REVIEW

Subject: dissertation work for awarding the educational and scientific degree " PHILOSOPHY DOCTOR" on the topic: "Invasive evaluation of hemodynamics in patients after Fontan operation"

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At the first absent meeting of the Scientific Jury, I have been appointed to prepare a review.

A review has been prepared in accordance with the Academic Staff Development Act (ACAS), the Regulations for the Application of the Academic Staff (PRAS) and the Regulations on the Terms and Conditions for Acquisition of Scientific Degrees and Occupation of Academic Positions (PURPNSZAD) in MHAT "NHH" EAD.

The presented set of materials on paper/electronic media is in accordance with the procedure for acquiring the scientific and educational degree "Doctor" and the regulations of MHAT "NHH" EAD. I do not find plagiarism in the review of the dissertation, abstract and publications submitted to me for review, related to the dissertation development.

I declare the absence of joint scientific developments with the doctoral student and a potential conflict of interest.

Actuality of the dissertation

The Fontan operation is the standard surgical treatment in children with complex congenital heart malformations in which biventricular correction is impossible. In patients with a functional single-chamber heart, the Fontan operation is currently the best option for long-term physiologic palliation. This type of operation has both beneficial effects and weaknesses.

Fontan palliation was introduced in 1968. This type of operation was initially used in patients with obstructive lesions of the right heart (specifically tricuspid atresia) and was accepted as a total right heart bypass procedure.

Globally, the Fontan patient population grew to approximately 70,000 patients in 2018, 40% of whom were over 18 years of age. The current estimate of 30-year survival after

completion of the Fontan operation is approximately 85%. Despite the remarkable improvement in their survival, quality and length of life in these patients still leaves much to be desired. This unique patient population requires close monitoring throughout life.

Postoperative results are usually good, but in some patients the Fontan circulation decompensates over time. Many of the health problems of Fontan patients are related to their cardiac anatomy and the consequences of serial surgical corrections. A hallmark of the post-Fontan circulation is persistently elevated central venous pressure in combination with chronically reduced cardiac output, particularly during periods of increased demands, resulting in a cascade of adverse physiological consequences.

Postoperative follow-up of Fontan patients is of utmost importance to recognize and possibly prevent the adverse evolutionary complications of this "unnatural" circulation. Only the direct measurement of pressures, saturations and calculation of hemodynamic parameters in an invasive study allow accurate assessment of hemodynamics and proactive behavior. Catheterizations are performed at various times, as part of "routine follow-up" or when problems arise such as reduced physical capacity, progressive hypoxia, treatment-refractory arrhythmia, or developing manifestations of Fontan insufficiency. There is still no consensus on the definition of "routine follow-up", which varies widely and is a matter of institutional conception.

Fenestration during the Fontan operation is performed with the aim of favorably influencing the early postoperative adaptation, but its effect is not unambiguous, especially in the long postoperative period. It has a favorable effect on hemodynamics in the early postoperative period, but its effect on the development of Fontan-circulation insufficiency and prognosis is not specified with certainty. Also, in the remote postoperative period, significant hypoxia is possible.

Selective pulmonary vasodilators are used in the treatment of patients with complex ventricular septal hemodynamics who have pulmonary hypertension. The vasodilatory and antiproliferative effects of Sildenafil are the basis of its use in patients with Fontan circulation and increased cavo-pulmonary pressure. The effect of phosphodiesterase inhibitors in Fontan patients has been evaluated in a limited number of studies, and those with invasive assessment of hemodynamics during long-term sildenafil administration in children are extremely few and the number of patients included in the studies was very limited.

Structure of the dissertation:

The dissertation is presented on 155 standard pages, includes 39 figures, 57 tables, with 25 in the main part and 32 in the appendices. The bibliography includes 297 sources, 11 of them in Cyrillic and 286 in Latin. The cited sources from the last 5 years are 80 and from the last 10 years 149.

