REVIEW

of a dissertation for the acquisition of an educational and scientific degree

"doctor" in the scientific specialty "Pediatric Cardiology"

on the topic: **"ECHOCARDIOGRAPHIC PREOPERATIVE ASSESSMENT OF PATIENTS WITH COMPLETE ATRIOVENTRICULAR SEPTAL DEFECT"**

Author: **Dr. Zornitsa Nikolova Vasileva**

Research supervisor: **Prof. Dr. Anna Kaneva, MD**

Reviewer: **Assoc. prof. Dr. Petar Shivachev, MD**

Department of "Pediatrics",

MU "Prof. Dr. Paraskev Stoyanov" Varna

This review was prepared according to Order No. 343 of 10/21/2022 of the executive director of MBAL "National Cardiology Hospital" EAD and on the basis of the materials presented by the doctoral student: dissertation, abstract, report on the contributions and publications on the topic of the dissertation work.

1. Relevance of the problem addressed in the dissertation and its scientific and practical significance

The thesis proposed for review concerns an area that is undoubtedly debatable, and the problem is not sufficiently well studied on a global and national scale, especially in a practical aspect. In this sense, the choice of the topic is relevant and necessary.

Complete atrioventricular septal defect (CAVSD) is a complex congenital heart malformation (CCM) occurring in 3.5 per 10,000 live births, comprising a spectrum of morphological changes, often associated with other anomalies. There is a balanced form, in which the common atrioventricular valve is located evenly between the two cardiac ventricles, and an unbalanced form, in which it is connected primarily to one of the ventricles, more often to the right one, while the other ventricle remains hypoperfused and hypoplastic. Echocardiography plays a leading role in the preoperative evaluation of the anomaly and in the selection of the operative strategy, as forms with a borderline degree of imbalance and borderline dimensions of the left ventricle represent a serious problem. In case of incorrect judgment, the performance of two-ventricle repair in these cases most often ends fatally.

Many echocardiographic criteria have been described for distinguishing the balanced from the unbalanced forms of CAVSD, but the problem is not definitively resolved on a global scale and a well developed diagnostic algorithm is still lacking.

In this regard, it can be concluded that the topic of the dissertation is successfully chosen, contemporary, with scientific significance and great practical application. In developing it, the dissertation student shows good theoretical preparation and analytical abilities. The dissertation is written in scientific language, with appropriate terminology and a very good style.

2. Degree of knowledge of the state of the problem and creativity;

interpretation of literature

The PhD student has used a total of 142 literary publications, of which 9 in Cyrillic and 133 in Latin. Literary sources have been used in good faith and correctly, and some of them are cited in the text of the dissertation, which makes it possible to highlight the personal contribution of the doctoral student. The bibliographic reference is sufficiently varied and rich to carry out an in-depth scientific study of the subject.

In her research, Dr. Zornitsa Vassileva has used scientific publications in Bulgarian and English, as well as Internet sources. The bibliographic reference gives reason to conclude that the selection and scope of the used legislative sources and scientific literature are an indisputable prerequisite for in-depth research on the subject of a scientific and applied nature. The choice of scientific publications, the style and analytical nature of the dissertation work, allow us to conclude that the doctoral student is well-acquainted with the scientific achievements in the research field, systematizes known scientific results, synthesizes scientific theses, highlights and formulates unsolved problems.

3. Brief analytical description of the dissertation work

The dissertation submitted for review has a volume of 148 pages and is structured as follows: introduction - 2 pages, literature review - 47 pages, aim and tasks of the research - 1 page, material and methods - 9 pages, results presented by tasks - 52 pages, discussion - 6 pages, inferences - 1 page, conclusion - 1 page, self-assessment of the contributions of the dissertation work - 1 page, bibliography - 15 pages, appendices - 4 pages, used abbreviations - 1 page. The content of the chapters is divided into separate paragraphs, and at the end, specific conclusions are made, which present the results of the research, summaries and assessments of the issues under consideration.

The main text contains 38 figures and 36 tables, which are appropriately formatted. The structure of the dissertation work is classic and meets the requirements for this type of research.

In the introduction, the doctoral student presents the relevance and significance of the topic (p. 6), the research problem (pages 54, 55), formulates the purpose and tasks of the research (p. 56), defines the object of research and the methodology (pages 57-65), as well as the statistical methods used (pages 66, 67).

The object and subject of the dissertation work are correctly specified.

