

REVIEW

on behalf of

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Subject:

Doctoral thesis entitled:

**„ECHOCARDIOGRAPHIC PRE-OPERATIVE
ASSESSMENT OF PATIENTS WITH COMPLETE
ATRIOVENTRICULAR SEPTAL DEFECT” for conferment of
educational and scientific degree “PhD” in professional area 7.1.
“Medicine”, scientific specialty „Pediatric cardiology” in higher
education field 7. “Healthcare and sports” of Dr.Zornitsa Nikolova
Vassileva-Enikova, doctoral student of independent training at the
Pediatric Cardiology Department, National Heart Hospital, Sofia.**

**Order № 343/21.10.2022 of the Executive Director of the
National Heart Hospital for the appointment of a scientific jury.**

I. Relevance of the dissertation

The topic of the dissertation is relevant and extremely useful in scientific and practical aspect.

The doctoral thesis of Dr.Zornitsa Vassileva addresses an important diagnostic problem which is crucial for the optimal surgical outcome in patients with one of the frequent congenital heart defects – Complete atrioventricular septal defect (CAVSD).

CAVSD is a congenital malformation with different pathomorphological characteristics (balanced and unbalanced forms with right or left dominance) whose diagnosis relies entirely on echocardiography. The role of preoperative echocardiography is precise classification of the CAVSD type which is of outermost importance for the choice of optimal surgical strategy.

The problem with echocardiographic differentiation of balanced and unbalanced forms of CAVSD is relevant, and the search of

sensitive criteria for their definition is still ongoing. The borderline forms of CAVSD are the most challenging ones, as the clinical outcome depends on the ability of the left ventricle to support the systemic circulation after biventricular repair. The doctoral thesis of Dr. Vassileva proposes an algorithm for accurate classification of CAVSD as balanced or unbalanced, which gives her work great clinical significance.

II. Structure of the dissertation

The dissertation of Dr. Vassileva is presented on 145 pages in a classical way including: 2 – introduction, 47 – literature review, 2 – purpose and tasks, 11 – materials and methods, 49 – results, 6 – discussion, 12 – conclusions and contributions, 11 – bibliography with 142 sources, 9 of them in Bulgarian, 4 – appendices. Good scientific language, accurate interpretation of the data and the conclusions.

a) Literature review

The literature review demonstrates excellent knowledge of this congenital heart defect: embryological development, anatomical characteristics, classifications, diagnostic methods, focusing on the anatomical and physiological features of balance.

The author has conducted a comprehensive search of the available scientific literature on the topic. Detailed review of the echocardiographic measurements and of surgical strategies by CAVSD has been performed.

Based on the data from the published trials (most of them retrospective, with small number of participants), the author summarizes the most important points of each of them and identifies the unsolved problems which are grouped in several conclusions:

- The problem whether the patient would be able to tolerate biventricular repair as the incorrect choice of surgical strategy is associated with increased mortality.
- The accurate classification of the defect and the choice of the most optimal surgical strategy require utilization of a complex echocardiographic algorithm. Even though different measurements for assessment of the balance by CAVSD have been proposed, an algorithm

facilitating the diagnosis and the choice of the optimal surgical strategy is still lacking, especially by the borderline forms.

All this justifies the conducted study. The definition of the purpose and the tasks of the doctoral thesis arise from the conclusions of the literature review.

b) Purpose and tasks

The purpose of the dissertation is creation of an algorithm for reliable differentiation between balanced and unbalanced forms of CAVSD based on a detailed and standardized preoperative echocardiographic assessment.

In order to fulfill this purpose the doctoral student has 5 clearly defined tasks:

- Selecting a group of patients with CAVSD admitted at the Pediatric cardiology department during the period 1.1.2014 - 31.12.21
- Description of the clinical outcome – operated, unoperated, lethal outcome
- Measurement of a group of predefined echocardiographic parameters by the retrospective group as well as measurements according to a protocol by the prospective group. Statistical analysis of the results and identification of the parameters with significant differences between the balanced and the unbalanced form of CAVSD
- Integration of the measurements by the retrospective and the prospective groups with creation of an algorithm for differentiation between the balanced and the unbalanced form of CAVSD
- Evaluation of the application of the proposed algorithm

c) Methods

The study includes 100 patients with CAVSD who have been admitted to the Pediatric Cardiology Department of the National Heart Hospital during the period 2014-2021 year.

For the purpose of the trial the doctoral student has examined 64 patients in the retrospective part of the trial, 44 of them were with

complete measurements and 42 underwent surgical treatment. The second subgroup includes 36 patients in the prospective part who are with complete measurements, 26 of them operated upon.

The data from the systems GlobalHis и BIS have been used for the retrospective part. The echocardiographic measurements have been performed offline on the saved in the system SyngoPlaza echocardiographic images and video clips. The clinical outcome has been followed up to day 30 after the last surgical intervention.

The protocol of the echocardiographic examination includes the following obligatory parameters which are well illustrated in the dissertation:

1. Ratio between the long axes of the left ventricle and the right ventricle from apical four-chamber view
2. Ratio between the diastolic dimensions of the left and the right ventricle from parasternal short-axis view
3. Diameters of the left and the right AV-valve
4. Right ventricle/left ventricle inflow angle
5. Atrioventricular septal angle
6. Atrioventricular valve index - the smaller divided by the larger valve surface area
7. Modified atrioventricular valve index – the left AV-valve area divided by the common AV-valve area
8. Indexed ventricular septal defect – the ratio between the size of the VSD and the common AV-valve diameter
9. Left AV-valve inflow – the ratio between the diameter of the color Doppler jet at the level of the papillary muscles (secondary annulus) and the diameter of the left AV-valve (primary annulus)
10. The degree of AV-valve regurgitation has been defined based on the vena contracta diameter and the ratio between the area of the regurgitation jet and the atrial area

The information regarding the conformity between the echocardiographic and the intraoperative findings and the type of surgical strategy – biventricular repair, single ventricle circulation, has been obtained from the operative protocols, and by the patients with lethal outcome the anatomical details have been retrieved from the autopsy protocols.

