

REVIEW

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Concerning the DISSERTATION

for the acquisition of an educational and scientific degree "DOCTOR"

with **title: CHANGES IN FIBROTIC ACTIVITY IN PATIENTS AFTER PERMANENT PACEMAKER IMPLANTATION**

by Ivaneta Dimitrova Yoncheva-Biserova, MD, for the award of the scientific and educational degree "DOCTOR"; Research area: 7. Health and Sports; Professional field: 7.1 Medicine; Scientific specialty: Cardiology.

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.

PROCEDURE DETAILS

The doctoral student was enrolled in part-time study for the acquisition of the scientific and educational degree "Doctor" by Order No. P-109-263/02.08.2019 of the Rector of the Medical University of Varna with supervisor Prof. Maria Negrinova Negreva, MD, PhD

The internal defense was conducted on 07/08/2024 before the Departmental Council of the First Department of Internal Medicine and a positive decision was voted on the readiness for defense: Departmental Council protocol No. 10/07/08/2024.

By Order No. R-109-265/31.07.2024 of the Rector of the Medical University of Varna, the dissertation of Ivaneta Dimitrova Yoncheva-Biserova was approved for public defense and the composition of the scientific jury was determined.

The documentation submitted by the doctoral student fulfilled all the requirements of the Act on Development of the Academic Staff in the Republic of Bulgaria, its Regulations and the Regulations for the Development of the Academic Staff at the Medical University of Varna.

I have no conflict of interest caused by my participation in the current scientific jury.

PROFESSIONAL DATA FOR THE DOCTORAL STUDENT

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.

Regarding her professional qualification, Dr Yoncheva has a recognized specialty in Cardiology in 2012. She acquired a basic level certificate in echocardiography at the Medical University of Sofia in 2013, and an expert level certificate in 2014. She received a basic level certificate in pacing in 2013 and an expert level certificate in 2017. The doctoral student upgrades her professional qualification with annual training courses at highly qualified training organizations such as EHRA, Bulgarian Association for Cardiac Stimulation and Electrophysiology, Bulgarian Society of Cardiology, training grants from companies such as Medtronic BG, Abbot BG, etc.

She is prepared for independent work in all the main areas of non-invasive cardiology and pacing.

She is fluent in written and spoken English and Russian.

As can be seen from the presented thesis and related articles and participation in conferences, Dr Yoncheva's scientific interests are focused on pacing and solving the main problems occurring in patients with an implanted pacemaker. This is a prerequisite for the doctoral student to enter into the essence of the pathogenetic mechanisms that are provoked by the induced asynchronous contraction of the left ventricle and resulting risk of heart failure. Investigating in detail the changes that occur in patients with apical right ventricular stimulation gives her the opportunity to discuss the problems and find a place for her scientific activity, which helps her in upgrading her professional experience and qualifications.

RELEVANCE OF THE DISSERTATION

Pacing entered medical practice more than 50 years ago, and currently more than 1,000 devices are implanted per 1 million people in developed countries around the world. Despite the undeniable benefits for patients of overcoming the conduction disorder, attention is increasingly being paid to the negative effects on cardiac function from right ventricular apical cardiac stimulation, and heart failure manifestation is one of the leading clinical problems in this group of patients. In a number of heart diseases, left ventricular dysfunction is associated with changes in the extracellular matrix responsible for the synthesis and deposition of collagen in the myocardial interstitium. Due to the increasing number of patients with implanted electronic devices and heart failure symptoms, we need a thorough investigation of the problem, and clarification of the pathological mechanisms is perceived as a key step towards understanding and influencing the process.

OBJECT OF THE DISSERTATION

The object of Dr Yoncheva's dissertation is the study of fibrotic activity in patients with an implanted pacemaker for a period of 6 months after the procedure. For the first time, markers for collagen synthesis and regulation were investigated in accurately selected patient and control groups without severe concomitant pathology, apart from the conduction disorder that necessitated the implantation of a permanent pacemaker.

STRUCTURE OF THE DISSERTATION

Dr Yoncheva's dissertation is 116 pages long without the references and is illustrated with 5 tables and 34 figures. Some of the figures are presented in the literature review. It is structured according to the traditional model adopted in our country. The ratio of text to illustrations is balanced and perceived without difficulty.

The bibliographic references contain 409 literary sources arranged alphabetically in Latin. Of all the cited source 163 (40 %) were published during the last 10 years. All reference included in the list were cited in the text. 5 of the tables and 21 of the figures were included in the extended abstract. The language is scientifically appropriate.

