

To the Chairman of a Scientific Jury
appointed by order
of the NHH Executive Director
No 228/04.07.2022

OPINION

From Prof. Borislav Georgiev Georgiev, MD,
Head of the Cardiology Clinic at the National Heart Hospital
Member of the Jury for awarding the scientific and educational degree "PhD", designated
by order №-228/04.07.2022 by the Executive Director of the National Heart Hospital

Regarding: Dissertation of Dr. Elisaveta Dimitrova Levunlieva, PhD student on a self-study basis in
"pediatric cardiology"

Topic of the PhD thesis:

"Invasive assessment of hemodynamics in patients following Fontan surgery"

Scientific tutor: Prof. Dr. Anna Kaneva-Nencheva

For the competition Dr. Elisaveta Dimitrova Levunlieva has submitted all necessary documents - dissertation work, abstract, and additional documents, in accordance with the requirements of the regulation for the acquisition of an educational and scientific degree "PhD" and rules of the National Heart Hospital.

I can't find any gaps in the documentation submitted.

I declare that I have no conflict of interest with the candidate.

All presented materials are precisely arranged and described.

There is no evidence of plagiarism.

Importance of the topic

Fontan surgery is usually a multi-stage surgical treatment aimed at complete separation of the systemic and venous circulation. It includes two main stages – creation of bidirectional cavopulmonary anastomosis and total cavopulmonary anastomosis. The complexity of the operative technics also defines the complexity in the understanding and evaluation of these patients, which hinders the frequent discussion of the problem at medical forums. Although the first steps are as early as the 1960s, the topic is difficult to understand for the medical community. The main publications in Bulgaria are of Dr. Levunlieva, who is among the most familiar with the problems, actively follows-up these patients and is aware of scientific searches in the field.

Structure of the dissertation work:

The scientific work of Dr. Elisaveta Levunlieva is shaped on 155 p. according to the requirements and contains an introduction, literature review, objectives and tasks, material, methodology, results, discussion, and publications, contributions and bibliography.

The literature review, presented on 38 pages, shows the author's very good awareness of the issues.

- Fontan-circulation, created as a palliative correction of complex cardiopathies with single-chamber circulation, favorably affects arterial hypoxemia at the cost of adverse changes in hemodynamics and is associated with increased morbidity and mortality.
- The only method for accurate and direct measurement and calculation of the indicators of hemodynamics is cardiac catheterization.
- Currently, there are no generally accepted hemodynamic criteria for fenestration closure.
- There are no precise data on whether and to what extent the administration of a pulmonary vasodilator can favorably modulate hemodynamics.
- In Bulgaria, there was no assessment of the long-term results after Fontan-surgery, including an invasive assessment of hemodynamics in patients with complex congenital heart disease with single ventricular physiology operated in childhood.

The bibliography contains 297 titles, including 11 in Cyrillic and 286 in Latin.

Dr. Elisaveta Levunlieva **aimsto** evaluate postoperative hemodynamics in patients with single ventricle type of congenital heart disease and completed stages of surgical treatment with extracardiac conduits and the influence of anatomical and functional factors on the late postoperative evolution.

In order to achieve this goal, the dissertant set the following **tasks**:

1. Sampling of patients with "common ventricle" congenital heart disease operating in the Clinic of Pediatric Cardiology for the period from 2000 to 2020 and description of the demographic characteristics.
2. Shaping a target group for the study on the basis of the inclusion and exclusion criteria.
3. Invasive assessment of hemodynamics based on at least one postoperative intracardiac study.
4. Determination of:
 - anatomical (morphological type of common chamber) *and*
 - functional (palliation and fenester creation) factors influencing hemodynamics.
5. Determination of the influence of defenestration on hemodynamic indicators.
6. Determination of the influence on hemodynamics by the administration of selective pulmonary vasodilators.
7. Create a scoring system to predict the long-term result based mainly on invasive hemodynamic parameters.
8. Establishment of a protocol for monitoring and hemodynamic invasive evaluation of patients with single ventricle type of CHD after completed stages of Fontan type physiological correction.

Methodical approach and results: Out of 130 living patients, 71 patients met all the inclusion criteria. Patients were analyzed by preoperative and last examination hemodynamic parameters (oxygen saturation, pulmonary blood flow, systemic blood flow, Qp/Qs ratio, end-diastolic pressure, mean pulmonary pressure, pulmonary vascular resistance, transpulmonary gradient), pre-palliation ventricular morphology, fenestration during Fontan operation, treatment with sildenafil after Fontan-surgery, decompensation of Fontan circulation, analyzing the prognosis after Fontan-surgery.

The author presents a summary of the results of the overall study, which shows Dr. Levunlieva's impressive knowledge of the subject.

The statistical analysis includes various analyses which are consistent with the hypothesis and the objectives set. The collected data were processed using an SPSS 21.0 statistical package for Windows.

The discussion of the results comprises 27 pages and demonstrates not only a good analysis of the data received, but also a thorough knowledge of the international publications and results, which makes it extremely valuable from a scientific point of view. A protocol for follow-up and hemodynamic invasive assessment of patients with congenital heart disease will help everyone who is dealing with the issues discussed.

Conclusions: Dr. Elisaveta Dimitrova Levunlieva offers 9 conclusions.