The dissertation is written in the literary Bulgarian language, well structured in accordance with the accepted standards for the preparation of scientific work for the acquisition of a scientific and educational degree "Doctor". Contains the following pages:

1. Title page – 1 page.

2. Abbreviations used – 1 page.

3. Introduction – 2 pages.

4. Literature review - 39 pages.

5. Purpose and tasks - 1 page.

6. Material – 1 page.

7. Methodology – 5 pages.

8. Results – 35 pages.

9. Discussion – 27 pages.

10. Conclusions – 2 pages.

11. Contributions – 1 page.

12. Appendices – 21 pages.

13. Literature – 13 pages.

The proportional distribution between the individual sections is respected.

The introduction is on 2 pages and raises expectations about the essence of the scientific work.

Review of the literature

The review of the literature is presented on 39 pages, extremely detailed and informative, it shows the good awareness of the dissertation regarding the clinic, the postoperative follow-up of Fontan-patients, the possible prevention of evolutionary complications, the consequences of serial surgical corrections, the impact of single-chamber hemodynamics on the quality of life of these children, the "routine follow-up" and problems such as progressive hypoxia, treatment-refractory arrhythmia, developed manifestations of Fontan-insufficiency, reduced physical capacity.

The author has made a precise summary of the effects of the Fontan operation in patients with complex LVH with common chamber hemodynamics - positive and unfavorable. Effective surgical modifications and accumulated experience in preoperative selection and postoperative care greatly improve the survival and quality of life of these patients. The established non-physiological circulation in these patients is associated with an increased risk of multi-organ dysfunction.

In the late evolution after the operation, a number of problems are observed, potentiated both by the inherent problems of the single-chamber heart and the disturbances in the ventricular function, the compliance of the pulmonary vascular bed, the increased pulmonary vascular resistance, the increased pulmonary arterial pressure, the deformation of the pulmonary artery, atrio-ventricular valve regurgitation, ventricular dysfunction, etc.

Invasive assessment of hemodynamic parameters before and after Fontan-operation, transcatheter interventional procedures for modulating postoperative hemodynamics are described in detail.

Over the years, as a result of a series of effective surgical modifications and accumulated sufficient experience in preoperative selection and postoperative care, the survival and quality of life of these patients have significantly improved, but the created nonphysiological circulation is associated with an increased risk of multiorgan dysfunction. In the late evolution after the operation, a number of problems are observed, potentiated both by the inherent problems of the single-chamber heart and by time-occurring disturbances in the ventricular function, the compliance of the pulmonary vascular bed, the increased pulmonary vascular resistance, the increased pulmonary arterial pressure, the deformation of the pulmonary artery , atrio-ventricular valve regurgitation, ventricular dysfunction, etc.

The author shows very good and in-depth knowledge of the subject of the dissertation, which allows him, on the basis of the detailed literature review, to draw the following conclusions, from which the purpose and tasks of the dissertation derive:

1. The Fontan-circulation, created as a palliative correction of complex cardiopathies with single-chamber circulation, favorably affects arterial hypoxemia at the cost of hemodynamic disturbances and is associated with increased morbidity and mortality.
2. The only method for accurate and direct measurement and calculation of hemodynamic indicators is cardiac catheterization.
3. Currently, there are no generally accepted hemodynamic criteria for fenestra closure.
4. There is a lack of precise data on whether and to what extent the administration of a pulmonary vasodilator can favorably modulate hemodynamics.
5. We have not evaluated long-term results after Fontan surgery, including invasive assessment of hemodynamics in patients with complex SCM with common chamber physiology, operated in childhood.

Purpose and tasks

The aim of the dissertation is clearly and precisely formulated: Evaluation of postoperative hemodynamics in patients with congenital heart malformations of the "common chamber" type and completed stages of surgical treatment with an extracardiac conduit and the influence of anatomical and functional factors on the long-term postoperative evolution.

