

OPINION

For a dissertation work for the acquisition of an educational and scientific degree "doctor" by field of higher education 7: "Health and sport", professional direction 7.1 "Medicine" and specialty 03.01.47 "Cardiology"

Author: Dr. Ivaneta Dimitrova Yoncheva-Biserova, assistant professor of internal medicine and cardiology, Faculty of Medicine, University "Prof. Dr. Asen Zlatarov", Burgas, correspondence doctoral student at the First Department of Cardiology, Varna

Topic: "Fibrotic activity in patients after permanent pacemaker implantation"

Scientific supervisor:

Prof. Dr. Maria Negrinova Negreva, MD, Head of the Department of Cardiology, First Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

Prepared the statement: Prof. Dr. Yoto Trifonov Yotov, MD, cardiologist, professor at the Department of Cardiology, First Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

By order No. R- 109-265 / 31.07.2024 of the Rector of the MU, Varna, based on the decision of the Faculty Council of the Faculty of Medicine under protocol No. 25 / 29.07.2024 r. I have been elected as a member of the Scientific Jury for the defense of Dr. Ivaneta Dimitrova Yoncheva-Biserova's dissertation. At the first meeting of the Scientific Jury, I am assigned to prepare an opinion on the procedure for acquiring the educational and scientific degree "doctor".

Brief data on the professional development and qualification of the doctoral student:

Dr. Ivaneta Dimitrova Yoncheva-Biserova graduated in Medicine in 2000 at Medical University-Sofia, after which she worked as a specialist doctor in Stara Zagora and Sveta Ekaterina, Sofia. He successively leads an intensive cardiology sector and a cardiology department in "Deva Maria" UMBAL, Burgas. From 2022, she was selected as an assistant at the Department of Skin Diseases of the Faculty of Medicine, University "Prof. Dr. Asen Zlatarov", Burgas.

In 2013, he acquired the specialty of Cardiology. Dr. Yoncheva is qualified in echocardiography - basic and expert level, and in cardiac stimulation - basic and expert level.

Significance of the topic: technological progress in the field of cardiology and cardiac stimulation has led to an increase in the number of patients with implanted pacemakers to overcome existing rhythm-conduction pathology. Right ventricular apical pacing is traditionally used in practice, but this modality provokes electrical and mechanical dyssynchrony, leading to an increased risk of developing heart failure (HF) and atrial fibrillation (AF). Already by the end of the second year, patients with PECS develop HF. And the asynchronous ventricular contraction leads to a difference in the workload of cardiomyocytes, to a slowdown in cellular metabolism and to left ventricular remodeling, which is associated with dynamics in the extracellular matrix (ECM) and collagen deposition in the myocardium. The dynamic follow-up of changes in the fibrosis status in patients with PECS has been the subject of single studies, the results of which are contradictory and insufficient.

Structure of the dissertation: The current research is written on a total of 134 pages. The dissertation is well balanced in 9 chapters and includes an introduction, literature review, aim and objectives, material and methods, own results and discussion, conclusions, scientific contributions, publications and participation in scientific forums, reference literature. It is

illustrated with 5 tables and 34 figures. The bibliography includes a total of 409 titles, all in Latin. Overall, 22 of the figures and 5 of the tables are included in the autoabstract.

Literature review: This section begins with a historical overview of cardiac electrostimulation, then addresses the epidemiology and indications for pacing. The frequency of implantation varies worldwide from 25/1 million to 1000/1 million population. When indicated, survival is improved and hospitalizations are reduced, as well as a better quality of life is achieved. DDDR implantation is recommended instead of the VVIR modality in all patients with preserved sinus activity.

A separate section of the literature review is dedicated to the indications and advantages of dual chamber pacing. A possibility of "physiological" electrocardiostimulation is achieved. This is done through sequential atrioventricular stimulation and by achieving an adaptive rate, with optimally coordinated atrial and ventricular depolarization time. It is emphasized that atrioventricular synchrony and electrical activation along the native conduction system are of equal importance for the realization of normal cardiac function.

The review emphasizes that chamber remodeling, in which extracellular matrix proliferation and cardiac fibrosis play a major role. Fibrosis processes, various signaling molecules, biomarkers and inflammatory and other molecules are discussed in detail. Experimental and clinical data on the fibrotic remodeling process are reviewed. The main diagnostic methods for assessing asynchrony, remodeling and fibrosis are pointed out. As conclusions, the lack of clarity regarding the processes of collagen deposition, as mainly responsible for the remodeling of the ECM of the myocardium, in patients with an implanted dual chamber PECS, as well as the lack of a clinical study that comprehensively analyzes and follows the mechanisms over time, is imposed of collagen synthesis and degradation and their regulation in patients after dual chamber PECS implantation.

Aim and tasks: the main aim of the project is: To study the fibrotic process in dynamics in patients after implantation of a permanent electrocardiostimulator. It is well formulated but it is a little bit too wide. The 4 related tasks are a logical continuation of the literature review and the main objective and are clearly and precisely defined. They reflect the individual steps to achieve the goal by evaluating different signaling molecules and markers of collagen synthesis, as well as diagnostic ultrasound and ECG methods to assess function and asynchrony.