LITERATURE REVIEW

The literature review takes 55 pages. It is current, logically constructed and examines sequentially the evolution in cardiac stimulation, its positive and negative sides. The review presents the modern views regarding the changes in the myocardial interstitium in various cardiovascular pathologies, as well as the unresolved and open for discussion issues related to this problem.

Changes in left ventricular function after pacemaker implantation and how they can be minimized by various techniques in programming the implanted device are described. The review provides insight into the structure and function of the extracellular matrix in the myocardium and how its remodeling affects cardiac function. Particular attention is paid to the different regulatory mechanisms and signaling pathways involved in ensuring the balance between synthesis and degradation of proteins in the intercellular space and how these processes are disturbed in a realized pathological state. The data from the literary sources on the specificity and sensitivity of the studied markers for collagen synthesis and regulation are analyzed, which justifies the selection of specific molecules in the scientific study. Special attention has been paid to literature data on studies of fibrotic processes after pacemaker implantation. Data on changes in the myocardial interstitium in physiological and pathological conditions and how this can be objectified with imaging methods of research such as echocardiography are presented. Attempts to influence the fibrotic processes in the myocardium with medication and data on future perspectives in this area are discussed.

6 conclusions were made from the literature review, related to the justification of the dissertation work. They are well-formed, clearly articulated and logically present the unexplored aspects of changes in fibrotic activity in patients after PPM implantation. The main identified issues identified were:

- the manifestation of heart failure, remaining one of the main clinical problems occurring after PPM implantation in apical right ventricular stimulation;
- the intimate mechanisms of myocardial remodeling, an object of significant research interest, based on the processes of collagen synthesis and degradation;
- the research carried out to date in this area is mostly in experimental animal settings;
- human studies in this direction are mainly based on histological and echocardiographic studies data;
- the analyzed populations are most often heterogeneous with a number of accompanying diseases that are associated with increased fibrotic process;
- 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

dual-chamber PPM implantation.

The conclusions drawn are a solid argument in favor of the need to conduct a thorough study of the fibrotic response in dynamics in patients after PPM implantation.

AIM AND OBJECTIVES

The aim of the dissertation is correctly and accurately formulated: To study the dynamics of the fibrotic process in patients after implantation of a permanent pacemaker.

The objectives are well formulated and correspond to the set aim:

- investigating the fibrotic status before dual chamber PPM implantation, at 12 and 24 weeks after implantation, by determining the plasma levels of the signaling molecules and collagen synthesis markers TGF- β 1, CTGF, PIP3 and PI3K.
- echocardiographic monitoring of left atrial volume and the width of the paced QRS complex at baseline, on the day after, at 6, 12 and 24 weeks after PPM implantation.

The identified objectives help for a correct approach in the selection of applied methods to achieve the aim of the dissertation, which is a prerequisite for achieving clinically significant conclusions and contributions.

MATERIAL AND METHODS

The dissertation presents and analyzes the results of a study. It is conceived and designed as prospective and single-centered.

The criteria for patient participation in the study were clearly and unambiguously formulated into two groups: inclusion and exclusion criteria. It is worth noting the precise, well-planned selection of the material with a view to achieving the objectives of the study. Extremely purified groups (patient and control) were formed with respect to comorbidities and conditions that would in themselves have an effect on fibrotic activity. Thus, the doctoral student has eliminated to the maximum extent the possibility of their impact on the obtained results, which allows to account as objectively as possible in the conditions of a scientific setting, the net effect of pacing on the investigated indicators.

45 patients after PPM implantation and 46 controls were included in the study, meeting the predefined inclusion and exclusion criteria.

The analyzed groups were very well balanced in terms of demographic and clinical indicators. The optimal selection of the participants enabled an objective comparison of the two groups, which contributed to the credibility of the conclusions drawn and established causal relationships. All participants were selected in such a way as to minimize external influence on the fibrotic processes in the body, taking into account the medical therapy applied during the follow-up. Both patients and controls underwent follow-up for a period of 6 months, with blood samples collected and an echocardiographic examination conducted. Regarding the operative technique, dual-chamber MRI-compatible pacemakers from Medtronic were implanted in all patients. During their programming, constant apical right ventricular stimulation was verified in more than 80% of the time, which also contributed to the maximum elimination of the influence of external factors when reporting the results of the studied indicators.

