

**TO THE SCIENTIFIC JURY,
ESTABLISHED ACCORDING TO ORDER № R – 492 / 04.02.2025
OF THE RECTOR OF MU - PLOVDIV**

REVIEW

by PROF. MAYA Ts. BELITOVA, M.D., PhD
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REGARDING: PROCEDURE FOR A DISSERTATION THESIS DEFENSE AND AWARDING THE EDUCATIONAL AND SCIENTIFIC DEGREE “DOCTOR” IN THE DOCTORAL PROGRAM “ANESTHESIOLOGY AND REANIMATOLOGY” IN THE 7.1 MEDICINE, IN THE FIELD OF HIGHER EDUCATION 7. HEALTH AND SPORTS, AT THE DEPARTMENT OF ANESTHESIOLOGY, EMERGENCY AND INTENSIVE CARE MEDICINE – MU PLOVDIV; ON THE TOPIC:

**“Assessment of the body fluids volumetric distribution and the effect of infusion therapy
in intensive care by bioimpedance analysis”**

I. Regarding the Procedure:

The review was prepared following Order № R – 492/04.02.2025 of the Rector of MU – Plovdiv, according to which I was appointed as an external member of the scientific jury. The review is prepared in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDSRB), the Regulations for its implementation and the Regulations for the Development of the Academic Staff in MU – Plovdiv.

In my capacity as a member of the appointed jury under this procedure, I declare that I have no general publications and/or cause for a conflict of interest subject to declaration, within the meaning of Art. 4, para. 5 of the ADSRB.

Author of the dissertation: Dr. Emral Seyfiev Kyosebekirov, full-time doctoral student at the Department of Anesthesiology, Emergency and Intensive Care Medicine, Ministry of Health, Medical University – Plovdiv. The dissertation was discussed at extended Departmental Councils (Rev. №. 7/19.06.2024 and Rev. №. 9/21.11.2024), was accepted by Faculty Councils (Rev. №. 6/26.06.2024 and Rev. №. 10/04.12.2024) and is intended for public defence.

Scientific supervisor: Prof. Chavdar Stefanov Stefanov, MD, MSc

The set of materials for the Thesis defence presented to me is in accordance with the requirements of the Law on the Development of Academic Staff at Medical University – Plovdiv and includes all necessary documents and evidentiary material.

II. Analysis of the career profile of the doctoral student.

University education and Professional experience: Dr. Kosebekirov graduated from the Medical University of Plovdiv in 2018 with a degree in Medicine. He began his career as a medical doctor at the Central Emergency Medical Station in Plovdiv in 2019, and for the period 2019-2023 he specialized in Anaesthesiology and Intensive Care at the Department of Anaesthesiology and Intensive Care of the University Hospital “St. George” in Plovdiv, where he works to this day. In 2023 he obtained a specialty in Anaesthesiology and Intensive Care.

Dr. Kosebekirov has a very good theoretical background, rich erudition and broad general culture. His scientific interests are in the field of all sections of anaesthesiology and intensive care with a strong interest in modern and innovative monitoring methods.

He is fluent in written and spoken English; he has excellent computer literacy.

Dr. Kosebekirov is a member of the Bulgarian Medical Association.

III. Significance of the topic.

One of the most difficult problems we face in our daily practice as anaesthesiologists and intensivists is: How much fluids to infuse into a particular patient? In most cases, infusion therapy, when it is well dosed, saves lives, but it is never safe and requires to be treated as a "prescription" - with the exact infusion solution, in the exact dose and time interval of administration. There are many unresolved questions that are daily faced: Is the specific patient hypovolemic? Or hypervolemic? Or is a syndrome of heart failure present? Or is the vascular permeability because of the pathological process pathologically increased and we are faced with a patient with empty circulation, but with a filled interstitium – which is the usual scenario for patients in intensive care units, after extensive surgery or in patients in critical conditions – sepsis, severe trauma, multiple organ failure? When and which of all infusion solutions should we start with? /What vascular access should we choose? How to prevent complications from sub-/or overdose of infusions? The lack of a clear answer in the scientific community to these questions, as well as the need to personalize infusion therapy for the needs of the specific patient, makes Dr. Kosebekirov's dissertation not only relevant, but also particularly significant and useful for all doctors working in intensive and emergency medicine, because it provides answers to these questions, focusing on bioimpedance analysis (BIA). This is a new method for assessing body composition and the distribution of body fluids in individual compartments, which has many advantages over conventional methods: non-invasive, does not burden the patient and staff with radiation rays, is easily performed at the patient's bedside and allows for repeated measurements and comparison over time, and is based on the application of a low-amplitude electrical impulse and measurement of tissue resistance.

