem, pituitary gland, corpus callosum, Arnold-Chiari malformations, cerebellar disease and idiopathic intracranial hypertension. AACE is considered rare, but no statistics are available on its actual incidence or prevalence (11).

The cause of acute acquired esotropia appears to be related to the inability to maintain a balance between the converging and diverging powers of the eye, especially in patients with uncorrected myopia or after physical or psychological stress, in type 3 AACE. Recently, after the rise of the COVID-19 pandemic, it has also been associated with excessive close-up viewing, due to the increased use of computers, tablets and smartphones (12).

It can be concluded that AACE can be of diverse etiology, ranging from convergent spasm to those having severe intracranial diseases. AACE has a small but significant association with intracranial disorders. Neuroimaging is definitely needed in cases that cannot be proven to be type 1 or 2 (13).

Treatment of AACE

There are various treatments for AACE, including extraocular muscle surgery, botulinum toxin injection, prisms and orthoptic exercises. However, no standard treatment protocol has been established. Surgery of the extraocular muscles remains the main method of treatment.

Botulinum toxin injection has a good effect on AACE in adults and children. The results achieved with injected botulinum toxin are similar to those achieved with surgery (14).

Discussion

Numerous studies have been done on the association of acute strabismus with neurological conditions. Thus, in a study that includes 500 patients, in 24.3% acute strabismus was accompanied by a neurological condition, it was a case of non-isolated strabismus, and 70% of them had abnormal findings on neurological examinations. It is concluded that non-isolated strabismus

in children is a significant predictor of neurological abnormalities and requires immediate neuroimaging, as well as close observation and follow-up by an appropriate pediatric team (1).

In another study, where the frequency and cause of acute strabismus was investigated, it shows that in one out of four children who appear in the emergency department of ophthalmology, it is a neurological disease that is responsible for that strabismus (2).

One study examined the association between metachromatic leukodystrophy (MLD) and acute esotropia. Metachromatic leukodystrophy (MLD) is a fatal lysosomal storage disease characterized by progressive demyelination in the central and peripheral nervous system. Acute strabismus was identified as an early sign in patients with late-infantile MLD, with a prevalence of 27%. The onset of strabismus preceded gross motor symptoms and brain white matter abnormalities in 71% and 46% of cases, respectively. Important features were acute paralytic esotropia, partly accompanied by other eye motility abnormalities, as well as brain white matter and cranial nerve changes, as imaged by gadolinium-enhanced MRI (15).

It was concluded that acute-onset paralytic strabismus in young children should be considered a potential early sign of late infantile MLD, and may result from early cranial nerve involvement. Brain MRI with gadolinium contrast can facilitate early diagnosis (15).

Another 15-years study examined the incidence of acute strabismus, where after identifying 36 cases with the third, fourth and/or sixth cranial nerve palsy, the incidence was concluded to be 7.6 per 100,000. The most commonly affected nerve was the fourth (36%), followed by the sixth (33%), the third (22%) and multiple nerve palsy (9%) (16).

A total of forty children were examined in the study, out of which nineteen were male and twenty-one were female, aged from 5 months to 12 years (average age 5.7 years), twenty-four children complained of acute strabismus, and sixteen of diplopia. Symptoms were at first noticed hours to nine months before they called the emergency room (17). The clinical examination revealed esotropia in 12 children, exotropia in 4, pseudostrabismus in one child, paralysis of the cranial nerves in a total of 4 children, three of them with paralysis of the VI nerve and one with paralysis of the III nerve. One child also had proptosis, two had amblyopia and three had a high refractive error (17).

Fundus examination showed bilateral optic nerve edema in three children, suspected posterior pole retinoblastoma in two children, and diffuse retinal hemorrhages in one child. Further investigations revealed primary intracranial hypertension in two patients with optic nerve edema and T-cell acute lymphoblastic leukemia in a case with retinal hemorrhages (17).

Neuroimaging findings were abnormal in five children. Magnetic resonance imaging was consistent with rhabdomyosarcoma of the orbit in one case, astrocytoma of the pons, thalamus, and hippocampus in one case, cavernous sinus thrombosis in one case, and retinoblastoma in two patients (17).

The conclusion was that 55% of the children had positive clinical findings of ocular, neurological or oncological origin (17).

In the study by Erkan et al., 9 patients with acute strabismus were examined, out of which 5 were female and 4 were male, aged 20-43. None of the patients had a history of recent trauma,

occlusion of one eye or recent illness. The best-corrected visual acuity was 1.0 in all patients, with spherical correction in cycloplegia of -1.50 and +0.50 diopters. The Ishihara test was normal. Anterior segment examinations and fundoscopic examinations were normal in all patients. All patients had full duction and versions, without A or V-pattern strabismus (8).

Angles of deviation were evaluated with an alternating prism cover test, in all 9 cardinal positions of gaze. Motility, nystagmus and Lees screen test were examined, which were also normal.

These patients were initially suspected of having paresis of the lateral rectus (n. abducens), but all these investigations were normal. All patients had a large angle of curvature of 16 to 45 prism diopters, at distance and near.

In total, 8 patients were successfully treated (3 with prisms, 4 with strabismus surgery and 1 with botulinum toxin injections), while 1 patient refused treatment. Four patients were successfully treated with recession/resection and all regained binocularity on the Worth 4-point near and distance test. In three patients, binocular fusion of the 4-point Worth test was restored with prism therapy. Botulinum toxin A was administered to one patient who was unwilling to undergo surgical correction. The patient required 3 injections to normalize the Worth 4-point test (8).

It was concluded that this is an acute acquired comitant esotropia, which often resolves without neurological pathology and has a good motor and sensory outcome with surgical or non-surgical treatment. It is emphasized that in the case of nystagmus in abduction or lack of binocularity, it can be a neurological disease, so additional investigation, careful approach and long-term follow-up are needed in such patients (8).

Acute acquired comitant esotropia (AACE) is used to describe esotropia with dramatic onset and a relatively large angle of curvature with diplopia and minimal refractive error. The prevalence of acute esotropia is not known, but it is considered rare (18, 19).

Although the etiology of acute acquired comitant esotropia is still debated, it is thought to be related to excessive use of computers, tablets and smartphones.

In particular, Lee et al., documented a series of 12 teenagers with acute acquired comitant esotropia who used smartphones for more than 4 hours per day. The authors speculate that excessive smartphone use may lead to vergence abnormalities, resulting in dynamic activation of the medial rectus muscles, and thus the development of manifest esotropia. Interestingly, the exodeviation improved in all patients after abstaining from smartphone use for only 1 month. However, strabismus surgery was required in 5 patients, who had good postoperative outcomes in terms of ocular balance and stereoscopic vision (12, 20).

Tumors of the cerebellum, brainstem, pituitary region and corpus callosum may be associated to acute esotropia. Anderson and Lubow reported a patient with acute-onset esotropia who had an astrocytoma of the corpus callosum, and the esotropia resolved spontaneously after surgery and radiotherapy (21).

In one case report, a 10-years-old child with acute esotropia was described, where at the time of evaluation, the neurological finding was fixed and strabismus surgery was performed 10

months after the finding. Clinical signs of brain involvement appeared 18 months after surgery, that is, 28 months after the onset of diplopia, when medulloblastoma was diagnosed. This study emphasizes the importance of long-term follow-up of patients with acute strabismus and occasional neurological reevaluation (22).

Arnold-Chiari malformation, anomalies of the craniocervical trunk, pontine glioma, acute myeloid leukemia, etc., have been described as other related neurological diseases (23-25).

The association between acute comitant esotropia (AACE) in patients with Arnold-Chiari syndrome has been attributed to coexisting hydrocephalus. Acute comitant strabismus is also well documented in patients with intracranial tumor without hydrocephalus (23, 25).

A case of acute onset comitant esotropia with diplopia in a 5-years-old boy with diffuse pontine glioma is described. Neurological symptoms appeared 10 weeks after the first examination (26).

Hentschel et al., describe a rare case of Chiari I malformation presenting with acute acquired comitant esotropia (AACE) in a 5-years-old boy. Decompression of the posterior fossa with duraplasty and C1-2 laminectomy was performed. There was immediate postoperative improvement in esotropia, which completely disappeared 7 months after surgery (27). The literature discusses and presents the advantages of the posterior fossa decompression in certain patients, rather than strabismus surgery, as the initial treatment for esotropia in this disease. The authors suggest that in patients with AACE, even subtle symptoms and signs of Chiari I malformation should prompt imaging of the posterior cranial fossa (27).