Contemporary statistical analysis has been performed and the statistical methods have been optimally chosen and allow answering the predefined tasks. Statistical software IBM, version 22 of SPSS (Statistical Package for Social Science) has been used.

The following statistical methods have been utilized: Student's t-test, Mann-Whitney U-test, as well as correlation and discriminant analysis. The sensitivity and specificity of the identified through discriminant analysis echocardiographic measurements for differentiation of the balanced from the unbalanced forms of CAVSD have been determined through analysis of the ROC-curve.

d) Results and ensuing conclusions:

The results from the study are very well illustrated with tables and figures and are didactically presented for each task separately. Their presentation is followed by analysis and comparison of the data with those of other centers published in the scientific literature.

Task 1

The author emphasizes that CAVSD is an anomaly with a high percentage of prenatal diagnosis which in our country is suboptimal. According to the obtained data, in 66% of the cases no prenatal diagnosis was performed. Regarding the anatomy of the defect, the associated anomalies and the degree of the AV-valve regurgitation, the data correspond to those in similar clinical centers in other parts of the world.

Task 2 – clinical outcome

Out of 89 children who underwent surgery, in 14 there was discrepancy between the echocardiographic and the intraoperative findings, and the failure to recognize the unbalanced form is associated with the most unfavorable outcome (in 2 children). The author underlines the need for complex analysis – not only of the sizes of the ventricles but also of the two halves of the common AV-valve and of the size of the ventricular septal defect.

The detailed analysis of the mortality data shows that they are comparable with those reported in the scientific literature with significantly higher mortality by patients with unbalanced forms of CAVSD.

Task 3 – echocardiographic parameters by the retrospective group

The author finds a significant overlap between the values of the different echocardiographic measurements by the balanced and the unbalanced forms of CAVSD. The measurements by the larger part of the retrospective group are incomplete (there are no patients with measurements of the inflow angle, the atrioventricular septal angle and the indexed VSD). Based on three stages of statistical analysis – Student's T-test, correlation and discriminant analysis, the author identifies 3 parameters with significant differences between the groups with balanced and unbalanced CAVSD. The discriminant function for balanced and unbalanced CAVSD has been calculated for each patient and the results from the application of the model by the retrospective group with intraoperatively confirmed diagnosis show that 95% of the cases are accurately classified.

Tasks 4,5 – echocardiographic parameters by the prospective group and unified data

Again, the author finds a significant overlap between the echocardiographic measurements by the balanced and the unbalanced forms of CAVSD.

After statistical analysis of the unified data by the retrospective and the prospective the author finds significant differences in the following parameters: right ventricle/left ventricle inflow angle, atrioventricular valve index, modified atrioventricular valve index, indexed VSD, left AV-valve inflow. The conducted Fisher's linear discriminant analysis with adaptation of the created for the retrospective group formula (through adding the parameter left AV-valve inflow, which is an indicator of the redistribution of blood flow), allows the creation of a score-system which accurately differentiates the balanced from the unbalanced form of CAVSD in 97% of the cases.

After inserting the values of four echocardiographic measurements (right ventricle/left ventricle inflow angle, ratio between the long axes of the right and the left ventricle, atrioventricular valve index, left AV-valve inflow), the system gives the most probable diagnosis. After reviewing several cases with borderline forms of CAVSD the author establishes that the predictive model is not absolute and should be considered in combination with the associated anomalies and the anatomical details by each patient.

The obtained results enable Dr.Vassileva to make logical conclusions.

I agree and accept the formulated conclusions and contributions of the dissertation.

Critical notes and recommendations:

I think that the work would benefit of making an analysis of the intra- and interobserver variability of the echocardiographic measurements. Human interpretation of transthoracic echocardiograms is operator dependent even when the measurements are performed by the same person.

Artificial intelligence has been proposed as a method for accuracy improvement. If created and integrated properly, certain algorithms of artificial intelligence could be very effective and could contribute not only to the quality of the final echocardiographic conclusion, but would increase the efficacy of the study, saving time and efforts for the time-consuming, difficult and important echocardiographic analyses. Therefore, the work of Dr.Vassileva could serve as a part/basis of future artificial intelligence for the diagnosis of congenital heart defects and to ensure the optimal choice of surgical strategy.

CONCLUSION:

The reviewed doctoral thesis of Dr.Vassileva has persuasive merits. The in-depth knowledge of the problem, the excellent expertise in echocardiography, the very good application of the statistical methods allow Dr.Vassileva precise processing of the obtained information and reaching scientific and practical results – the proposed algorithm for differentiation between the balanced and the unbalanced forms of CAVSD.

With its results and qualities as well as with the logical conclusions the doctoral thesis meets entirely the criteria for obtaining the scientific and educational degree ‘Doctor’. Based on this, I vote positively and I strongly suggest that the other members of the scientific jury also vote positively for the conferment of the educational and scientific degree “Doctor” to Dr. Zornitsa Nikolova Vassileva-Enikova. “

