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Review Report
on PhD Thesis of Mullen Aigerim
entitled:
"Comprehensive diagnosis and therapy of pulmonary arterial hypertension in children with congenital left-to-right shunt",
presented as an application for the PhD degree on the speciality "Medicine" 6D 110100

Co-Supervisor: Professor Ghazwan Butrous (UK)

Dr Aigerim Mullen submitted the doctoral thesis dealing with the comprehensive approach to diagnosis and therapy of pulmonary arterial hypertension in children with congenital left-to-right shunt.

Pulmonary arterial hypertension associated with congenital heart disease (APAH-CHD) is a unique type of pulmonary hypertension (PH), as it also knows an early phase of the arteriopathy. APAH-CHD has the potential for reversibility which was first identified in the 1950's, but mechanisms, timing, and identification of such reversibility are still obscure today.

All children born with a systemic-to-pulmonary shunt are at risk for APAH-CHD. Modern targeted pharmacotherapy of PH may stabilize disease progression, and improve clinical condition of patients, but still does not cure the disease itself. Reversible PAH was first described in children with APAH-CHD. Timely correction of the shunt, removing the disease trigger, was found to result in full disease regression.

In this doctoral dissertation, in order to improve comprehensive diagnosis and treatment of APAH-CHD in children, Dr Mullen initiated a controlled nonrandomised clinical observational single centre study in Scientific Centre of Paediatrics and Paediatric Surgery, Almaty, Kazakhstan. Therefore, the novelty as well as the scientific level of the thesis is very good, considering the importance of the research subject, healthcare system requirements and educational demands.

This PhD thesis is well structured and correctly presented. It consists of 6 main chapters. At the beginning of this dissertation lists of abbreviations and symbols are introduced. Finally, summary, scientific activity of the PhD student and appendix are presented. The thesis is written on 119 pages altogether and enriched by a number of figures (17), equations and (3) and tables (30). The theoretical principles as well as the research part were validated with 234 valuable references.

In the first chapter Dr Aigerim Mullen introduces readers to the dissertation topic and literature review that presents the background of history, aetiology, pathogenesis, clinical manifestation, diagnostic tools and treatment methods. In this work valuable literature review regarding national patient registers, genetics and cohesion between congenital left-to-right shunt and pulmonary arterial hypertension have been performed. Very useful piece of information regarding the intervention and surgical treatment options is presented.

To summarize the theoretical part of this thesis is worth to note that the Author has studied carefully research subject with critical view and used an appropriate number of bibliographic sources. It is an evidentiary fact that Dr Mullen deeply understood the theoretical knowledge and the discussed problems.

Chapter 2 is dedicated to the description of the used materials and methods. The next part of the dissertation (chapters 3-6) is focused on results and discussion. The results obtained by Dr Aigerim Mullen were analysed with descriptive statistics and comparisons with convenient statistical methods. Two groups were homogeneous to each other by the type of congenital left-to-right shunt and basic echocardiography data.

Firstly, the medical records of patients with congenital left-to-right shunts between 2012 and 2014 have been examined. The diagnosis of APAH-CHD was estimated by echocardiography report and right heart catheterisation reports. The dynamic follows up of the selected patients was determined by echocardiography examination in 1-month period after the surgery / transcatheter correction of the CHD. The prospective observation and management of the patients between 2015 and 2016 have been registered by the Author.

The next step of the investigation was focused on the interpretation of the results of the acute vasoreactive test. Iloprost as a selective vasodilator agent is approved by international guidelines and was well tolerated by patients with APAH-CHD. Dr Mullen has modified criteria for operability assessment in a more simple and understandable fashion. Moreover, during AVRT, the non-invasive hemodynamic criteria were measured by echocardiography.

The next part of the thesis, in my opinion is very interesting, focused on the impact of left-to-right shunt size on the AVRT results. The influences of shunt volume and level of the pulmonary vascular reaction and early postoperative course were investigated. The results demonstrate that the large shunt will lead to positive AVRT and better effect of the shunt repair.

At the end of the dissertation, the general conclusions of the performed research were described.

This thesis is well written in a clear and concise manner. The figures and tables are shown properly as well. The hypothesis and arguments are well formulated with meritorious conclusions based on valuation and actual literature. The conclusions confirm that the formed objective of the work was successfully finished.

However, the are some remarks which occurred to me and need to be explained in detail.

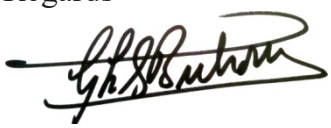
- In my opinion, for better understanding of the presented results regarding the influence of complex therapy (basic drug, targeted drug APAH-CHD therapy, the surgical or transcatheter correction of the CHD) reference sample should be followed up for 6, 12, 24 months.
- Please in further research clarify the main criteria for the selection of the patients for AVRT in respect to their different age, type of CHD or right ventricle pressure level.

To sum up, the dissertation thesis represents high level scientific work. It is an interesting topic for medical doctors working on congenital heart diseases in childhood. All examinations are well arranged, and measurements techniques and methods are correctly applied taking in consideration the limitation of the routine clinical practice. The explanations are suitable and focused on the relevant topics. It is noteworthy that the wide spectrum of work executed new research ideas.

In my opinion, the reviewed thesis fulfils all requirements based on the thesis aimed for obtaining the PhD degree. This thesis is ready to be publicly defended, in front of the respective committee.

I would like also to propose to reward Dr Aigerim Mullen's doctoral dissertation due to the following aspects: scientific novelty, an extensive range of research, meritorious presentation and discussion of obtaining results, outstanding scientific activity confirmed by papers published in commonly known and highly ranked scientific journals (Cardiology in the young: 52nd Annual Meeting of the Association for European Paediatric and Congenital Cardiology (May 9-12, 2018). Vol 28. ISSN: 1047-9511. DOI: 10.1017 / S1047951118000318. Cambridge University Press. IF (2016) 0.905 (ResearchGate), "Russian Cardiology Journal" (Российский кардиологический журнал. 2018;23(7):41–46. http://dx.doi.org/10.15829/1560-4071-2018-7-41-46. SCOPUS database, Russian, Science Citation Index (RINC) Science Index, Club of editors-in-chief of the European Society of Cardiology) and two copyright applications.

Best
Regards



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