STATISTICAL PROCESSING OF THE RESULTS

A wide range of modern, diverse and developmentally adequate statistical methods was used, which allowed for clear and specific conclusions to be drawn. A sufficient number of parameters were analyzed that fully corresponded to the design of the study and the set aim and objectives. Statistical data analysis was performed using specialized software STATISTICA 13.3.0 (Version 11.0, 2018). Descriptive statistics, parametric indicators for statistical hypothesis evaluation, comparison of relative shares and dependency analysis were used. Power analysis was conducted, representing the adequacy of the sample size and correctness of the conclusions made, related to the hypothesis of equality of the mean values of the investigated fibrotic indicators. Its use is in itself a testament to the thorough statistical approach to achieve the formulated aim.

RESULTS AND DISCUSSION

The processing of the data and obtained results are presented in the eponymous chapter of the dissertation in 37 pages. The obtained results derive from the formulated aim and objectives and are very well illustrated. The discussion of the results was performed simultaneously with their presentation, in the course of the exposition. In the discussion, the doctoral student presents his own analysis, comparing it with that of a number of other authors who worked on the problem, correctly cited by her.

The value of the results and the resulting contributions are determined by a number of factors, chief among which are the significance of the investigated indicators and the clinical model in which they were obtained. In this sense, the presented study has two distinguishing characteristics. The fibrotic activity was studied in patients **without severe accompanying pathology**, thereby minimizing external influence on the changes occurring in the monitored objects. Also, the investigated indicators were tracked **in dynamics and in the control group as well**, where no change in the values was detected for a period of 6 months. Activation of the regulatory mechanisms responsible for enhanced collagen synthesis in the extracellular matrix was unequivocally shown. Conclusions were made regarding the specific features of deposition of structural proteins in the myocardium in patients with HF manifestations and implanted pacemaker. Of particular interest were the results in the dynamics of the two investigated collagen synthesis markers, discussing the effect of surgical trauma during implantation on changes in the levels of one of the indicators. This gives reason to assume that the obtained results are not only significant, but are also the basis for the seven conclusions drawn. They clearly outline the most important highlights of the conducted research. The study was conducted on well-balanced patient and control groups, which allowed the changes in the studied indicators to be associated with a high probability with PPM implantation. The main regulatory molecules responsible for collagen synthesis underwent significant unidirectional changes during the follow-up period.

Serum levels of PICP showed a steady upward trend 24 weeks after PPM implantation and indicated an enhanced synthesis of cardiac interstitium-specific collagen type I during this period.

PIIINP was characterized by specific dynamics in the values: a significant increase early after the intervention and a recovery to baseline levels 6 months after it. This is a prerequisite to regard the perioperative tissue trauma as a possible source for the increased synthesis of type III collagen.

Dynamic changes in the monitored electrocardiographic and echocardiographic parameters

confirmed the deepening changes in the myocardium in patients after PPM implantation.

CONTRIBUTIONS

The author of the review acknowledges the following contributions of the dissertation:

ORIGINAL SCIENTIFIC CONTRIBUTIONS

1. A first-of-its-kind clinical study on the fibrotic process after PPM implantation was performed by simultaneously and dynamically investigating signaling profibrotic molecules and markers of collagen synthesis.
2. For the first time, direct objective evidence of enhanced collagen synthesis after PPM implantation with significant activation of key regulatory mechanisms responsible for it is presented.
3. Specific dynamics in TGF- β 1, CTGF, PICP, and PIIINP levels were found, presenting evidence for a myocardial origin of enhanced collagen synthesis after PECS implantation.
4. It has been shown that structural and electrophysiological changes in the myocardium begin to develop early (by the 6th month) after PPM implantation.
5. Regulatory molecules of enhanced collagen synthesis after PPM implantation have been refined, providing an opportunity to search for new therapeutic options to influence myocardial remodeling.

The PUBLICATIONS related to the topic comprise of 3 full-text publications, in specialized journals and three communications at scientific forums: one abroad and two in Bulgaria.

CONCLUSION

Dr Yoncheva's dissertation with a title: "Changes in fibrotic activity in patients after permanent pacemaker implantation" is very well structured with a clearly defined aim, correct selection of material, critical evaluation on the results and precisely formulated conclusions. The development meets the requirements of the Act on Development of the Academic Staff in the Republic of Bulgaria, it's Regulations and the Regulations for the Development of the Academic Staff at the Medical University of Varna.

The in-depth nature of the research conducted, the results obtained and contributions allow me to categorically give a **POSITIVE** evaluation of the dissertation.

Заличено на основание чл. 5,
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