1. Hemodynamic evaluation of patients with complex SML type common chamber after Fontan-surgery with extracardiac conduit shows a favorable result with:
 - i. increase in oxygen saturation,
 - ii. increase in Qp/Qs ratio,
 - iii. decrease in ventricular end-diastolic pressure and
 - iv. absence of significant changes in cavopulmonary pressure, pulmonary vascular resistance, and systemic blood flow.
2. Morphologically, the left type of common chamber indicates more favorable hemodynamics, an expression of which is significantly lower ventricular end-diastolic pressure and the higher lung/systemic blood flow ratio established in the last postoperative catheterization.
3. In late postoperative evolution, an increase in the transpulmonary gradient is found.
4. Fenestration favors early postoperative adaptation, but is the cause of significant hypoxia in the distant postoperative period.
5. Correct hemodynamic evaluation in test occlusion allows selection of patients in whom "safe" defenestration can take place.
6. With defined clear criteria, the closure of fenestration has a beneficial effect on hemodynamics with a significant increase in oxygen saturation.
7. Increased pulmonary vascular resistance, which is a key factor for adverse postoperative evolution, can be effectively modulated with the administration of selective pulmonary vasodilators.
8. Selective pulmonary vasodilators significantly lower the cavopulmonary pressure and pulmonary vascular resistance and improve transpulmonary blood flow and systemic oxygen saturation.
9. The assessment of the result on the basis of the proposed scoring system, including invasive hemodynamic indicators, is of high specificity and sensitivity and could allow proactive behavior.

Contributions: Contributions are 6, divided into two groups - of original nature (3) and of confirmatory nature (3).

1. Contributions of an original nature

1. For the first time in Bulgaria, a systematic analysis of invasively evaluated indicators of hemodynamics was carried out in patients with functional singleventriclehearts with completed stages of Fontanpalliation.

2. A scoring system has been created to assess the prognosis after Fontan surgery with extracardiac conduit based on hemodynamic catheterization data.

3. The sensitivity and specificity of the score system for assessing the prognosis have been assessed and this score system has been found to have a high sensitivity and specificity with regard to prognosis in patients with completed stages of Fontan palliation.

II. Confirmatory contributions

1. The beneficial hemodynamic effects of Fontan palliation have been confirmed in patients with functional single ventricle hearts.

2. It has been confirmed that in patients with a surgically created fenester, correct hemodynamic evaluation in test occlusion allows selection in which a "safe" defenestration can take place.

3. The beneficial effect of treatment with selective pulmonary vasodilator (sildenafil) on hemodynamic indicators in patients after TCRC with extracardiac conduits has been confirmed.

Publications: In connection with the dissertation work, the author presents 3 full-text publications.

The abstract is presented in Bulgarian, contains 58 pages and reflects the contents of the dissertation. It is in accordance with the requirements.

General remarks

It is very rare for me to read a dissertation with interest and pleasure. Dr. Levunlieva's dissertation enriched me because of the comprehensive presentation of such a complex and difficult problem in pediatric cardiology. I couldn't make any remarks about such sustained scientific work.

Recommendations to the PhD student:

To publish some of the results of the study in an international journal, preferably with an impact factor.

According to the minimum requirements of the National Center for Information and Documentation (NACID) Dr. Elisaveta Dimitrova Levunlieva meets the requirements as follows:

Metric Group	minimum number of points	Indicator	Points
But	50	1. Dissertation on the award of an educational and scientific degree "Doctor"	50
		<i>"Invasive assessment of hemodynamics in patients following Fontan surgery"</i>	
D	100	5. Published monograph not presented as basic work	
	40	6. Published book on the basis of a dissertation on the award of an educational and scientific degree "Doctor" or for the award of a doctor of science degree	
	60/n or divided in proportion	7. Publications and reports published in scientific publications, referenced and indexed in world-renowned databases of scientific information	

	30/n or divided in proportion	8. Publications and reports published in unreferenced journals with scientific review or published in edited collective volumes	66
	·Levunlieva E., A. Kaneva, R. Lekova, K. Nenova, L. Dimitrov. Invasive hemodynamic evaluation of the effect of sildenafil treatment after Fontan operation. ISSN 2683-1015 (Electronic version) ISSN 1310-7488 (Printed version). (6,00) ·Levunlieva E. Hemodynamics after Fontan surgery in complex congenital cardiac disease with single ventricle circulation. Bulgarian cardiology. 2022, 28, 1: 120-134; ISSN 2683-1015 (Electronic version) ISSN 1310-7488 (Printed version) (30) ·Levunlieva E. Congenital cardiac malformations with single ventricle circulation – diagnostic and therapeutic approach in the period of newborn and early nursing age. Practical pediatrics. 2018, 1: 24-27; ISSN 1311-0756 (Printed version) (30)		
20/n	9. Published chapter of collective monograph		
Total points:		116.00	

Conclusion: I appreciate the work of Dr. Elisaveta Dimitrova Levunlieva on the topic "Invasive assessment of *hemodynamics in patients after Fontan surgery*" as interesting in scientific terms and important for clinical practice. I consider this dissertation meets the requirements for awarding the educational and scientific degree "PhD" according to the Academic Staff Development Act in the Republic of Bulgaria and the Rules for the Academic Staff Development at the National Heart Hospital.

Based on the above merits of the dissertation of Dr. Elisaveta Levunlieva, I strongly recommend to the honorable members of the Scientific Jury to vote positively and to award Dr. Elisaveta Dimitrova Levunlieva the educational and scientific degree "PhD" in the scientific specialty "Pediatric Cardiology", professional department 7.1 Medicine, field of higher education 7 Health and Sport.

29.09.2022



Prof. Borislav Georgiev Georgiev, MD