To achieve the set goal, 8 specific tasks have been identified:

1. Forming a sample of patients with "common chamber" type BSM operated on children's cardiology clinic of NHH for the period from 2000 to 2020 and description of demographic characteristics.
2. Forming a target group for the study based on inclusion and exclusion criteria.
3. Invasive evaluation of hemodynamics based on at least one postoperative intracardiac study.
4. Determination of:
   - anatomical (morphological type of common chamber) and
   - the functional (prior palliation and creation of a fenestra) factors affecting hemodynamics.
5. Determination of the influence of defenestration on hemodynamic parameters.

6. Determination of the influence on hemodynamics from the application of selective pulmonary vasodilators.
7. Creation of a point system for predicting the distant outcome, based mainly on invasive hemodynamic parameters.
8. Creation of a protocol for follow-up and hemodynamic invasive assessment of patients with "common chamber" BCM after completed stages of Fontan-type physiologic correction.

Material and methods

The study is ambispective (retro and prospective) and covers patients with total cavo-pulmonary anastomosis, operated in the Children's Cardiology Clinic of MBAL "NKB" over a 20-year period. 71 children meeting all inclusion criteria were included. Of them, 31 are girls (43.7%) and 40 are boys (56.3%). The mean age at surgery in the study group was 4.48 ± 2.01 years.

The research methodology in terms of the investigated non-invasive and invasive indicators and the adopted definitions was well chosen in view of the credibility and reliability of the obtained results - body mass, body surface area, ventricular morphology, previous Fontan-palliation, hemodynamic indicators - systemic oxygen saturation, caval and pulmonary pressure , ventricular systolic and end-diastolic pressure, transpulmonary gradient, systemic arterial pressure, pulmonary and systemic blood flow, pulmonary and systemic vascular resistance. Right and left heart catheterizations were performed. Manometry and oximetry were performed in basal conditions (before angiocardiographic examinations). Hemodynamic parameters were calculated according to Fick's formula. Angiographic examinations were performed in frontal and right hair 0/30°, profile and additionally angulated projections. In a selected group of patients with a fenestra, transcatheter closure of the fenestration (defenestration) was performed.

Modern statistical processing of results was done using the statistical package SPSS 21.0 for Windows. Data are presented as mean ± standard deviation (mean ± SD). The obtained results are presented as absolute values and relative frequencies (percentages). Other modern statistical methods were also used to verify the correctness of distribution and uniformity of variations, methods for testing hypotheses T-test and U-test, correlation analysis, etc., which gives grounds for the reliability of the results obtained. The critical level of significance used was $\alpha = 0.05$, with the corresponding null hypothesis rejected at P-value $< \alpha$.

Results

The results obtained by Dr. Elisaveta Levunlieva are presented correctly on 35 pages of the dissertation work, illustrated with sufficiently informative tables and figures. They include demographic characteristics, morphological diagnosis, hemodynamic parameters and other data on the examined children. Patients with double outlet right ventricle (DORV), tricuspid atresia, left double inlet ventricle and pulmonary atresia have the highest incidence. The results of hemodynamic parameters preoperatively and at the last catheterization are presented - oxygen saturation (SatO2), pulmonary blood flow (Qp), systemic blood flow (Qs), pulmonary-systemic blood flow ratio (Qp/Qs), end-diastolic pressure, mean pulmonary pressure, pulmonary vascular resistance, transpulmonary gradient. Hemodynamic results at completed stages of Fontan-correction show a favorable outcome with an increase in oxygen saturation and pulmonary/systemic blood flow ratio, with a decrease in end-diastolic pressure and unchanged

mean pulmonary pressure and pulmonary vascular resistance. The hemodynamic indicators in right ventricular and left ventricular morphology of the common chamber are presented and compared. Hemodynamic indicators were examined depending on the type of preoperative palliation. In both groups, at the last postoperative catheterization, a statistically significantly higher systemic oxygen saturation was found compared to the preoperative one.