Mott et al., describe a 15-months-old girl with acute unilateral ophthalmoplegia as a sign of acute myeloid leukemia. They believe that her presentation emphasizes the importance of appropriate laboratory and radiographic evaluation in a young child with new-onset strabismus, which can easily be overlooked as a benign finding in daily clinical practice (28).

Conclusion

Acute strabismus is still an enigma for ophthalmologists. To date, there are no clearly defined protocols for the diagnosis and follow-up of these patients. From the review of the literature, we can conclude that a very careful investigation is needed to rule out neurological signs or symptoms, especially nystagmus, diplopia, ptosis, etc. On the other hand, it is necessary to make a cycloplegic refraction, to exclude the accommodative component. If it is proven to be acute comitant esotropia, surgical and botulinum treatment have been shown to be successful. In cases where there is a neurological background of acute strabismus, which can be detected even months after the appearance of diplopia, the treatment is aimed at the primary neurological cause, and the strabismus resolves spontaneously in the most of the cases. Finally, it should be noted that in patients with acute strabismus, ophthalmic and neuro-ophthalmic diseases should be ruled out for the cause of the condition, before applying any conservative or surgical procedures for its treatment.

References

1. Chong C, Allen N, Jarvis R, et al. Ten-year review of neuroimaging in acute paediatric strabismus. Clin Experiment Ophthalmol. 2021; 49(7): 724– 728. https://doi.org/10.1111/ceo.13960.
2. Garone G, Ferro V, Barbato M, et al. Acute strabismus in neurological emergencies of childhood: A retrospective, single-centre study. European Journal of Paediatric Neurology, 2021; 32: 80-85. https://doi.org/10.1016/j.ejpn.2021.03.016.
3. Broxterman E, Ariss MM. Acute Strabismus. In: Traboulsi, E., Utz, V. (eds) Practical Management of Pediatric Ocular Disorders and Strabismus, 2016. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-2745-6_59.
4. Goldman HD, Nelson LB. Acute acquired comitant esotropia. Annals of Ophthalmology, 1985; 17(12): 777–778.
5. Clark AC, Nelson LB, Simon JW, et al. Acute acquired comitant esotropia. British Journal of Ophthalmology, 1989;73 (8):636–638. doi: 10.1136/bjo.73.8.636.
6. Baker L. Acute acquired comitant esotropia. Eye. 1999;13(5):611–612. doi: 10.1038/eye.1999.167.
7. Burian HM, Miller JE. Comitant convergent strabismus with acute onset. American Journal of Ophthalmology. 1958;45(4, part 2): 55–64. doi: 10.1016/0002-9394(58)90223-x.
8. Erkan Turan K, Kansu T. Acute Acquired Comitant Esotropia in Adults: Is It Neurologic or Not? J Ophthalmol. 2016; 2016:2856128. doi: 10.1155/2016/2856128.
9. Swan KC. Esotropia following occlusion. Archives of Ophthalmology. 1947; 37(4):444–451. doi: 10.1001/archopht.1947.00890220457004.
10. Bielschowsky A. Das Einwartsschielen der Myopen. Bericht über die Zusammenkunft. Deutsche Ophthalmologische Gesellschaft. 1922; 43: 245.
11. Hoyt CS, Good WV. Acute onset concomitant esotropia: when is it a sign of serious neurological disease? British Journal of Ophthalmology. 1995;79(5): 498–501. doi: 10.1136/bjo.79.5.498.
12. Vagge A, Giannaccare G, Scarinci F, et al. Acute Acquired Concomitant Esotropia From Excessive Application of Near Vision During the COVID-19 Lockdown. Journal of Pediatric Ophthalmology & Strabismus, 2020;57: e88-e91. https://doi.org/10.3928/01913913-20200828-01.
13. Kemmanu V, Hegde K, Seetharam R, et al. Varied aetiology of acute acquired comitant esotropia: A case series. Oman J Ophthalmol. 2012 May;5(2):103-5. doi: 10.4103/0974-620X.99373.
14. Shi M, Zhou Y, Qin A, et al. Treatment of acute acquired concomitant esotropia. BMC Ophthalmol, 2021; 21: 9. https://doi.org/10.1186/s12886-020-01787-1.
15. Beerepoot S, Wolf IN, Wehner K, et al. Acute-onset paralytic strabismus in toddlers is important to consider as a potential early sign of late-infantile metachromatic

leukodystrophy. European Journal of Paediatric Neurology, 2022; 37: 87-93. https://doi.org/10.1016/j.ejpn.2022.01.020.

16. Holmes JM, Mutyala S, Maus TL, et al. Pediatric third, fourth, and sixth nerve palsies: a population-based study. Am J Ophthalmol. 1999 Apr; 127(4):388-92. doi: 10.1016/s0002-9394(98)00424-3.

17. Kourti P, Michos A, Tsina E. Acute strabismus and diplopia in a large series of pediatric patients. Invest. Ophthalmol Vis Sci, 2017; 58(8): 2417.

18. Kothari M. Clinical characteristics of spontaneous late onset acute comitant nonaccomodative esotropia in children. Indian J Ophthalmol, 2007; 55: 117–20.

19. Lueder GT, Coats D. Acute comitant esotropia. J Pediatr Ophtalmol Strabismus. 2007; 44: 270-2.

20. Lee HS, Park SW, Heo H. Acute acquired comitant esotropia related to excessive Smartphone use. BMC Ophthalmology, 2016;16: 37. doi: 10.1186/s12886-016-0213-5.

21. Anderson WD, Lubow M. Astrocytoma of the corpus callosum presenting with acute comitant esotropia. American Journal of Ophthalmology, 1970;69(4):594–598. doi: 10.1016/0002-9394(70)91625-9.

22. Zweifach PH. Childhood esotropia with delayed appearance of cerebellar tumor. Neuro-Ophthalmology, 1981;1(4):291–293. doi: 10.3109/01658108109010251

23. Lewis AR, Kline LB, Sharpe JA. Acquired esotropia due to Arnold-Chiari I malformation. Journal of Neuro-Ophthalmology, 1996;16(1):49–54.

24. Akman A, Dayanır V, Sanaç AS, Kansu T. Acquired esotropia as presenting sign of cranio-cervical junction anomalies. Neuro-Ophthalmology. 1995;15(6): 311–314. doi: 10.3109/01658109509044620.

25. Lyons CJ, Tiffin PAC, Oystreck D. Acute acquired comitant esotropia: a prospective study. Eye. 1999;13(5): 617–620. doi: 10.1038/eye.1999.169.

26. Schreuders J, Thoe Schwartzenberg GW, Bos E, Versteegh FG. Acute-onset esotropia: should we look inside? J Pediatr Ophthalmol Strabismus. 2012 Dec 4; 49 Online: e70-2. doi: 10.3928/01913913-20121127-05.

27. Hentschel SJ, Yen KG, Lang FF. Chiari I malformation and acute acquired comitant esotropia: case report and review of the literature. J Neurosurg, 2005 May;102(4): 407-12. doi: 10.3171/ped.2005.102.4.0407.

28. Mott J, Carlson MD. Acute unilateral ophthalmoplegia as the presenting sign of acute myeloid leukemia in a 15-month-old girl. Pediatr Neurol. 2012 Nov;47 (5):366-8. doi: 10.1016/j.pediatrneurol.2012.08.007.

SARS-COV-2 INFECTION: CARDIAL AND MULTI-ORGAN INVOLVEMENT

Furnadziski A[1], Mitevski G[1], Nikolovski R[1], Nikolov I[2,5], Plashevski T[3,5], Georgiev A[1,5]

[1] *University Clinic of Cardiology, 1000 Skopje, Republic of North Macedonia*
[2] *University Clinic of Nephrology, 1000 Skopje, Republic of North Macedonia*
[3] *University Clinic of Endocrinology, 1000 Skopje, Republic of North Macedonia*
[4]*University Clinic of Traumatology, Orthopedic Disease, Anesthesiology, Reanimation, and Intensive care Medicine and Emergency Department,1000 Skopje, Republic of North Macedonia*
[5] *Faculty of Medicine, "Ss. Cyril and Methodius" University in Skopje, Republic of North Macedonia*

ABSTRACT

Background

SARS-COV-2 is a single-strain RNA virus that attacks primarily the respiratory system. The second most commonly affected system is the cardiovascular. Often it attacks multiple organ systems causing multi-organ failure. Atrial fibrillation (AF) is the most common sustained supraventricular arrhythmia in acute settings of COVID-19 infection and is associated tomore complications and mortality rates. The presence of AF in patients with COVID-19 pneumonia should be managed with increased attention to prevent adverse outcomes. COVID-19 may be a cause of multiple organ damage in some infected patients.