Methods and examined persons: For the purposes of the dissertation, a total of 91 persons were examined, divided into two groups - 45 patients (25 men and 20 women) out of a total of 144 screened with indications for cardiac stimulation and in whom dual chamber PECS were implanted, and 46 controls of healthy subjects (24 men and 22 women) from a total of 102 screened without CVD and without accompanying diseases. Efforts to match the two groups in terms of basic demographic and clinical characteristics, as well as to eliminate medications with a potential effect on fibrosis, are essential. This makes the two groups comparable, which is evident from the baseline data. In this way, potential confounding factors that would affect the analysis of the role of fibrosis were removed. Each participant underwent a clinical assessment, echocardiographic and ECG examination. They have been tested in a laboratory for four indicators reflecting fibrotic activity: two signaling molecules (TGF- β 1 and CTGF) and two collagen synthesis markers (PICP and PIIINP). The biomarkers were drawn at baseline and tracked on the 12th and 24th week. Statistical methods are diverse, modern and tailored to the purpose and tasks.

Results: From the presented data, it is clear that in patients with PECS there is a significant increase in the signaling molecules for fibrosis TGF- β 1 and CTGF, which increase already at week 12 and remain high at week 24, while in controls there was no difference in values during follow-up. It is argued that, as a result of the change in the mechanics of cardiac

contraction due to apical right ventricular stimulation, activation of signaling pathways that influence the fibrotic response and remodeling of the ECM is provoked.

This signal modulation in the direction of profibrotic readiness resulted in an increase in PICP values in the group of patients with apical PECS compared to the baseline and compared to the control group. The difference between the two groups was already present at week 12 (90.51 ± 4.28 vs 79.34 ± 3.49 ng/ml, $p=0.0445$) and increased even more at week 24 (161.35 ± 14.05 vs 79.34 ± 3.49 ng/ml, $p < 0.001$). In healthy controls, there was no significant difference in PICP levels compared to baseline. An interesting change is observed in the values of another fibrosis marker - PIIINP. Baseline values did not differ between the two groups. At week 12, PIIINP increased in both groups, significantly in PECS patients and less and non-significantly in controls. At week 24, these values decreased and did not differ significantly from baseline in both groups, although in the PECS group they were higher than baseline. This is probably related to the fact that PIIINP is a marker of reparative fibrosis and less reflects myocardial and ECM remodeling.

The power analysis of the t-test for the changes in the markers of the fibrotic system shows that the number of selected participants for each group is sufficient and adequate for the obtained values of the investigated fibrotic indicators.

Echocardiographic changes in LV systolic and diastolic function are an important marker of remodeling and fibrosis. The obtained results show that LV EF did not differ at baseline between the two groups and showed no change during follow-up. The indexed LV volume, however, differed dynamically in the two groups. Patients with PECS have a higher LAVI at baseline and this volume increases over time. There was no significant change in the control group. This brings to the fore the importance of monitoring LV volumes in patients with an implanted pacemaker and stratifying the risk of atrial arrhythmia. Correlations between markers of fibrosis and echographic parameters were sought. After the analysis, a good linear relationship ($r=-0.57$; $r^2=0.33$) was found between the values of CTGF and LV EF.

This study shows that after PECS implantation with an electrode in the apex of the RV, there is a trend for widening of the paced QRS complex, registered with a surface ECG during subsequent visits. At 12 weeks post-implantation, the QRS complex was of increased duration compared to baseline values, but without statistical significance ($p=0.06$). At 24 weeks, the upward trend was maintained, and the difference with baseline values was already borderline significant ($p=0.048$). This confirms the hypothesis that pacemaker-induced asynchronous ventricular contraction plays a major role in the development of left ventricular systolic dysfunction.

The discussion is both at the separate results parts and also at the end of the Results chapter. As a recommendation, it is good to separate the discussion from results into a separate chapter.

Conclusions: The conclusions drawn are complete and summarize the presented results in detail. They correspond to the goals and objectives set by the dissertation student. Their number – 7, is sufficient and reflect the importance of the obtained results.

I fully agree with the conclusions drawn and contributions indicated by the dissertation. The discussion of the potential limitations of the development is positive.

For dissemination of the results, 4 full-text publications have been made in an international medical journal with an impact factor, as well as 3 scientific announcements at renowned scientific forums, 1 of them being international and 2 at national congresses.

The autoabstract meets the requirements of the law on the development of academic personnel.

I have not found any gaps in the documentation submitted by Dr. Ivaneta Dimitrova Yoncheva-Biserova, the requirements of the law and of the Regulations for the development of the academic staff at MU-Varna have been met.

Conclusion: The dissertation work of Dr. Ivaneta Dimitrova Yoncheva-Biserova treats an extremely important and up-to-date problem in cardiology - the development of fibrotic processes and remodeling of the myocardium after implantation of a permanent pacemaker, the solution of which is important for the prognosis and the quality of life of the patients and which includes a change in the way of pacing and, possibly, drug treatment. The goal has been achieved and the set tasks have been completed. The conclusions are sufficiently accurate and comprehensive, clearly formulated. Contributions have not only scientific but also practical value. Submitted publications and scientific communications meet the requirements.

Under these circumstances, I consider that the dissertation work of Dr. Ivaneta Dimitrova Yoncheva-Biserova meets all the requirements for awarding the scientific and educational degree "Doctor" and I warmly recommend the esteemed jury to vote positively.

09/22/2024

Varna

Prepared the opinion:

(Prof. Yoto Yotov, MD, PhD)

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679