Patients with fenestration were 52 children, in 18 the fenestra closed spontaneously, 10 children had a persistent fenestra, and in 24 transcatheter defenestration was performed. The results of a study of hemodynamic parameters in children with spontaneously and interventionally closed fenestra compared to those with persistent fenestra are presented. In patients with persistent fenestra, the only hemodynamic parameter that differed significantly between preoperative and last postoperative catheterization was systemic oxygen saturation. A tendency towards an increase in cavo-pulmonary pressure and pulmonary vascular resistance was also established, which did not reach a statistically significant value. The results of trial occlusions with subsequent definitive defenestration in 24 children are shown. In 7 cases, after the test occlusion of the fenestration, definitive defenestration was not performed due to unfavorable hemodynamic indicators - an increase in cavo-pulmonary pressure above 16 mmHg and a significant decrease in systolic arterial pressure, regardless of the improvement of oxygen saturation during the occlusion. In the remaining 3 children without definitive defenestration, the fenestra was not closed due to unsuitable initial hemodynamic parameters for defenestration in 2 children and the presence of hypoplasia of the branches of the pulmonary artery in 1 child. Results of remote catheterization according to ventricular morphology – right ventricular or left ventricular – are presented.

In 26 children treated with Sildenafil due to increased cavopulmonary pressure, at least two invasive hemodynamic studies were performed - before and after starting therapy with Sildenafil. The medication has been administered for at least 6 months.

Hemodynamic parameters before and after treatment with sildenafil according to the type of pre-Fontan palliation as well as according to the presence of fenestration are presented.

Dr. Elisaveta Levunlieva-Ivanova offers a point system for evaluating the prognosis. It has high specificity and sensitivity, and allows proactive behavior.

Discussion

The discussion of the obtained results is presented on 27 pages illustrated with sufficiently informative tables and figures. Until now, we have not performed a systematic analysis of the invasively evaluated hemodynamic indicators in patients with a functional single-chamber heart with completed stages of Fontan-palliation. The dissertation student skilfully handles the accumulated information and compares his results with those published by foreign authors. The patients participating in the study have a severe risk profile and a different prognosis depending on the ventricular morphology, the age at surgery, the pre-Fontan palliative interventions, the presence or not of a fenestra, the inclusion or not of sildenafil treatment, as well as the evaluation of the various invasively recorded hemodynamic parameters.

At long-term follow-up, overall mortality was higher in the non-fenestrated group than in the fenestrated group. The analysis of the survival data using the point system proposed by the author shows that at the last catheterization one of the deceased patients had a score between 5 and 8 points (suboptimal), and the remaining three deceased fell into the group with an

unfavorable score (≥ 9 points.), with the patient with the maximum unfavorable score being 15 points. No patients with an optimal score at the last catheterization died during follow-up.

The presented protocol for the follow-up and hemodynamic invasive evaluation of patients with common chamber BCM after completion of the Fontan-type functional correction stages suggests routine catheterization of all patients after Fontan-fenestrated surgery at the end of the first year after surgery. Early catheterization before the end of the first year is recommended for elevated early postoperative CPN or evidence of "surgical debris." Catheterization with invasive hemodynamic assessment at 5 years postoperatively and before age 18 is recommended in all Fontan patients. With cavo-pulmonary pressure over 15 mmHg and transpulmonary gradient over 6 mmHg yes add a pulmonary vasodilator, and if one is already available, add a second medication.

The conclusion corresponds to the results obtained.

Conclusions

The 9 conclusions made are clearly formulated in the context of the tasks.