In addition, the assessment of volemic and the volumetric distribution of body fluids in a particular patient is a challenge, because most often in practice it is based on surrogate indicators such as arterial pressure, pulse rate, diuresis, etc., which depend on many variables: on the method of their reading, on comorbidity, on the state of the cardiovascular system and the pathology that makes it insufficient. Therefore, Dr. Kosebekirov's dissertation is timely and significant both from a scientific and practical point of view, as it is dedicated as a whole to the study of the predictive value and application of bioimpedance analysis, with a particular emphasis on bioimpedance vector analysis, in which the parameters are not calculated, but measured, for the assessment of volemia and the volumetric distribution of body fluids, as well as the effect of infusion therapy in patients in the intensive care unit. The results obtained by the dissertation and the conclusions from the study are applicable to all patients undergoing infusion therapy.

IV. Relevance of the topic under development

Dr. Kosebekirov's dissertation thesis was conducted on an unselected cohort population of patients and is particularly relevant because:

1. It introduces a new method for assessing body composition, which expands our knowledge. There is a lack of data in the literature on the capabilities of BIA for assessing the distribution of body fluids in critically ill patients at the intensive care units.

2. It validates the results obtained, comparing them with a set of known and well-established methods in practice, thereby confirming the applicability of the method.

3. Based on the results obtained, it presents a protocol/algorithm for clinical conduct and personalization of infusion therapy, which makes the work original and relevant!

V. Structure of the dissertation

The dissertation is written on 119 standard pages, illustrated with 41 figures and 25 tables. The bibliographic reference contains 167 sources, of which 6 are by Bulgarian author teams, and the remaining 161 sources are by foreign authors in Latin. Another advantage of the work is the dating of the literary reference – twenty percent of the cited sources are from the last five years, and more than half (51%) are from the last ten years. This speaks of the importance of the topic and the attention it is receiving from the scientific community around the world.

It includes the following separate parts: bibliographic layout (title page, content, abbreviations used and introduction – 6 pages; literature review and summary – 34 pages; goal and objectives – 1 page; materials and methods, including statistical processing – 22 pages; results – 26 pages; discussion – 10 pages; conclusion – 2 pages; conclusions – 1 page; scientific contributions – 1 page; appendices – 3 pages, bibliographic reference – 10 pages, which makes its structure consistent with the requirements and standards for preparing a scientific work for obtaining a scientific and educational degree “Doctor”.

The proportion between the individual structuring parts of the work is observed.

The literature review contains sufficient material in volume, which reflects the abundance of literary data and information about scientific research on the topic to date. It is systematically presented, and all information is grouped into separate sections. The author analyses it critically, which reveals a very good knowledge of the material related to the essence of water and electrolyte balance, infusion therapy - types and applications in different clinical situations of different infusion solutions; the method of bioimpedance analysis of body composition and the distribution of body fluids, technique, characteristics of the measured indicators. The conclusion and conclusions from the literature review are logically drawn and justify the topic chosen by the author.

The exhaustive content, as well as the manner of presenting the literature review to the reader is an exceptional merit of Dr. Kosebekirov's dissertation work and I recommend its popularization, together with parts of the Methodology in the BIA presentation, among a wider audience as an independent university publication. The overall presentation of the information is clear, logical and easy to read. The rich content of the scientific facts and the information provided regarding the types of infusion solutions, the principles of application and modern methods of targeting infusion therapy in patients in shock, multiple traumas, etc., as well as the detailed description of the technical aspects of performing BIA/BIVA - are circumstances that allow its formation and publication as a separate monograph or book written on the basis of a dissertation work with great practical application to students, specialists or practicing anaesthesiologists, intensivists and emergency physicians.

