

## STATEMENT

**On the dissertation with a title: Changes in fibrotic activity in patients after permanent pacemaker implantation,** presented for public defense before a scientific jury for awarding the educational and scientific degree "Doctor", professional field 7.1 Medicine, scientific specialty "Cardiology"

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**Reviewer: Prof. Zhaneta Georgieva Tyaneva, MD, PhD, Medical University of Varna**

member of the Scientific Jury, confirmed by order P-109-265/31.07.2024 of the Rector of the Medical University of Varna.

### **Biographical data:**

Dr. Yoncheva received MD in 2000 from the Medical University of Sofia. Her professional experience began as a general practitioner in Sofia, and in 2004 she began specializing in Internal Medicine at the First Internal Clinic of the University Hospital at 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.

## **Research activity**

**The dissertation:** Changes in fibrotic activity in patients after permanent pacemaker implantation investigates the change in markers for collagen synthesis and regulation in patients without severe concomitant pathology other than the conduction disorder that led to the PPM implantation. In recent years, the issue of the negative impact of apical right ventricular stimulation has been discussed more and more often, looking for alternatives and ways to minimize it. Although the long-term negative effects on cardiac function after PPM implantation are evident, the molecular mechanisms responsible for myocardial remodeling over time have not been elucidated. In her study, Dr. Yoncheva investigated established biomarkers for collagen synthesis and regulation, tracking them dynamically in both patients and controls. This makes the dissertation particularly relevant and would contribute to understanding the subtle mechanisms of the regulation of the exchange of structural proteins in the myocardial interstitium in patients after an implanted pacemaker.

## **Structure of the dissertation**

The dissertation is 138 pages long, and the structure of the work is logically constructed. The results are presented in 5 tables and visualized in 34 figures. The bibliographic references contain 409 literary sources arranged alphabetically in Latin.

**The doctoral student has 3 publications related to the topic in a specialized journal and 3 communications at scientific forums, 1 abroad and 2 in Bulgaria.**

**Literature review:** The presented review demonstrates a very good knowledge of the literature sources and extraction of in-depth information from them. The author emphasizes the unresolved problems of myocardial interstitium remodeling in various cardiovascular pathologies. Special attention is paid to data from studies conducted on changes in the extracellular matrix after PPM implantation with apical right ventricular stimulation. These studies were mostly in experimental animals. Human studies were mainly histological and echocardiographic, and the populations analyzed were mostly heterogeneous. There is a lack of clarity regarding the processes of collagen deposition as primarily responsible for myocardial ECM remodeling in patients with implanted dual-chamber PPM.

**The purpose** of the study is clearly formulated and specific: a dynamic study of the fibrotic process in patients after permanent pacemaker implantation. **The objectives** are precisely

formulated and defined, aimed at achieving the chosen purpose - 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- $\beta$ 1, CTGF, PIP3 and PIIINP. Echocardiographic study was also performed of the LV volume and width of the paced QRS complex by following the changes in these parameters from baseline on the day after PPM implantation, at 6, 12 and 24 weeks after that.

The study was comprehensive, representative and exhaustive. A wide range of modern, varied and adequate statistical methods were used, which allowed to draw clear and specific conclusions.

**Results and discussion:** The author presented the results grouped sequentially in response to the previously set tasks. The discussion supports the thesis that permanent pacemaker implantation affects serum levels of markers of collagen synthesis and regulation. It is suggested that their increase in the patient group towards the end of the follow-up period can be associated with changes in the myocardial interstitium, provoked by the asynchronous ventricular contraction as a result of the apical right ventricular stimulation. Various alternative causes that can lead to dynamics in the investigated indicators are discussed, thus suggesting additional directions for extended scientific research of the problem in the future. *The results are* convincing and precise. They are of scientific value and contributory in nature. The discussion presents a relationship between own results and data from the literature review. I agree with the conclusions drawn and the report for the dissertation's contributions.

**Conclusions:** The doctoral student systematized 7 conclusions in response to the tasks set. The study was conducted on well-balanced patient and control groups. The main regulatory molecules responsible for collagen synthesis underwent unidirectional significant 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. The change in PIIINP levels was characterized by specific dynamics - a significant rise early after the intervention and a recovery to baseline levels 6 months after it. This was a prerequisite to consider perioperative tissue trauma as possible source for the increased synthesis of type III collagen.

**Scientific contributions:** The obtained results have an original character. A first-of-its-kind study was conducted on the fibrotic process after PPM implantation. For the first time,

objective evidence has been presented for the enhancement of collagen synthesis after PPM implantation with significant activation of basic regulatory mechanisms. Specific dynamics in the levels of TGF- $\beta$ 1, CTGF, PICP and PIIINP were found, providing evidence for the myocardial origin of enhanced collagen synthesis after PPM implantation. It has been proven that structural and electrophysiological changes in the myocardium begin to develop by the 6th month after PPM implantation. Regulatory molecules of enhanced collagen synthesis after PPM implantation have been defined. Dr. Yoncheva has traced a further extension of her studies in order to objectify the change in myocardial fibrosis by conducting MRI in patients after PPM implantation and looking for correlations with the dynamics in markers of collagen synthesis and regulation and conducting a study to investigate the change in fibrotic activity after pacemaker implantation.

#### **Conclusion:**

The dissertation presented by Dr. Yoncheva is relevant for modern cardiology. It precisely combines an in-depth analysis of literary data with own research and conclusions. The doctoral student contributed to a significant clarification of the changes occurring in patients after implantation of a permanent pacemaker.

The presented dissertation and scientific publications **cover the minimal scientometric criteria for awarding the scientific and educational degree "doctor" according to the Regulations for the Development of the Academic Staff at the Medical University of Varna. The dissertation has important original and confirmatory contributions.**

**I give a positive vote for awarding the scientific degree "Doctor" to**

**IVANETA DIMITROVA YONCHEVA-BISEROVA, MD**

**16.09.2024**

**Varna**

**Reviewer:**

**Prof. Zh. Georgieva, MD**

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