1. The hemodynamic assessment of patients with complex LVEF of the common chamber type after Fontan-operation with an extracardiac conduit shows a favorable result with an increase in oxygen saturation, an increase in the Qp/Qs ratio, a decrease in ventricular end-diastolic pressure in the absence of significant changes in cavo-pulmonary pressure, pulmonary vascular resistance and systemic blood flow.
2. Morphologically, the left common ventricular type shows more favorable hemodynamics, which is reflected by the significantly lower ventricular end-diastolic pressure and the higher pulmonary/systemic blood flow ratio found at the last postoperative catheterization.
3. In the distant postoperative evolution, an increase in the transpulmonary gradient is found.
4. Fenestration favors early postoperative adaptation but causes significant hypoxia in the long postoperative period.
5. Correct hemodynamic assessment during test occlusion allows selection of patients in whom defenestration can be "safely" performed.
6. With defined clear criteria, fenestration closure favorably affects hemodynamics with a significant increase in oxygen saturation.
7. Increased pulmonary vascular resistance, which is a key factor in the unfavorable postoperative evolution, can be effectively modulated by the use of selective pulmonary vasodilators.
8. Selective pulmonary vasodilators significantly lower cavopulmonary pressure, pulmonary vascular resistance and improve transpulmonary blood flow and systemic oxygen saturation.
9. The evaluation of the result based on the proposed point system, including invasive hemodynamic indicators, is of high specificity and sensitivity and allows proactive behavior.

Contributions

The contributions of the dissertation, 6 in number, are of an original, markedly scientific-applied and confirmatory nature, well formulated and are the result of the study.

1. For the first time in Bulgaria, a systematic analysis of the invasively assessed hemodynamic parameters in patients with a functional single-chamber heart with completed stages of Fontan-palliation was performed.
2. A point system was created to evaluate the prognosis after Fontan operation with an extracardiac conduit, based on the hemodynamic catheterization data.
3. The sensitivity and specificity of the prognostic scoring system were evaluated, and this scoring system was found to have high prognostic sensitivity and specificity in patients with completed stages of Fontan palliation.
4. The favorable hemodynamic effects of Fontan palliation have been confirmed in patients with a functional single-chamber heart.
5. It has been confirmed that in patients with an operatively created fenestra, the correct hemodynamic assessment during test occlusion allows selection in which defenestration can be "safely" performed.
6. The beneficial effect of treatment with a selective pulmonary vasodilator (sildenafil) on hemodynamic indicators in patients after TCPC with an extracardiac conduit has been confirmed.

The abstract in a volume of 58 pages reflects the main results and discussion, conclusions and scientific contributions of the dissertation work.

Publications

The author presents 3 full-text publications related to the dissertation work in renowned Bulgarian medical journals, that meet the requirements, as well as other publications and contributions with fragments of the dissertation.

Recommendations

Given the high scientific value of the dissertation work and its relevance, I recommend the author to continue the observation of patients with Fontan operation and the collection of more data to optimize proactive behavior and adequate treatment of these children. To publish the obtained data in the foreign scientific periodical.

CONCLUSION

The dissertation presented to me by Dr. Elisaveta Dimitrova Levunlieva-Ivanova contains particularly valuable data, of an original and confirmatory nature, and is a significant contribution to medical science in our country, in particular to pediatric cardiology. For the first time in Bulgaria, a systematic analysis of the invasively assessed hemodynamic parameters in patients with a functional single-chamber heart with completed stages of Fontan-palliation was performed. The dissertation shows that the doctoral student has in-depth theoretical knowledge and professional skills in the scientific specialty, demonstrates qualities and skills for independent conduct and discussion of scientific research.

The dissertation meets the requirements for awarding the educational and scientific degree " Philosophy Doctor" laid down in the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Development of the Academic Staff of the MHAT "National Heart Hospital"- Sofia.

This gives me reason to vote with a positive vote and I strongly recommend to the respected members of the Scientific Jury to vote for awarding Dr. Elisaveta Dimitrova Levunlieva the educational and scientific degree " Philosophy Doctor" in the scientific specialty "Pediatric Cardiology", professional direction 7.1. Medicine, field of higher education 7. "Health care and sports".

30.09.2022 г.

Signature:

Assoc. Prof. L. Marinov, MD PhD