Aim

This case report aims to bring attention to increased follow-up and careful management in patients with COVID-19 infection and other comorbidities, especially cardiovascular.

Case Report

We present a 61 years male patient with a medical history of ablation of pulmonary veins 2 years ago because of AF and no new episode of AF after that. The patient came to the emergency department because of a collapse, swelling of inferior extremities, and hypotension. ECG was obtained and AF was diagnosed. He was tested with a rapid COVID-19 test and came out positive after which PCR for COVID-19 was taken and came out also positive. He was admitted to ICU and antiarrhythmic and anticoagulant therapy was started after which he was medically converted to sinus rhythm. A blood test was taken and came out with hyponatremia, hypoalbuminemia, hypothyroidism, and signs of rhabdomyolysis. The patient's condition was associated with a new COVID-indicated complication. In our case, a new COVID-indicated condition appears Hypothyroidism, rhabdomyolysis, and kidney involvement with

hypoalbuminemia. Consultation with an endocrinologist, infectologist, and nephrologist was made. Substitution with electrolyte, albumin, and thyroid hormone, as well as hydration was started after which his clinical condition started to improve and he was dismissed in good health.

Conclusion

AF is a frequent complication in COVID-19-positive patients. Often these patients show other complications with multiorgan involvement. Multidisciplinary approach is of crucial importance for a good outcome in these patients.

KeyWords

SARS-CoV-2,atrial fibrillation,hypothyroidism,rhabdomyolysis,kidney damage.

Introduction

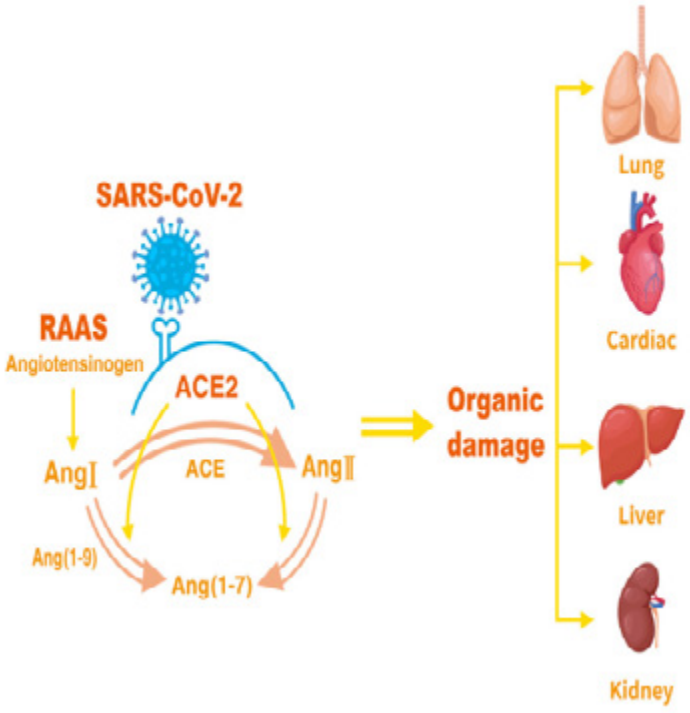
Coronaviruses are a family of single-strain RNA viruses. They can affect animals and humans. The most important for humans are SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), MERS-CoV (Middle East Respiratory Syndrome Coronavirus), and SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus 2). SARS-CoV2 causes COVID-19 (Coronavirus disease 2019) (1). SARS-CoV2 caused pandemia on 11th of March 2020. Until November 2022 there were 637,679,576 cases of COVID-19 and 6,605,406 death from COVID-19 worldwide. SARS-CoV2 has higher transmission than SARS-CoV (2). A considerable number of patients with COVID-19 how are asymptomatic which contributes to greater transmission of the virus. The most common symptoms of COVID-19 infection are fever, diarrhea, rhinorrhea, myalgia, dry cough, fatigue, ageusia, hyposmia, hemoptysis, dyspnea, and hypoxemia (3). Nasopharyngeal and oropharyngeal swabs help in virus identification with the help of polymerase chain reaction (PCR). Blood tests include lymphopenia, elevated lactate dehydrogenase (LDH), CRP, liver enzymes, ferritin, D-dimers, creatine phosphokinase, prothrombin time, troponin, and ground-glass opacity on radiological findings (4).

The most common cause of death from COVID-19 is acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndromes (MODS). MODS is a clinical syndrome in which two or more organ systems are damaged as a result of acute infection, poisoning, extensive burn or severe trauma (5). Extrapulmonary organotropism of SARS-CoV2 contributes to the involvement of multiple systems and myocardial, dermatological, gastrointestinal, neurologic, hepatic, hematology, and renal damage (3). SARS-CoV2 uses its spike to bind to Angiotensin-converting enzyme 2 (ACE2) receptors and enter the cell. ACE2 receptors are especially found in type 1 and type 2 pneumocytes (especially in type 2 alveolar cells), endothelial cells, cardiomyocytes, proximal tubule cells in the nephron, epithelial cells of esophagus and ileum, urothelial cells of the bladder (5). Renin angiotensin aldosterone system (RAAS) is important for the regulation of various functions in numerous organs especially for maintaining blood pressure, electrolyte balance, and inflammation. Renin is secreted from juxtaglomerular kidney cells and acts on angiotensinogen to convert into angiotensin I (AngI) which forms angiotensin II (AngII) and angiotensin III (AngIII) with the help of ACE. AngII increases blood pressure by

contracting smooth muscle of arteries and promoting the secretion of vasopressin and oxytocin from the pituitary gland, stimulating the secretion of aldosterone by the adrenal cortex, and this lead to increase reabsorption of water and sodium by the renal tubule. ACE2 converts AngII to Ang and AngI to angiotensin and further to Ang (1-9). Angiotensin contributes to vasodilatation, inhibition of cell proliferation, regulation of blood pressure, diuretic, and natriuretic properties (1-7). Pulmonary injury mediated by ACE2 is characterized by diffuse alveolar damage with edema and the formation of hyaline membranes. The virus enters the cells via endocytosis and this activates A disintegrin and metalloproteinase-17 (ADAM17) to split the ACE2 N terminal which results in the downregulation of ACE2 expression. Decreased ACE2 brings increase vascular permeability, destruction, and repair in the alveolar wall and diffuse alveolar damage.

The cardiovascular system is the second most commonly affected after the pulmonary system. High activity of RAAS in the heart and the production of AngII accelerate the progression of heart failure (5). Kidney injury is also mediated by the reduced expression of ACE2 after SARS-CoV-2 enters the kidney cells to inhibit its anti-inflammatory protective effect. An elevated level of Ang II concentration because of the disrupted balance between ACE and ACE2 in the injured kidney cells, is leading to further kidney damage (Picture 1).

Picture 1.*Multiorgan failure mechanism in Covid-19 patients*



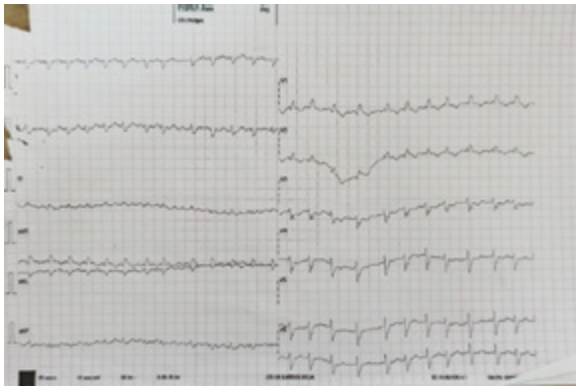
Reprinted from "The mechanism of multiple organ dysfunction syndrome in patients with COVID-19" by Wenbin Zhao, Hanmeng Li, Jianghua Li, Bin Xu, Jian Xu; J Med Virol. 2022 May; 94(5):1886-1892; 2022

MODS is caused by inflammatory cytokine storm, oxidative stress and disseminated intravascular coagulation. When SARS-CoV-2 infects endothelial cells, IL-6 is released and increases vascular permeability, and promotes the release of pro-inflammatory in the endothelial cells, enhancing the release of cytokine. This large release of inflammatory molecules eventually evolves in uncontrolled systemic inflammatory cytokine storm and MODS (3).

Case Report

A 61-years-old man presented for examination due to swelling of the lower extremities, low blood pressure and sweating. During the examination he collapsed, an ECG was performed and atrial fibrillation was diagnosed (Picture 2).