The formulated **research goal** - the development of an algorithm for reliably distinguishing balanced from unbalanced forms, based on a detailed and standardized preoperative echocardiographic assessment of CAVSD, including systematic measurements of pre-set parameters, is correctly defined and corresponds to real achievements, shown in the dissertation.

The tasks of the dissertation work are precisely and comprehensively defined, related to:

1. Formation of a sample of patients with CAVSD who were admitted at the Pediatric Cardiology Clinic of the National Cardiology Hospital (NCH) in the period 01.01.2014 - 31.12.2021 and description of their demographic characteristics, determination of anatomical features of CAVSD and the accompanying abnormalities from the echocardiographic examination.
2. Description of the clinical outcome in the entire group of patients - operated (two-ventricle or single-ventricle repair), non-operated, ending with a fatal outcome, as well as assessment of the correspondence between echocardiographic and intraoperative or autopsy findings.
3. Measurement of predefined echocardiographic indicators in the retrospective group, statistical processing of the results and identification of the parameters that differ significantly between the groups with balanced and unbalanced CAVSD.
4. Carrying out the protocol-specified echocardiographic measurements in the prospective group, combining the measurements in the retrospective and prospective groups and statistical analysis of the results, development of an echocardiographic algorithm for distinguishing between balanced and unbalanced forms of CAVSD.
5. Evaluation of the application of the developed algorithm.

The formulated **research thesis** is mainly related to the fact that the application of a complex of echocardiographic measurements in an algorithm leads to a more accurate determination of the type of CAVSD and the choice of a correct operative strategy.

The doctoral student presents the obtained **results** according to the assigned tasks with a subsequent discussion.

According to task 1, the demographic structure of patients with CAVSD is analyzed - anatomical characteristics, balanced or unbalanced form of the defect, age at diagnosis, gender, presence of trisomy 21 and accompanying cardiac anomalies, looking for relationships between individual indicators. Attention is paid to the prenatal diagnosis of the anomaly, which still has a low sensitivity in Bulgaria.

According to task 2, the clinical outcome of patients with CAVSD - who underwent two-ventricle repair, awaiting surgical intervention, with single-ventricle repair at a different stage and ended with a fatal outcome - is examined. Two of the patients with unbalanced CAVSD in whom dual-chamber correction was incorrectly performed died. The statistical analysis shows that the mortality rate in patients with an unbalanced form is significantly higher than in those with a balanced form, and in 40% of cases, the mortality is due to inappropriate undertaking of two-ventricle repair. No significant discrepancies were found between the echocardiographic and intraoperative or pathoanatomical findings in the autopsied deceased children. The relationship between individual preoperative echocardiographic findings and patient outcome was analyzed in view of an increased risk of adverse outcome.

According to task 3, the predefined echocardiographic parameters were measured in the patients from the retrospective group, which include: ratio between the long axes of the left and right ventricles (LV/RV long axis), ratio between the diastolic dimensions of the left and right ventricles (RV/LV diastole), diameters of the left and right halves of the atrioventricular (AV) valve (z-score LAVV and z-score RAVV), angle of the inflow of blood in the right and left ventricles (RV/LV inflow angle), AV septal angle (AVs-angle), AV valve index (AVVI), modified AV valve index (mAVVI), indexed ventricular septal defect (inVSD), inflow through the left AV valve (LAVV inflow). The statistical analysis of the obtained measurements found significant differences between the groups with balanced and unbalanced CAVSD regarding: LAVV Z-score, LAVV/RAVV ratio, inflow index and inVSD. Correlation analysis showed a statistically significant relationship with diagnosis for the following echocardiographic parameters: z-score RV, z-score LAVV, z-score RAVV, RV/LV inflow angle and inVSD. Linear discriminant functions were developed for balanced and unbalanced CAVSD, and testing them as an index in the retrospective group showed correct classification in 95.5% of cases.

According to task 4, echocardiographic parameters were measured in the prospective group. A combined statistical analysis of the measurements in the prospective and retrospective groups was performed. The following echocardiographic parameters were identified that were statistically significantly different between balanced and unbalanced CAVSD: LV/RV inflow angle, AVVI, mAVVI, inVSD and LAVV inflow. Based on the above analyses, an algorithm (scoring-system) was developed to distinguish the balanced from the unbalanced forms of CAVSD. With a result <-1.273, the patient falls

into the group with unbalanced CAVSD, with a result > -1.273 - into the group with balanced CAVSD, and with the result equal to -1.273, the diagnosis cannot be determined. A link to access the score system is also provided.