The main goal of the dissertation is presented clearly, correctly and concerns the role of bioimpedance analysis for the assessment of water balance disorders and the management of infusion therapy in critically ill patients.

The tasks, 4 in total, arise from the set goal. They are formulated precisely, selected accurately, logically justified, and their solution enables the achievement of the set goal. Dr. Kosebekirov focuses on proving the applicability of BIA as a method for assessing volemic status; searching for a correlation between the volemic status determined by BIA and the outcome for the patient; developing an algorithm for personalized infusion therapy in critically ill patients.

The materials and methods used in the dissertation are classical and selected with a view to the specifics of the study. The following facts are impressive:

1. The study is prospective, cohort and was conducted on 94 patients. The methods used are Clinical observation of target parameters, such as colour, turgor and skin moisture, cognition and coherence; measurement of routine indicators of water balance (BP, CSF, diuresis, CVP, CGA, temperature, creatinine) and BIA/BIVA as all BIA measurements of volemia parameters performed within 3 hours of admission, at 24 hours, at 48 hours and at 72 hours.

2. In methodological terms, a clear and easily applicable, at the same time informative protocol has been developed for collecting the necessary demographic characteristics of the individual patient and the data obtained from the measurements of classic volemia indicators and BIA results. The compiled Clinical Card of the patient reflects this. This card is systematic, and I believe that it can be introduced into the routine practice of every doctor working in an intensive care unit and having BIA.

3. The statistical methods are selected in accordance with the type of parameters studied, and the statistical analyses are highly evidential, support the tasks set, are prepared punctually, and the analysis was performed with the SPSS.22 program.

The results obtained are presented clearly and well-structured for each aspect of the study, well-illustrated with figures and tables. Analysing critically the results obtained, the doctoral candidate establishes:

The studied patient population is heterogencous, but the paticnts are comparable; the male gender and age 64-74 years predominate; BMI in men is higher than in women, and the most common leading pathology for hospitalization of patients in the ICU is sepsis of abdominal origin, followed by TBI and Polytrauma, determining the presence of sub-/decompensated circulatory shock. The BIA indicators $TBW=48.46$ and the ratio $ECW/TBW = 0.52$, measured, show that even upon admission to the ICU, the patients are in a state of absolute deficiency of body water, but already with a pathological distribution – a significant accumulation of extracellular fluids. By the end of the study, Dr. Kosebekirov observed a tendency towards their normalization. A disadvantage of the method in critically ill patients is the reported inaccuracy and number of incorrect measurements, which led to the exclusion of patients from the initial number, due to the high sensitivity of the method.

The highest measured TBW volume and ECW/TBW ratio were reported in patients with sepsis (both at admission and by the end of the study), and the lowest values were in patients with polytrauma. The result is expected, given the pathogenesis of VEB disorders and resuscitation measures (crystalloid balanced solutions and blood products) in both nosologies. Of particular interest is the third group of patients – those with TBI, because in them both the pathological processes leading to disorders in the VER are fundamentally different – there is usually no severe blood loss, and the rules for resuscitation aimed at limiting the extracellular volume in the cranial cavity, and therefore the intracranial pressure. They had the lowest average ECW/TBW ratio, both at admission and by the end of the study. During resuscitation,

the results obtained from BIA show that the administration of osmotic diuretics leads to a decrease in the ECW/TBW ratio, but the average measured ICW volume remains high against the background of resuscitation with crystalloid solutions and an activated systemic inflammatory response.

The dissertation also establishes significant clinical benefits when monitoring the parameters of the VBIA - OHY, IR, VL, in terms of their variability in the study times depending on the intensity of resuscitation therapy, nosology and the reflection of cell damage and disruption of cell membranes, through the change in reactance in patients with polytrauma. As an integral indicator of the excess or deficiency of body water, mainly due to the extracellular space, OHY shows the most significant increase from admission to the 72nd hour in patients with sepsis, in whom the highest calculated CVP is also found.