Picture 2.*ECG at admission.*



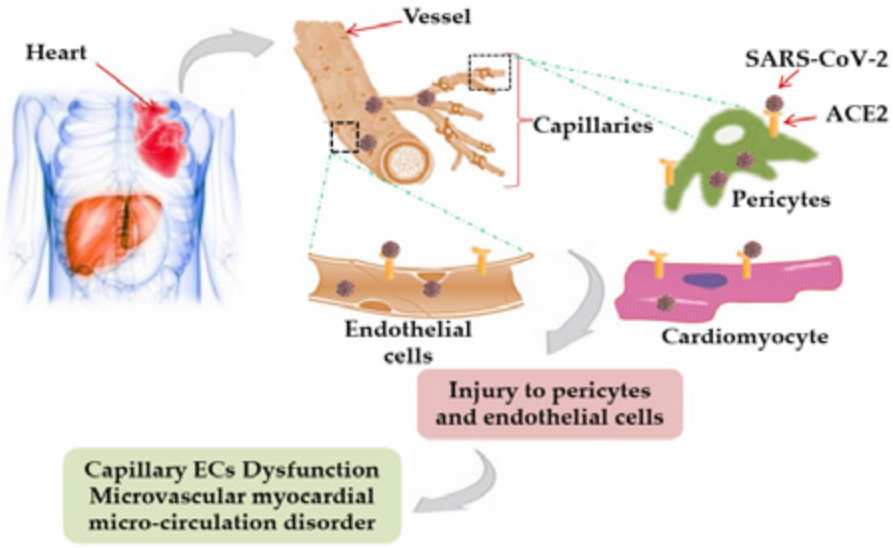
He gives information that seven days ago he had a fever that lasted for three-four days. Two days ago, he collapsed at home. He has a history of pulmonary vein ablation two years ago because of atrial fibrillation. After the procedure, he had no episodes of atrial fibrillation. He also gave information about venipuncture due to elevated values of hemoglobin and erythrocytes. Regularly takes Tbl. Acenocoumarol once daily according to the scheme with INR 2-3, Tbl. Metoprolol a 95mg S. 1x1, Tbl. Furosemide a 40mg S. 1x1/2, Tbl. Diazepam a 5mg S. 1x1 and Tbl. Digoxin a 0.25mg when needed. His blood pressure was 90/70mmHg, his heart rate was 95/min, and his SpO2 was 90% without supplemental oxygen. He was tested with a rapid COVID-19 test and came out positive. A control PCR for SARS-CoV-2 was taken which came out also positive. He was admitted to the intensive care unit. A blood test was taken and come out RBC 5.86 10^{12}/L, HGB 176g/L, HCT 0.482, WBC 21.4 10^{9}, LYMPH 5.2%, NEUT 79.5%, PLT 114 10^{9}, Troponin I 51ng/L, CRP 4.5mg/L, K 5.4mmol/L, Na 123mmol/L, Creatinin 68.4umol/L, Urea 9.9mmol/L, AST 463U/L, ALT 115U/L, creatine kinase (CK) >42670U/L, CK-MB 1452.76U/L, Myoglobin 1104.27ng/mL, IL6 54.16pg/ml, Albumins 27g/L, Total proteins 49g/L, LDH 603U/L. His arterial gas analysiswere pH 7.59, pCO2 33 mmHg, pO2 150mmHg, Lac 1.2mmol/L, HCO3 32.4mmol/L, BE 9.5mmol/L. 24-hours proteinuria was 1.15ng/L with diuresis 2.5L. Echocardiography was performed with normal ejection fraction (EF 71% M-mode) and normal heart dimensions. Treatment was started with an anticoagulant (LMWH-enoxaparin),

antiarrhythmic IV (Amiodarone), correction of electrolyte disbalance was made, substitution with albumins and plasma, antibiotic IV (Ceftriaxone) and IVhydration (with NaCl 0.9%). Consultation with an infectologist and nephrologist was made. He was medically converted to sinus rhythm. Thyroid hormones are checked and came out fT4 13.32pmol/L, T3 1.15nmol/L, TSH 13.9uIU/ml, fT3 2.25pmol/L, a-TPO 28.5U/ml, ATG 1.6IU/ml after which consultation with an endocrinologist was made and substitution with thyroid hormone (Levothyroxin) were started. The patient's condition began to improve with control blood samples taken with decreasing levels of Myoglobin 613.96ng/mL, CK 2386U/L, and normalizing of other laboratory values. He was discharged in a stable clinical condition with a recommendation for further regular cardiac, endocrinologic, and nephrological medical controls.

Discussion

Cardiac injury is common in patients with COVID-19 and this may be a secondary manifestation of systemic infection (Picture 3). The cytokines released in the inflammatory process may strengthen the myocardial injury and directly cause arrhythmias due to cellular lesions, disturbed oxygen supply unstable coronary plaques and micro-thrombosis (6).

Picture 3.*Mechanism of cardiac injury*



Reprinted from Multi-Organ Involvement in COVID-19: Beyond Pulmonary manifestations by Vikram Thakur, Radha KantaRatho, Pradeep Kumar, Shashi Kant Bhatia, Ishani Bora, Gursimran Kaur Mohi, Shailendra K Saxena, Manju Devi, Dhananjay Yadav, SanjeetMehariya; J Clin Med. 2021 Jan;10(3);446 doi: 10.3390/jcm10030446; 2021.

The thrombogenic phenomenon in AF is not only limited to local factors, but also a generalized hypercoagulable state may be present too. Similar factors like age, arterial hypertension, history of myocardial infarction, renal dysfunction, and a higher value of D- dimer acted as possible

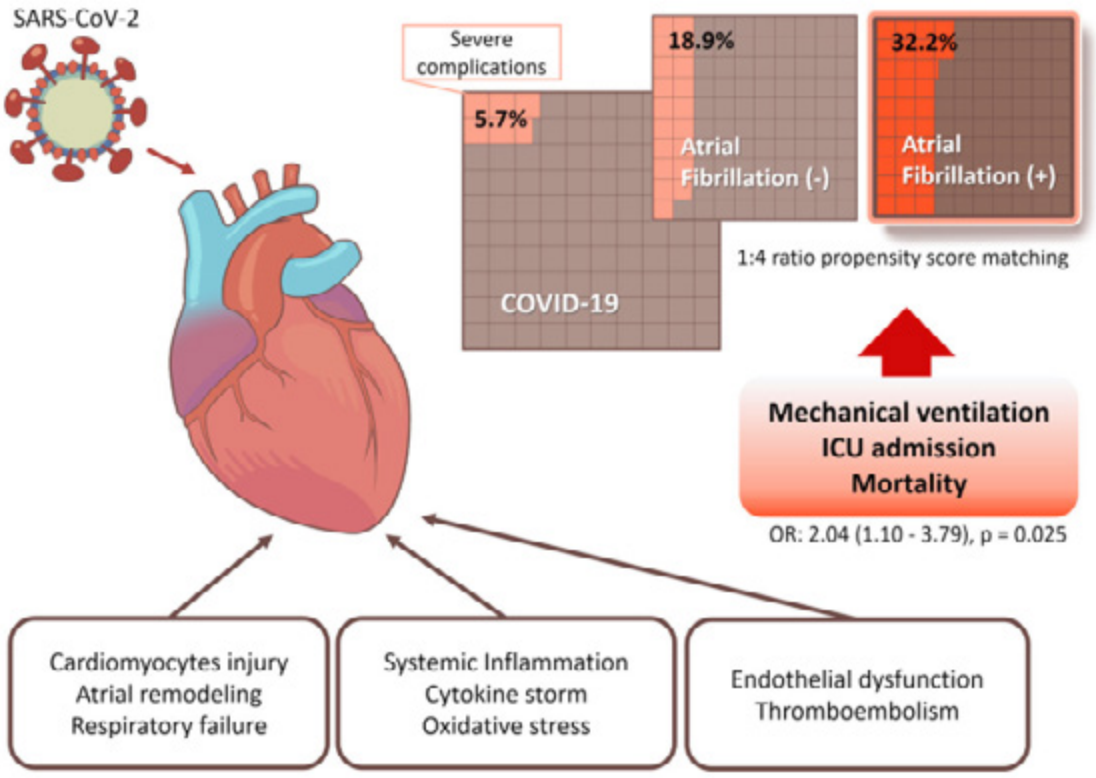
co-factors for the onset of AF in patients with COVID-19. Viral infection is one of the leading causes of myocarditis, but direct detection of the virus in the heart is rarely reported and it is the mostly confined to interstitium or macrophages. The prevalence of myocarditis in autopsy cases is less than 2%. Cardiac injury in COVID-19 cases varies between 5-40% which is unlikely to be myocarditis that has a low prevalence (7). Myocarditis associated with viral invasion may cause fatal arrhythmias. Serum cardiac troponin I levels can be used as an indicator of severe SARS-CoV 2 infection and a marker of complications caused by the infection itself. In 15,8% of COVID-19 patients, the level of hsTnI was higher than that in the normal range while the average level of his-TnI in patients who died was significantly higher than that in survivors (7). Therefore, higher myocardial enzyme profiles are a hallmark of COVID-19 heart injury and their careful monitoring is necessary to reduce COVID-19-associated complications including AF. Patients with AF are at a 2,4-fold risk higher of all-cause mortality than patients without AF (8).