According to task 5, an evaluation of the results of the application of the developed algorithm was carried out. A high degree of reliability is considered when distinguishing between balanced and unbalanced forms of CAVSD. The doctoral student correctly emphasizes that the result is not absolute, but the anatomical details and associated abnormalities in each specific patient must be taken into account.

In the **discussion**, it is emphasized that according to the data from the literature and those of the doctoral student, it is not possible to determine the form of CAVSD - balanced or unbalanced, based solely on one echocardiographic measurement, but the use of a complex of parameters is necessary. An important advantage of the created score-system is that it allows, on the basis of a small number of relatively easy-to-perform echocardiographic measurements, to determine the shape of AVSD, including parameters reflecting different aspects of the balance.

The **abstract** is compiled according to the requirements and correctly reflects all the main parts of the dissertation. In terms of content, the contributions indicated in the abstract reflect objectively the achievements of the doctoral student.

Doctoral student Zornitsa Vasileva published three **publications** in Bulgarian publications on the problems treated in her dissertation.

4. Summary of strengths of the dissertation work

The most significant positive aspects of the dissertation work are the following:

1. The dissertation deals with current and significant issues. Based on the literature data and his own research, the doctoral candidate developed a protocol for echocardiographic differentiation of unbalanced from balanced forms of CAVSD with a high degree of reliability, which is of crucial importance for determining the operative strategy.

2. The dissertation is very informative and demonstrates the author's rich awareness of the issues presented in the analysis. The logical sequence of the exposition allows the author to argue his conceptual thesis.

3. In the introduction, the topicality of the topic is adequately commented, the research problem and the thesis of the study are formulated. The subject, object, purpose and tasks of the dissertation research are correctly defined.

4. The PhD student knows the problem in depth. The dissertation is based on a wide range of researched scientific sources. The author demonstrates analyticity and conceptuality.

5. The doctoral student shows indisputable research skills - she is well-acquainted with the subject and highlights the unsolved problems of the researched issue.

6. The results achieved in the course of the dissertation research have been practically approved.

5. Scientific and scientific-applied contributions

The dissertation research has scientific and scientific-applied contributions in the following areas:

1. The study of a wide range of literary sources allows the doctoral student to systematize the existing methods for echocardiographic analysis of AVSD, as well as the trends in their development.

2. The dissertation is the first systematized study of pediatric patients with AVSD conducted in Bulgaria, covering in detail the anatomical and echocardiographic characteristics of the malformation, as well as the outcome of surgical treatment.

3. Based on detailed echocardiographic measurements of a number of parameters and in-depth statistical analysis, an algorithm was developed to qualify CAVSD as balanced or unbalanced with a high degree of reliability. It is based on a relatively small number of echocardiographic parameters, which makes it easily applicable and reproducible in clinical practice.

4. The developed protocol for preoperative echocardiographic assessment of CAVSD and score- system are the basis for prospective validation in a larger number of patients.

I consider that the mentioned contributions are the personal work of the doctoral student, which she achieved alone and without personal interests, with the assistance of her supervisor.

6. Publications on the dissertation work

Three publications of the doctoral student on the dissertation are indicated, which are sufficient and present the main points of the dissertation. It is clear that the PhD student's ideas and scientific achievements have received public recognition and are being used by the scientific community.

CONCLUSION

The dissertation proposed for review on the topic **"Echocardiographic preoperative assessment of patients with a complete atrioventricular septal defect"** is the personal work of PhD student **Dr. Zornitsa Nikolova Vasileva**. The abstract is correctly composed as a development, layout and presentation of the scientific achievements and contributions. The publications correspond to the topic and content of the dissertation work. The dissertation research was developed in accordance with the requirements for the acquisition of the educational and scientific degree "doctor" of ZRASRB, and the Regulations for its application. Dissertation work has a completely finished form. It demonstrates current scientific and applied achievements, which represent a contribution to the practical solution of a wide range of problems related to the preoperative assessment of patients with CAVSD and the choice of an operative strategy. All the required criteria are fulfilled and I categorically declare my positive assessment of the dissertation research of Dr. Zornitsa Vasileva.

In conclusion, I strongly suggest that the respected scientific jury awards Dr. Zornitsa Vasileva the educational and scientific degree "doctor" in the scientific specialty "Pediatric Cardiology".

January 12, 2023,

Reviewer:

/Assoc. Prof. Dr. Petar Shivachev/