REVIEW

of a dissertation with title:

CHANGES IN FIBROTIC ACTIVITY IN PATIENTS AFTER PERMANENT PACEMAKER IMPLANTATION

For awarding the scientific degree "DOCTOR" in MEDICINE

Research area: 7. Health Care and Sport;

Professional field: 7.1 Medicine;

Doctoral program in Cardiology.

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Reviewer: Assoc. Prof. Vasil Dimitrov Velchev, MD, PhD

1. Defence procedure

Based on Order No. R-109-265/31.07.2024 of the Rector of the Medical University of Varna, I have been elected as a member of the scientific jury for the defense of Ivaneta Yoncheva's dissertation and Protocol No. 1 of the first meeting of the scientific jury, I have been appointed to present a review.

2. Brief biographical data

Dr. Yoncheva received MD in 2000 from the Medical University of Sofia. She worked as general practitioner in Sofia, and in 2004 she began specializing in internal medicine at the First Internal Clinic of the University Hospital at the Trakia University in Stara Zagora. In 2008, she began her specialization in cardiology at the same clinic, and from 2009 to 2012 she continued her specialization at the University Hospital "Prof. Dr. Alexander Chirkov". Since 2013, she worked as cardiologist at the cardiology department of the Virgin Mary University

Hospital, Burgas as the head of the ICU and started to work actively with pacing. For the period 2018-2022, she has been the head of the cardiology department at the same hospital. Since 2022, Dr Yoncheva has been an assistant professor in internal medicine at the University “Prof. Dr. Asen Zlatarov" - Burgas, and since September 2022 she has been working as a cardiologist at Hospital MBAL Burgas AD, where her profile is cardiac stimulation and resynchronization therapy. She speaks English and Russian, and has good computer literacy.

3. Publications and scientific activity

In support of the dissertation Dr. Yoncheva has a total of 3 scientific publications. She is the first author in all publications, which testifies to her leading role in conducting the research, preparing the publications and reporting scientific results at scientific forums. Publications are from 2021 and 2023 and reflect the relevance of the topic. She has presented three reports with the data from her research, one abroad and two in Bulgaria.

4. Structure of the dissertation

The disertation is structured according to the standards adopted in our country for obtaining the scientific degree "Doctor" in medicine. It is written on 135 standard pages and includes: table of contents (3 pages), abbreviations (2 pages), introduction (1 page), literature review (63 pages), aim and objectives (1 page), material and methods (18 pages), own results and discussion (37 pages), conclusions (1 page), contributions (1 page), bibliography. The bibliography contains 409 literary sources arranged alphabetically in Latin. Of all cited literature sources, 163 (40%) were published in the last 10 years. The work is illustrated with 5 tables and 34 figures.

5. Relevance and significance of the dissertation

The topic of the dissertation is characterized by considerable relevance both for our country and worldwide. Markers for collagen synthesis and regulation were studied in patients after implantation of a permanent pacemaker and apical right ventricular stimulation, and how this affects heart function over a period of 6 months. The observed dynamic changes in the studied indicators suggest a probable link between implanted pacemaker and remodeling of the myocardial interstitium, which causes a change in cardiac function over time. The results

confirm the need for further investigation of the problem. This, in turn, determines the scientific and practical relevance, the aim, and objectives of the dissertation.

6. Literature review

The literature review impresses with its versatility and depth of content analysis of available literature. The exposition is characterized by logical consistency, conciseness, and sufficient specificity in presenting the published international experience regarding the effect of apical right ventricular stimulation on the development of cardiac dysfunction over time. The current trends in attempting to overcome the development of heart failure in this group of patients are highlighted, with various methods that have been increasingly entering the field of cardiac pacing in recent years being thoroughly examined. The review presents the author as a well-informed, critically minded, and thorough researcher. Dr. Yoncheva has managed to select the vast information and present it in a summarized form. This approach in presenting the literature shows skillful analysis of available sources and presentation of controversial and poorly clarified issues.

From the data in the literature review, 6 conclusions are drawn, which are related to the rationale of the dissertation. They are well-formed, clearly formulated, and logically pose the unexplored aspects of changes in fibrotic activity in patients after permanent pacemaker implantation. The main points of the conclusions can be outlined as follows: The manifestation of heart failure remains one of the main clinical problems occurring after permanent pacemaker implantation and apical right ventricular stimulation. The mechanisms of myocardial remodeling are the subject of significant research interest, at the core of which are the processes of collagen synthesis and degradation. To date, numerous studies have been conducted in this area, but it should be emphasized that the studies are primarily in experimental conditions on animals, and studies on humans are mainly histological and echocardiographic. Also, the analyzed populations are most often heterogeneous with several comorbidities that are associated with enhanced fibrotic processes. There is no clinical study that comprehensively analyzes and tracks over time the mechanisms of collagen synthesis and degradation and their regulation in patients after implantation of a dual-chamber permanent pacemaker.

The **aim** is clearly formulated and fully corresponds to modern scientific pursuits in this direction: To investigate the dynamics of the fibrotic process in patients after implantation of a permanent pacemaker.

The **objectives** are specific and realistic. They are well-defined and adequate for solving the set aim, namely:

- To investigate the fibrotic status before implantation of a dual-chamber permanent pacemaker, at 12 and 24 weeks after implantation, by determining plasma levels of signaling molecules and markers for collagen synthesis TGF-β1, CTGF, PICP, and PIIINP.
- To echocardiographically examine the left atrial volume and the width of the paced QRS complex by tracking changes in these parameters initially on the day after permanent pacemaker implantation, at 6, 12, and 24 weeks thereafter.