Cardiac dysfunctions, such as cardiomyopathy, cardiac arrhythmias and hemodynamic instability, are known as acute COVID-19 cardiovascular syndrome (8). The presence of fever in COVID-19 patients may promote the development of LQTS by altering K+ dependence (7). Inflammatory factors acting on the peripheral pathway lead to increased left stellate ganglion remodeling, which also leads to the same result: release of a large amount of cytokines that act on the hypothalamus, leading to activation of the sympathetic nervous system via the central pathway and consequent arrhythmia occurrence (7). Transient inflammatory hypotestosteronemia is associated significantly with an increased risk of long QT syndrome and TdP (7). Intravascular volume imbalance is common in severely ill patients, and one of the most common types of arrhythmias in COVID-19 patients is AF (7). The progressive catecholamine release and autonomic nervous system dysfunction, anemia, pain, excitement, ventilator synchronization, hypoxia, hypercapnia and acidosis contribute to the arrhythmia occurrence (7). The liver is an extrapulmonary site of SARS-Cov 2 infection causing liver injury ranging between 14.8-78% and this could be either virus-related or infection-induced cytokine storm. 59.7% of the patients with COVID-19 have significant ACE2 expression in cholangiocytes (3). SARS CoV 2 enters by TMPRSS2 which facilitates its entry in the cholangiocyte and that causes direct liver injury by the accumulation of bile acids. Patients with COVID-19 exhibit a 14.8-53% probability of developing a concurrent liver injury, with abnormal serum ALT/AST levels and mildly elevated bilirubin levels (5). In severe cases, the albumin level decreased to26.3-30.9g/L, and the proportion of liver injury is significantly higher in patients with severe disease than in those with mild disease (5). Liver injury caused by SARS-COV 2 through multiple pathways mainly includes moderate steatosis, lobular and portal inflammation, apoptosis, and bile duct proliferation (5). The expression of ACE2 in hepatic duct cells is much higher than that in hepatocytes so the damage in the hepatic duct cells caused by COVID-19 infection may be more serious. ACE 2 expressions is found to be high in the bile duct cells as evidenced by elevated liver enzymes. Ablation of tight junction protein claudin 1 and down-regulation of apical sodium dependent bile acid transporter (ASBT) and cystic fibrosis transmembrane conductance regulator (CFTR) might be the contributing factors towards liver injury in COVID-19 (3). Activated virus-mediated

lymphocytes and macrophages secrets among others IL6, as seen in our case above causing hepatic injury. IL6 can directly block hERG channels in ventricular myocytes and over-activate the sympathetic nervous system (7). There is an independent association between SARSCoV2 infection and QTc prolongation IL 6 levels and QTc max in hospitalized patients with COVID-19 (10). IL6 can inhibit cytochrome P450, especially CYP3A4 which may lead to QT prolongation and increase the danger of VT. However, this is uncommon and the most often seen in the end-stage of disease progression.

Elevation of inflammation biomarkers including CRP, Il 6, and LDH can predict severe COVID-19, and at the same time, early normalization of these markers has been observed in patients with better prognoses (8). As we can see in our case, protein levels and albumin with proteinuria are affected too, as a sign of kidney injury (3-15%) by ACE2 which is predominantly found in the brush-like proximal margin of the tubules, the endothelium of the renal vessels and smooth muscle (5). ACE2 deficiency is associated with the formation of lipid peroxidation products in the kidney and the increased activation of mitogen-activated protein kinase and extracellular signal-regulated kinases 1 and 2 in the glomeruli (5). SARS CoV 2 can be directly mediated through ACE2 causing acute renal failure, tubular necrosis, Bowman's capsule protein leakage, glomerular collapse, and mitochondrial damage by decreasing ACE2 levels and its direct anti-inflammatory protective effect (5).

Picture 4. *Influence of COVID-19 infection in the outcome of AF*



Reprinted from Association of atrial fibrillation with infectivity and severe complications of COVID-19: A nationwide cohort study by Jin Park, Jae Il Shin, Dong-Hyeok Kim3, Junbeom Park, Jimin Jeon, Jinkwon Kim, Tae-Jin Song;J Med Virol. 2022 Jun;94(6):2422-2430; 2022.

Summary of possible mechanisms and the influence of AF on worsens outcomes of COVID-19

The precise mechanism of AF in patients with COVID-19 is not yet clear; general therapeutic guidelines may be considered for the treatment of such patients (Picture 4). Echocardiography should be used to assess myocardial function. it is also important to find the trigger and correct it in time. In AF patients it is necessary to determine whether it is recurrent as in our case or new onset AF (9). If it is a recurrent AF the drug interactions should be considered especially antiviral drugs with CCBS and BBC. If the cause of arrhythmia is not corrected in time, the risk of recurrence is high, so timely and targeted treatment is needed. If a medical conversion is not successful electro cardioversion should be considered (10). Intravenous amiodarone is a drug of choice for rhythm control. Drug interactions with antiviral medicines also should be considered in such patients.Thromboprophylaxis is recommended in AF patients with a CHA2DS2-VASc score of 2 or more(3 in women). The use of anticoagulation witha therapeutic dosage is not recommended in general for all patients with COVID-19 if they do not have AF or other indications. However, the incidence of embolism is higher in patients with new-onset AF (41.7%). Supportive care treatment according to the laboratory findings should be optimized. General measures for virus protection of susceptible persons are implemented as social distancing, vaccination, and teleconsultation with remote rhythm and rate monitoring enabling comprehensive AF management.SARS CoV 2 infection may increase the risk of thrombosis, and it is necessary to assess the risk of thromboembolism during and after infection recovery and to improve anticoagulant strategies (11).

Conclusion

AF, new onset and recurrent, may be one of the clinical manifestations of COVID-19-infected persons. Prompt diagnosis and management of the predisposing factors are paramount in its treatment. There are no special guidelines for the treatment of such patients and the general guidelines for AFF are applied for rate and rhythm control. Electrocardioversion should be considered in hemodynamically unstable patients and also in acute myocardial infarction and heart failure.Multiorgan damage is usual outcome of COVID-19 infection.Multidisciplinary approach is necessary in such patients and many specialists are involved in treating these patients ascardiologists,endocrinologists,nephrologists and others as were in our case.

Intravenous amiodarone is a drug of choice for rhythm control. Drug interactions with antiviral medicines also should be considered in such patients. Thromboprophylaxis is recommended in AF patients with a CHA2DS2-VASc score of 2 or more(3 in women). The use of anticoagulation witha therapeutic dosage is not recommended in general for all patients with COVID-19 if they do not have AF or other indications. However, the incidence of embolism

is higher in patients with new-onset AF (41.7%). Supportive care treatment according to the laboratory findings should be optimized. General measures for virus protection of susceptible persons are implemented as social distancing, vaccination, and teleconsultation with remote rhythm and rate monitoring enabling comprehensive AF management.