Dr. Kosebekirov defines BIA as an extremely useful tool for targeting infusion therapy in all three groups of patients, because it reflects the compartmental distribution of body fluids. This is evident from the corresponding correlation coefficients between the individual indicators of BIA and CVP. In this regard, the author notes the lack of correlation between the CVP and CWB indicators. Also, an expected result, given the different nosology of the patients and the resuscitation methods, as a good predicative value of the indicator is given to its "low" values in terms of preload and the ratio of the capacity of the vascular system and the volume of circulating blood. The CWB indicator also somewhat reduces its value as a clinical target for conducting infusion therapy, since the patient is not a closed system: determining his real weight is difficult, *prespiratio insensibilis* cannot be measured in clinical conditions, during the hospitalization, patients acquire more and more open localizations of unaccounted losses – wounds, drains, open body cavities.

The conclusions are logically systematized, in accordance with the collected and analysed data. I accept all of them, as I believe that Conclusions 1, 4 and 5 are also original in nature, and conclusions under numbers 2 and 6 are confirmatory in nature, requiring more in-depth validation on larger patient populations in intensive care units.

VI. Contributions of the dissertation work – according to the reference for the contributions of the dissertation work, the dissertation candidate offers two contributions of a scientific-theoretical nature and three scientific-applied contributions. I unconditionally accept each of them.

VII. Abstract and publications

The abstract is prepared in accordance with the requirements of the Regulations on the conditions and procedure for acquiring scientific degrees and occupying academic positions at the Medical University – Plovdiv; it contains 52 pages and correctly reflects the essence of the dissertation work, the results obtained and the scientific contributions.

In accordance with the requirements of the Higher Education Act, the doctoral candidate submits three full-text publications in scientific journals related to the dissertation, as well as three (3) scientific communications at authoritative Bulgarian and international forums. Two (2) of the three (3) publications are in the scientific journal "Anaesthesia and Intensive Care" (2023, 2023), which is a publication from the National Reference List. These two publications are literature reviews presenting the theoretical foundations and methodology of the dissertation work. The third publication is published in a journal referenced and indexed in international databases (Scopus/WoS): "Folia Medica" (2024) and presents the actual

experimental work of the doctoral candidate. All three publications present the data from the research in the dissertation work, with Dr. Kosebekirov being the first author of both the three publications and the three scientific communications. This fact clearly speaks and is indisputable evidence of his role in the implementation of the publications and his personal participation and contribution to the process of developing the topic.

VIII. Critical notes:

1. Regarding the style of expression:

2.1. In many places in the text of the dissertation, patients are called not only "patients", but also: "persons", "persons", "patients", "men", "women"... , which is undesirable for a scientific text.

2.2. The loanword from the Russian language "level" of significance (on p. 64 of the dissertation work and p. 14 of the abstract), should be replaced with the wonderful Bulgarian word – "level" of significance.

2. Regarding the layout of the work:

2.1. Some of the comments in the presentation "Methodology", concerning the principles of bio-impedance analysis - should be moved to that part of the "Literature Review", which is dedicated to the BIA method.

2.2. The figure on page 103 of the Dissertation work - would be better if it were presented on a full page, the reader can guess about the individual indices that are not visible in this form.


I emphasize that these critical remarks do not refer to methodology, but to the style of presentation and structure of the work. Therefore, they do not belittle the essential contribution of the work - namely the introduction of a new and unpopular, but sufficiently sensitive, non-invasive, informative and easily accessible method for diagnosis, monitoring and targeting of infusion therapy of patients in the intensive care unit. Therefore, they do not affect my overall assessment and do not reduce the merits of the dissertation work.

IX. Conclusion

Dr. Emral Seyfiev Kosebekirov has mastered valuable research, methodological and clinical skills. The written dissertation shows that he can independently formulate a scientific hypothesis, correctly build a methodology and conduct scientific research, select and work with appropriate statistical methods, as well as accurately and adequately interpret the results obtained. Proof of this are the publications on the topic in prestigious journals.

All this gives me reason to vote positively for the award of the educational and scientific degree "Doctor" in the doctoral program "Anaesthesiology and Resuscitation" to Dr. Emral Seyfiev Kosebekirov - a doctoral student in independent training at the Department of Anaesthesiology, Emergency and Intensive Medicine, Ministry of Health, Medical University - Plovdiv.

28.03.2025
city of Sofia


Заличено на основание
Чл.5 §1, 6."В" Регламент (ЕС)2016/679
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/Prof. Maya Ts. Belitova, MD, PhD/