7. Clinical contingent and methods

A prospective clinical-epidemiological study was conducted on a sufficient number of patients. The study included 45 patients after permanent pacemaker implantation and 46 controls, meeting predefined inclusion and exclusion criteria. The analyzed groups are maximally identical in terms of demographic and clinical indicators.

The study was conducted at the Virgin Mary University Hospital in Burgas between April 2018 and August 2022. For statistical processing, the data were entered and processed with the statistical package STATISTICA 13.3.0, developed by StatSoft Inc., USA (StatSoft, Inc., STATISTICA Manual (Data analysis software system), Version 11.0, 2018. The author has applied sufficient statistical methods, through which she achieved a qualitative analysis of the investigated issue.

The analyzed groups were very well balanced in terms of demographic and clinical indicators. The correct selection of participants based on multiple exclusion criteria allows for objective comparison of the two groups, which contributes to the reliability of the conclusions drawn and established cause-and-effect relationships. All participants were selected to minimize external influence on fibrotic processes in the body, taking into account the applied drug therapy during follow-up. Both patients and controls were subjected to follow-up for a period of 6 months, with blood samples collected and echocardiographic examinations conducted.

8. Main results and contributions of the dissertation

During the study, a large number of results were obtained and successfully analyzed, systematized, and illustrated, appropriately presented with tables and figures. They create a complex representation of the complex relationships between the depolarization of the heart from the apex of the right ventricle and the provoked cardiac dysfunction. The doctoral candidate has correctly investigated the changes in the studied markers for activated collagen synthesis and regulation, minimizing side factors that can affect fibrotic processes. She conducted a comparative analysis of the investigated indicators and the effect on some echocardiographic parameters. The dynamics of the indicators in the control group were also investigated. I was impressed by the precisely selected patient and control groups, which are without serious concomitant pathology, except for the conduction disorder that led to the need for permanent pacemaker implantation. For the first time, direct evidence is presented for the activation of collagen synthesis after permanent pacemaker implantation with a significant increase in the signaling molecules responsible for it. A specific dynamics in the levels of TGF-β1, CTGF, PICP, and PIIINP has been established, presenting evidence for the myocardial origin of activated fibrotic response after permanent pacemaker implantation. In the discussion of the dissertation, the author's results are compared with those from contemporary specialized literature. Special attention is paid to the need for precision in the therapeutic approach for this group of patients. The conclusion summarizes the most important results of the study.

The dissertation concludes with 7 specific, well-formulated conclusions and 5 contributions.

The conclusions are clear, well-formulated, and reflect the main highlights of the conducted study. It was conducted on well-balanced patient and control groups, which allows the changes in the studied indicators to be associated with high probability with the implantation of a permanent pacemaker. The main regulatory molecules responsible for collagen synthesis undergo unidirectional significant changes during the follow-up period. Serum levels of PICP show a stable upward trend 24 weeks after permanent pacemaker implantation and indicate an increasing synthesis of the specific cardiac interstitial collagen type I during this period. PIIINP is characterized by specific dynamics in values - a significant increase early after the intervention and recovery to baseline levels 6 months after it. It is a prerequisite to assume perioperative tissue trauma as a possible source for increased synthesis of collagen type III. The dynamic changes in the followed electrocardiographic and echocardiographic parameters

confirm the deepening changes in the myocardium in patients after permanent pacemaker implantation.

The scientific contributions are 5 and are of an original nature:

1. The first of its kind clinical study on the fibrotic process after permanent pacemaker implantation was conducted, simultaneously and dynamically investigating profibrotic signaling molecules and markers for collagen synthesis.
2. For the first time, direct objective evidence is presented for the enhancement of collagen synthesis after permanent pacemaker implantation with significant activation of main regulatory mechanisms responsible for it.
3. A specific dynamics in the levels of TGF-β1, CTGF, PICP, and PIIINP has been established, presenting evidence for the myocardial origin of enhanced collagen synthesis after permanent pacemaker implantation.
4. It has been proven that early (up to the 6th month) after permanent pacemaker implantation, the development of structural and electrophysiological changes in the myocardium begins.
5. Regulatory molecules of enhanced collagen synthesis after permanent pacemaker implantation have been specified, which provides an opportunity to seek new therapeutic possibilities for influencing myocardial remodeling.

The abstract is structured according to the requirements. Its content fully corresponds to the dissertation.

9. Critical remarks and recommendations

From a critical perspective, it is appropriate to mention that determining the width of the paced QRS complex is better done automatically at a recording speed of 100 mm/sec, which would allow for more precise measurement of changes in values.

My second remark is that the presentation of results is more appropriate to be separate from their discussion, which would contribute to achieving a chronological perception of the information and the line of reasoning, as well as avoiding some repetitions in the text.

The critical remarks made do not diminish the value and significance of the doctoral candidate's work, but rather aim to encourage personal and creative growth and improvement.

10.Conclusion

In conclusion, Dr. Yoncheva has managed to produce a thorough and comprehensive scientific work. I find the topic very relevant, and the research is very well planned and executed. She has managed to achieve such a result thanks to the in-depth study of the problem, and the statistical methods used guarantee the reliability of her work. The dissertation is coherent, with well-formulated tasks that correspond to a clearly defined aim, there is an exact selection of material, critical evaluation of results, which leads to precisely formulated conclusions.

All this gives me reason to propose to the members of the Scientific Jury at the Medical University of Varna that Dr. Yoncheva be awarded the educational and scientific degree "Doctor".

Reviewer

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

Assoc. Prof. Vasil Dimitrov Velchev, MD, PhD

26.09.24