References

1. IndranillBasu-Ray, Nureddin k. Almaddah, et al. Cardiac Manifestations of Coronavirus (COVID-19); StatPearls [Internet]. Treasure Island (FL): StatPears Publishing; 2022.
2. Amir Tajbakhsh, Seyed Mohammad Gheibi, Hayat, Hajar Taghizadeh, et al. COVID-19 and cardiac injury:clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up; Expert Rev Anti Infect Ther. 2021 Mar;19(3):345-357; 2020.
3. Vikram Thakur, Radha KantaRatho, Pradeep Kumar, et al. Multi-Organ Involvement in COVID-19: Beyond Pulmonary Manifestations; J Clin Med. 2021 Jan;10(3);446 doi: 10.3390/jcm10030446; 2021.
4. Michael J. Paidas, Natarajan Sampath, Emma A. Schindler, et al. Mechanism of Multi-Organ Injury in Experimental COVID-19 and Its Inhibition by a Small Molecule Peptide; Front Pharmacol. 2022 May 30;13:864798; doi: 10.3389/fphar.2022.864798; 2022.
5. Wenbin Zhao, Hanmeng Li, Jianghua Li, et al. The mechanism of multiple organ dysfunction syndrome in patients with COVID-19; J Med Virol. 2022 May; 94(5):1886-1892; 2022.
6. Ismaheel O. Lawal, Mankgopo M. Kgatle, KgomotsoMokoala, et al. Cardiovascular disturbances in COVID-19: an updated review of the pathophysiology and clinical evidence of cardiovascular damage induced by SARS-CoV-2; BMC Cardiovasc Disord. 2022 Mar 9;22(1):93. doi: 10.1186/s12872-022-02534-8; 2022.
7. Yujia Zhan, Honghua Yue, Weitao Liang, et al. Effects of COVID-19 on Arrhythmia; J Cardiovasc Dev Dis. 2022 Sep 2;9(9):292. doi: 10.3390/jcdd9090292; 2022.
8. Jin Park, Jae Il Shin, Dong-Hyeok Kim3, et al. Association of atrial fibrillation with infectivity and severe complications of COVID-19: A nationwide cohort study; J Med Virol. 2022 Jun;94(6):2422-2430; 2022.
9. Ana Pardo Sanz, Luisa SalidoTahoces, Rodrigo Ortega Pérez, et al. New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis; Cardiol J. 2021;28(1):34-40; 2021.
10. Deesha Shah, ZaryabUmar , Usman Ilyas ,et al. New-Onset Atrial Fibrilation in COVID-19 Infection: A Case Report and Review of Literature; Cureus. 2022 Apr 7;14(4):e23912. doi: 10.7759/cureus.23912; 2022.
11. Monika Gawałko, Agnieszka Kapłon-Cies´licka, Mathias Hohl, et al. COVID-19 associated atrial fibrillation: Incidence, putative mechanisms and potential clinical implications; Int J Cardiol Heart Vasc. 2020 Oct;30:100631. doi: 10.1016/j.ijcha.2020.100631; 2020.

MRI FEATURES OF SACROCOCCYGEAL TERATOMA IN NEONATES

Ognenoska B, Stevkovski J, Pashoska M, Jovanovska Z, Kamcheva M, Dimitrijevikj K

Institute of Radiology, Skopje
PHI Zdravstven Dom Skopje, Skopje
PHI University Clinic for Pulmonology and Allergology

ABSTRACT

Magnetic resonance is a crucial imaging modality in evaluation and classification of lower lumbar region masses, in our case sacrococcygeal teratoma (SCT). Sacrococcygeal teratoma is the commonest congenital tumor in fetuses and neonates. Sacrococcygeal teratomas are derived from all three germinal layers and arise from the ventral surface of the coccyx. The American Academy of Pediatrics' Surgical Section (APPSS) classification helps in grading the extent of sacrococcygeal teratomas in four different types. The SCTs appear on MRI as hetero-signal, tumor-like masses of varying extent containing soft tissue, fat or liquid components. Treatment and further management depend profoundly on the type of SCT which is based on the exact MRI findings.

Objective

Subcutaneous tumor-like masses are routinely detected in prenatal ultrasonography, however, US as a modality for precise differentiation of these masses is not always sufficient, especially in pediatric patients. In our Case Report we point out the diagnostic purpose of postnatal magnetic resonance imaging in defining the exact type of presacral masses with a large external component, as well as the value of the findings for further management and treatment.

Introduction

Sacrococcygeal teratomas are derived from all three germinal layers and arise from the ventral surface of the coccyx. The American Academy of Pediatrics' Surgical Section (APPSS) classification helps in grading the extent of sacrococcygeal teratomas in four different types.

Sacrococcygeal teratoma is the commonest congenital tumor in fetuses and neonates. The incidence is estimated at ~1:35000-40000. There is recognized female predilection with a M:F ratio of 1:4. The sacrococcygeal region is the commonest location for non-CNS teratomas. These tumors may get enormous dimensions and contain large blood vessels that provoke blood depriving to the developing fetus. Large teratomas are highly vascular and contain significant amounts of blood which may lead to neonatal anemia and high levels of alpha fe-

toprotein (1). Almost all lesions are benign at birth, but malignant transformation becomes increasingly likely with time, and that is why an early management of the mass is crucial. The differential diagnosis of tumor-like presacral masses should include lipoma, hemangioma, meningomyelocele and myelocystocele. In our case sacrococcygeal teratoma is described by its characteristics on the neonatal MRI.

Case Report

A 6 weeks old male baby is presented to our Radiology department with the clinical findings of a large mass in the lower lumbar region. His mother, 26-years-old primiparous woman was previously referred to our Radiology Department by her obstetrician at 35 weeks of gestation after a prenatal ultrasonography exam, which was performed in a private hospital, with the findings of a presacral semi-cystic mass measuring 40x27mm in the male fetus. The prenatal ultrasonography scan, shows a well-defined, hetero-echogenic mass, with hypo-echogenic features as well as iso-echogenic compounds, which arises posteriorly from the coccygeal and lower sacral area. The mass had the following intrauterine dimensions: 40x27mm, measured in sagittal plane. No calcifications were seen. On Color Doppler imaging, it appeared highly vascular. Because the exam was performed in a private hospital, we are not able to present the findings.

Earlier in the pregnancy, the ultrasound and other prenatal exams showed no abnormalities. The patient denied any family history of genetic birth defects and disorders, alcohol or drug use during the pregnancy.

It was decided that the pregnancy should be closely monitored given the fact that the patient was due for delivery merely a few weeks after the sonographic finding.

Six weeks after the delivery, the patient was again referred to our Radiology Department for a follow up ultrasound.

The ultrasound of the mass identified an intramuscular, cystic lesion with signs of enlargement, measuring 47x32mm in sagittal plane, filled with an-echogenic content as well as small hyper-echogenic areas, smooth thick walls measuring 5mm thickness and normal vascularization.

For a better characterization and detecting the communication with local structures of the mass, our pediatric radiologist in correlation with a pediatrician, ordered a non-contrast magnetic resonance imaging (MRI) scan.

Figure 1

a. b. c.

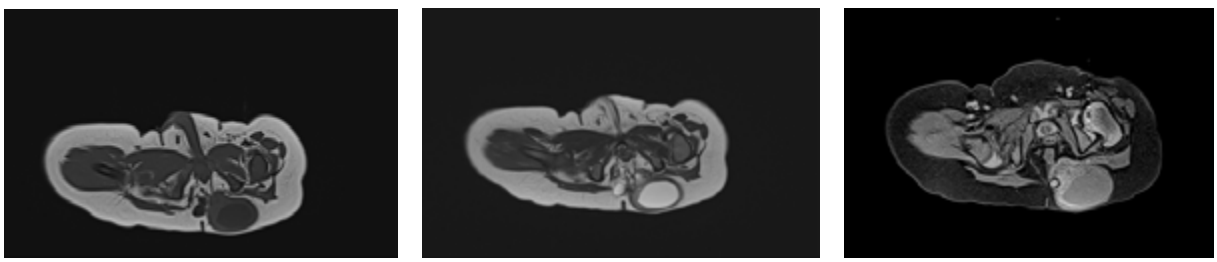


Figure 1. MRI of pelvis in neonate showing cystic, oval mass arising from the sacrococcygeal region on T1 axial plane (a) with predominantly hypo and iso signal components. T2 axial plane (b) showing hypersignal inner content with hyposignal thick wall, corresponding to fluid signal without any evidence of calcification (diamond shape showing the cystic component)

T2 fat-sat axial plane (c) showing heterogeneously enhanced cystic mass with a thick wall with a presence of fat and soft tissue components (arrow showing the solid soft tissue components).

The MRI findings confirmed the ultrasound findings, and the diagnosis was made of a predominantly subcutaneous, multi lobulated cystic mass with solid components measuring 50x38mm, arising from the sacrococcygeal region with extra pelvic and small intrapelvic components with a compressive effect on the rectum, which is ventrally migrated, but shows no association with the renal tract or spinal canal

Figure 2.

a. b. c.

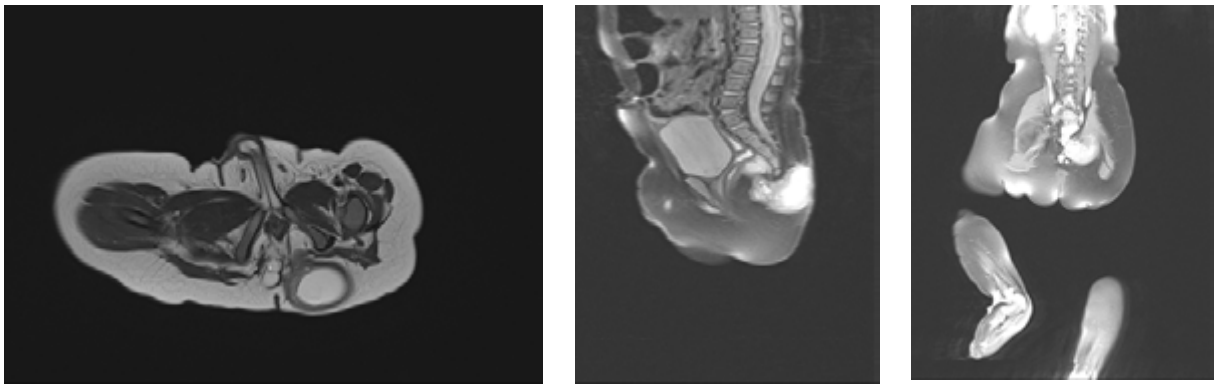


Figure 2. MRI T2 weighted images (axial, coronal and sagittal planes) showing a sacrococcygeal lobulated heterogeneously enhancing mass measuring 50x38mm. T2 axial plane (a) demonstrating the dominantly extrapelvic and small intrapelvic localization of the SCT. T2 coronal plane (b) confirming the predominant extrapelvic localization of the SCT. T2 sagittal plane (c) identifying the small intrapelvic component of the SCT.

Based on the different MRI pulse sequences signals, with the presence of hypo-signal, iso-signal, as well as hyper-signal on T1 and T2, the mass diagnostically the most likely corresponds to sacrococcygeal teratoma. Following the (APPSS) classification, because in our case the SCT has predominant external localization, we differentiated it as type I, although the MRI findings confirmed intrapelvic compounds, therefore corresponding to type II, "predominantly external SCT with significant intrapelvic extension".

Surgical resection has been proposed and the male newborn is appointed for surgery in a private hospital.

The surgery was performed successfully and the resection of the mass was sent for

histopathological evaluation, which confirmed the presence of benign neoplasm with germinal origin containing soft tissue, fluid-filed, with thick connective tissue wall, without histological alterations. All of the components are mature without signs for malignancy, which correlates with our MRI findings of a mature sacrococcygeal teratoma.

Discussion

Sacrococcygeal teratoma is one of the most common congenital tumors in newborns and infancy. It happens in 1 per 20,000 ~ 40,000 births and is more common in females (4). Classification of sacrococcygeal teratoma can be based on morphological characteristics or by their subcutaneous or intraabdominal extent. Mature teratomas are the most common in neonates (68%) and older children (73%). Immature teratomas are cystic, whereas malignant tumors are solid. Over 50% of sacrococcygeal teratomas have calcification and ossification.

The American Academy of Pediatrics' Surgical Section (APPSS) classification helps in differentiating 4 types of sacrococcygeal teratomas, as follows:

Type 1: Predominantly external with minimal presacral component.

Type 2: Present externally, but with significant intrapelvic extension.

Type 3: Apparent externally, but predominantly a pelvic mass extending into the abdomen.

Type 4: Presacral with no external presentation.

The first two types of the APPSS classification have better long-term prognosis in comparison to the remaining two, that is why it is an imperative to correctly identify the exact type of the lesion and this can be diagnostically confirmed by MRI in detail. Prognosis seems to be related not to the size of the mass, but rather to its content and extent (4). Ultrasound has its limitations as an imaging modality because of its limited field of view and variable tissue penetration, hence its findings can be non-conclusive, especially for large and giant sacrococcygeal teratomas. Diagnosis of a tumor-like mass protruding from the sacral or gluteal region with hetero-echogenic appearance is found on the prenatal ultrasound.

MRI is the modality of choice for confirmation of the diagnosis. MRI is superior to ultrasonography in the differentiation of the exact tumor extent, which helps in classification of the SCT type. The SCTs appear on MRI as hetero-signal, tumor-like masses of varying extent containing soft tissue, fat or liquid components.

Different MRI sequences help in identifying each of these components and their predominance in the lesion. The soft tissue component appears as iso signal on both T1 and T2 sequences whereas fat has a hypersignal appearance on T1 and T2 sequences and is suppressed on fat-saturation sequences. The liquid component appears as hypersignal on T2 sequences and hyposignal on T1 sequences. The vascular pattern can also be identified by using MRI sequences. Therefore, MRI is the modality of choice for classification of SCT using the aforementioned AAPSSS scale.

As any other imaging modality, MRI has its limitations, especially in pediatric patients where movement artifacts are the most frequent disadvantage which also applies in MRI exams. Other than that, contrast is contra-indicated

in neonatal MRI which can significantly limit the evaluation of blood vessels. Resection is the recommended treatment for SCT and it should be performed as early as possible after birth in order to avoid tumor rupture.

Statistically postsurgical evolution has a satisfactory results and cases remained free of disease during 36 months follow up. Some possible causal factors for recurrence include incomplete resection with microscopic residues, non all coccyx resection and tumor spread (5).

Treatment and further management depend profoundly on the type of SCT which is based on the exact MRI findings.

Conclusion

In the majority of cases, SCTs are benign masses, which are crucial to be detected in the fetal development by using proper ultrasonographic prenatal screening. Multidisciplinary approach to the diagnosis and management is of high importance. The literature suggests following alfa-fetoprotein levels, as well as regular obstetric ultrasound exams during pregnancy. Because of the non-conclusive findings of the ultrasonography, MRI is the diagnostic imaging method used to differentiate SCTs and further manage the surgical treatment.

In some cases, fetal MRI can be indicated as it overcomes the limitations of ultrasound in differentiating between different fast growing sacrococcygeal masses in the lower lumbar region.

References:

1. Firszt OP, Myga-Porosiło J, Pośpieszny K, et al. Radiological features of sacrococcygeal teratomas in fetal magnetic resonance imaging and computed tomography - a case report. Pol J Radiol. 2018;83: e19-e23. Published 2018 Jan 25. doi:10.5114/pjr.2018.74861.
2. Tuladhar R, Patole SK, Whitehall JS. Sacrococcygeal teratoma in the perinatal period. Postgrad Med J. 2000;76 (902): 754-9. doi:10.1136/pmj.76.902.754 - Free text at pubmed - Pubmed citation.
3. Roman AS, Monteagudo A, Timor-tritsch I et-al. First-trimester diagnosis of sacrococcygeal teratoma: the role of three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2004;23 (6): 612-4. doi:10.1002/uog.1055 - Pubmed citation.
4. Dedushi K, Kabashi S, Mucaj S, et al. Magnetic Resonance Imaging Verification of a Case of Sacrococcygeal Teratoma. World J Oncol. 2016;7(4):81-84. doi:10.14740/wjon965w
5. Molina Vital R, de Santiago Valenzuela JM, de Lira Barraza RC. Sacrococcygeal teratoma: case report. Medwave. 2015 May 12;15(4): e6137. English, Spanish. doi: 10.5867/medwave.2015.04.6137. PMID: 26079985.
6. Yoon HM, Byeon SJ, Hwang JY, Kim JR, Jung AY, Lee JS, Yoon HK, Cho YA. Sacrococcygeal teratomas in newborns: a comprehensive review for the radiologists. Acta Radiol. 2018 Feb;59(2):236-246. doi: 10.1177/0284185117710680. Epub 2017 May 22. PMID: 28530139.

GUIDELINES FOR AUTHORS

Macedonian Journal of Anaesthesia (MJA) is a scientific journal of the Macedonian Society of Anaesthesia (MSA) and Macedonian Society of Critical Care Medicine (MSCCM). The aim of this specialized medical journal is to speed and promote scientific achievements, novelties', clinical experience's, reviews, controversial topics in anesthesia, reanimation and intensive care, as well as other correlated medical branches.

The Journal is published four times a year (April, June, October and December), but additional supplements might be published when needed. MJA publishes original articles in basic and applied research, review articles, case studies, therapeutic and technological innovation, discussions, critics, surveys, impressions from meetings, information for international conferences and reviews of new books or variate.

Manuscripts that are published should have not been published previously. Manuscripts that have been previously published only in form of abstracts are eligible for publishing in the journal but should be followed by additional letter send to the Editor, where the abstract details are noted (abstract number, which book of proceeding or doi, date and place).

The authors are responsible for respecting the ethical guidelines for medical researches, as well as for all that is explained, attitudes, analyses and shown results.

The redaction sends the manuscripts to anonymous reviewing process from international or domestic reviewers and the Editors determine the definitive categorization of the manuscript. Once reviewed manuscript together with the reviewers' remarks is send back to the corresponding author, after what the author is omitted to deliver the final form of the manuscript to the Editorial board within one week.

Editorial board has the right to publish the manuscripts according to the reviewer's priority. The order in which the manuscripts are published does not reflect the scientific value of the article. The Editorial board keeps the rights to make changes to the manuscript to fulfil the criteria.

MANUSCRIPT PREPARATION

Manuscript should be sent together with the accompanying letter from the corresponding authors where declaration that the text has not been published previously is signed. Additional conflict of interests and confirmation by all the authors should be declared in this letter (example: Annex no. 1).

The guidelines for authors adhere to the uniform Requirements for Manuscripts submitted to Biomedical Journals: www.nlm.nih.gov.

Language and style of the manuscripts should be clear, simple to according the language, anesthesiological and medical taxonomy.

The manuscript has to be written in **English Manuscripts** should be written in **Microsoft Word** (*.doc format) with **Times New Roman** font and **size 12**. Margins on left, up and bottom should be 3 cm and right margin should be 2,5 cm.

The inline space should be 2. Do not use Bold or Italic letters for the whole text (only for parts that have to be emphasized). Manuscript should not exceed 10 pages (without the references).

Abbreviations and correct medical terms should be used according to the International Committee of Editors of Medical Journals (http://www.icmje.org). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

MANUSCRIPT SECTIONS

Manuscript should be organized in:

- Title page
- Text organized in IMRaD
- Acknowledgments
- Authors Contribution
- References

Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

TITLE PAGE

The title of the manuscript written in CAPITAL LETTERS.

Authors Surname and Name initial (Jovanov J, maximum 6 authors), without academic or other titles.

Name and address of the institution where the authors come from whit the subscribed digits

Abstract in English. Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words:** in alphabetical order.

TEXT

- Introduction
- Matherial and Method,
- Results
- Discussion
- Conclusion

Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

Introduction section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are citied and this section should not be longer than 2 pages.

Material and method sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

Title and the number of the charts and tables are placed above them while the explanations, abbreviations and comments are placed below. Images title and number is placed below and the image should include proper explanation.

Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

Conclusion section should not include more than 150 words and shoul be drown from the relevant elaborated results.

Acknowledgment and Author contributions sections are displayed after the conclusion and before the reference section.

REFFERENCES

This sections include only the citied references. **The references** are listed in order of appearance in the paper and the citation is standard numbers enclosed in small brackets in the same line with the text ( ).

For each reference if more than three authors appear provide the names of the first three authors and followed by **et al.**

1. Examples:

Journal references:

Nirmala BC, Kumari G. Foot drop after spinal anaesthesia: a rare complication. Indian J Anaesth. 2011; 55: 78 – 79.

Lynch EP, Lazor MA, Gellius JE, et al. The Impact of Posoperative Pain on the Development of Postoperative Delirium. Anesth Analg 1998; 86:781-785.

2. Journal supplements:

AzmanJ, Frkovic V, Bilic L, et al. Korelacija I regresija. Acta Med Croat 2006;60 (suppl I):81-89.| 70 |

3. Books

Brown, D.L. Spinal, epidural, and caudal anesthesia. In R.D. Miller Miller's Anesthesia, 6th edition. Philadelphia: Elsevier Churchill Livingstone; 2005.p 98-198

4. Doctoral or master thesis

Jelisavac Cosic S. Urokinazni I tkivni aktivator plazminogena i njihov inhibitor u raku dojke (Master thesis). Zagreb: Farmaceutsko-biohemijski fakultet 2004, p.50

5. Electronic reference

Dag Stat. Mackinnon A. Available from: http//www.mhri.cdu.au/biostats.Accessed May 5th 2006.

Webster NR. The anaesthetist as peri-operative physician. Anaesthesia. http://dx.doi.org/10.1046/j.1365-2044.2000.01722.x

References used from abstracts are marked as (abstr)., and from letters with (letter)

MANUSCRIPT SUBMISSION

Prepared manuscript should be submitted electronically to:
macedonianananesthesiology@gmail.com.

All manuscripts that don't fulfill the above criteria will not be accepted for reviewing

Accompany letter ANNEX no. 1

I _____. Here by declare that the article _____ (NAME OF THE ARTICLE) has not been previously published (fully or partialy) previously.

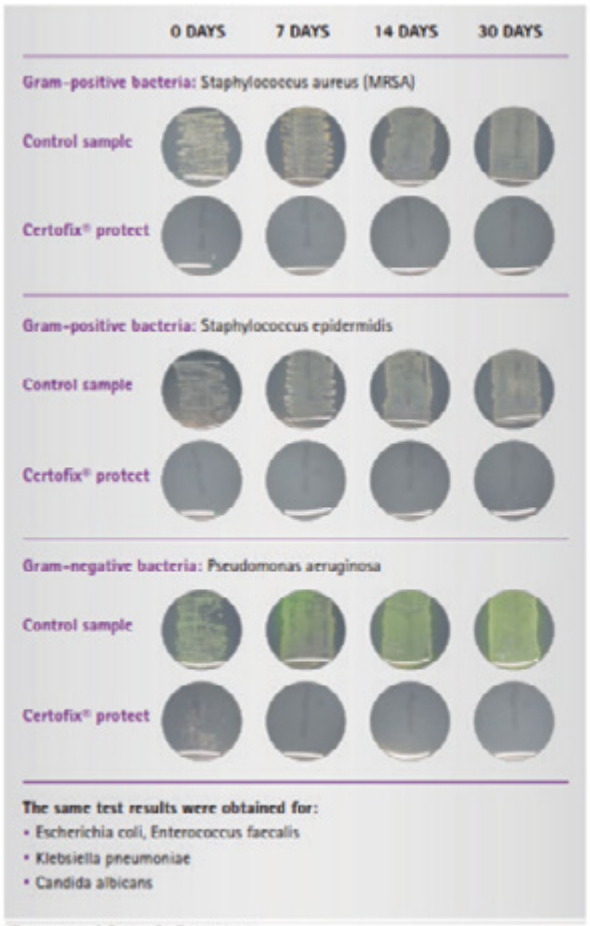
Weautors_____

_____ (FULL NAME AND SURNAMES OF THE AUTORS AND SIGNATURES) are responsible for the etic, profesional and scientific content of the study.

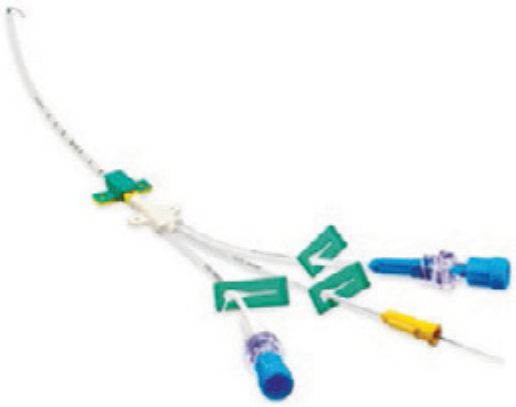
I _____ (THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

_____ (FIRST AND SURNAME OF THE CORESPONDING AUTHOR, ... (ADRESS), ..., ... (TELEPHONE NUMBER) ....., E-MAIL

B|BRAUN
SHARING EXPERTISE



Превенција на инфекции
Certofix® protect



Dr. PANOVSKI

Скупи 3 бр.55, 1000 Скопје, Р.Македонија
тел: +389 2 3093.600 • факс: +389 2 3093.610
e-mail: panovski@drpanovski.com.mk

E cacy of Certofix® protect
J. Brunke, T. Riemann, I. Roschke, 30 days antimicrobial efficacy of non-leaching central venous catheters (Poster 063), Critical Care 2016,Volume 20 Suppl 2

ВИНОРА ...Скопје, Генерален застапник и овластен сервис на... Dräger

Atlan, The new Family member in Anesthesia
Protective therapies: patient protection & patient safety

Dräger. Technology for Life®

Здружение на лекарите по
анестезија, реанимација
и интензивно лекување

MSA

Macedonian Society of Anesthesiologists
and Intensive Care Medicine

КБП

Здружение на лекари за
критично болни пациенти