STANDPOINT

on behalf of Prof. Nikolay Margaritov Runev, MD, PhD,
Clinic of Propaedeutics of Internal Medicine "Prof. Dr. St. Kirkovich" -
University Hospital "Aleksandrovska", Medical University - Sofia

Subject: dissertation on the topic:

"Cardiotoxicity in traditional and contemporary antineoplastic regimens"

in a doctoral program **"Cardiology"** at the professional direction **7.1 Medicine** of the field of higher education **7. Healthcare and Sports**

for the award of **the educational and scientific degree "Doctor" to Svetoslava Elefterova Slavcheva MD**, a full-time doctoral student at First Department of "Internal Medicine" of the Faculty of Medicine at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Order No. R-109-101/28.01.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna for the appointment of a scientific jury.

Structure of the dissertation work

The dissertation is written on 222 pages, of which 55 - literature review; 4 - purpose, tasks, material and methods; 87 - results; 37 pages - discussion; 3 - conclusions and contributions; 13 pages - bibliography (total number of cited sources - 262, of which 4 - in Cyrillic).

The dissertation is structured in the classical way with relative compliance of the proportions between its separate parts according to the generally accepted requirements in our country.

Relevance of the topic

The topic of the dissertation is relevant both in theoretical and scientific-practical aspects. I have the following reasons for this statement:

1. Cardiovascular and oncological diseases are the two most common causes of death in the population worldwide. This determines the **rapid development of the cardio-oncology** in recent years in the direction of conducting more effective antitumor treatment with a lower degree of cardiotoxicity.

2. In clinical aspect, special attention is paid not only to changes in the parameters of contractile-pump function, but also to the assessment of **early diastolic myocardial dysfunction** in patients on antitumor therapy in order to slow the progression to heart failure.

3. **Recommendations for the assessment of** asymptomatic or symptomatic **left ventricular (LV) dysfunction**, including changes in myocardial deformation in patients on oncological therapy (OT), have been created and are being updated in a timely manner.

Knowledge on the topic

The review shows that **Dr. Slavcheva has thoroughly acquainted with the available literature on the subject**. She summarizes that:

1. **Monitoring right ventricular (RV) function** in patients undergoing antitumor treatment **remains a challenge** in the clinical practice, as the data known so far come from studies of small and heterogeneous populations, and the obtained results do not provide unambiguous information.

2. **The clinical significance and prognostic value of the right ventricular myocardial damage** in patients undergoing oncological therapy **have not been sufficiently clarified**, as well as the possibilities for including preventive treatment in expected cardiotoxicity.

3. The modern assessment of early, subclinical changes in myocardial function is based on parameters derived from 3D EchoCG and Speckle-tracking EchoCG, which requires specialized equipment and serious cardiological expertise. These limitations make their routine measurement difficult during follow-up examinations of oncological patients and raise **the question of developing easily applicable clinical algorithms in practice.**

Thus, the author fully justifies the idea of her study.

The aim is clearly stated:

To perform prospective study on the change in right ventricular systolic and diastolic function in different chemotherapy regimens and to propose an easy-to-use algorithm for echocardiographic assessment of the right ventricle.

For the fulfillment of this goal, **5 specific tasks** have been set.

The material and the methods give full grounds to believe in the obtained results.

The study was conducted in the First Cardiology Clinic and the Clinic of Medical Oncology at the University Hospital "St. Marina" - Varna during the period June 2019 - February 2024. It included 60 patients with an average age of 53±12 years, (91.7% women) who were scheduled for chemotherapy for breast (83.3%) or gastrointestinal (16.7%) neoplasms.

The patients with the following diseases were excluded from the study:

- ✓ chronic lung diseases with pulmonary hypertension,
- ✓ pulmonary thromboembolism,
- ✓ hemodynamically significant valvular heart disease,
- ✓ permanent atrial fibrillation,
- ✓ known coronary artery disease,
- ✓ systolic left ventricular dysfunction,
- ✓ chronic heart failure.

All patients underwent clinical and echocardiographic evaluation before the start of OT and at subsequent visits (median: 5 visits) for 18 months. Half of the studied patients were treated with anthracyclines (epirubicin) for a period of 106 days (median), and 29 - on HER-2 targeted therapy with trastuzumab for 447 days (median).

The echocardiographic evaluation was performed by one cardiologist and included conventional parameters from 2D EchoCG and tissue Doppler for analysis of LV and RV function according to the Recommendations of the European Society for Cardiovascular Imaging and the American Society of Echocardiography.

Modern statistical processing of the results was performed, with the null hypothesis defined at a significance level of $\alpha = 0.05$.

The following analyses were used:

- ✓ descriptive statistics,
- ✓ t-test for comparison of quantitative variables,
- ✓ correlation analysis,
- ✓ linear and logistic regression univariate and multivariate analysis,
- ✓ Bland-Altman test for assessment of the variability of echocardiographic parameters
- ✓ ROC analysis.

Characteristics of the results and the discussion:

The author finds the following:

1. By assessing conventional echocardiographic parameters, early changes in the **left ventricular systolic and diastolic function** can be detected in the first 1-3 months after the start of OT.

2. The conventional echocardiographic parameters for **analysis of the right ventricular function** show significant dynamics in the first 1-3 months after the start of antitumor treatment.

3. The oncological therapy can lead to **asymptomatic changes in the parameters of the diastolic and systolic right ventricular myocardial function**, without being accompanied by left ventricular dysfunction.

4. Right **ventricular systolic tissue velocity S`** is an indicator that changes earlier after the start of OT and is characterized by lower variability compared to RVFAC (right ventricular fractional area change) in systole and diastole, therefore it is more suitable for monitoring the right ventricular function during oncological treatment.

5. In the studied population of patients on OT, there are **significant correlation and prognostic relationships between diastolic and systolic parameters from tissue Doppler** for both right and left ventricles, which suggests their routine monitoring in practice.

The results are presented in 41 tables and are well visualized with 83 color figures.

An analytical discussion of the obtained clinical and echocardiographic results for the changes in systolic and diastolic right ventricular function has been made in patients on different chemotherapy regimens, as well as a comparison with the literature data.

The limitations of the study are correctly indicated.

I agree with the reference about the contributions of the dissertation work.

Conclusion:

A single-center study was conducted on an insufficiently studied problem in the cardio-oncology: assessment of changes in right ventricular systolic and diastolic function during the follow-up of patients on OT.

The relevance of the chosen topic should be highlighted, as well as the **deep knowledge of the author** of the literature published to date on the discussed questions.

Based on the obtained results, important **conclusions** were drawn **for the inclusion** of the following indicators **as a mandatory minimum** in the echocardiographic assessment of cardiac function in oncological patients:

(1) **systolic tissue velocity of the right ventricle** as a reliable parameter with low variability and

(2) **early diastolic tissue velocity e` of the right ventricle**, which at a value of <9.8 cm/sec is a predictor of right ventricular dysfunction in the studied population.

Particularly valuable is the **algorithm** proposed by Dr. Slavcheva **for assessment and monitoring of patients undergoing oncological treatment**, including cardiac biomarkers and echocardiographic parameters for systolic and diastolic function of the left and right ventricles.

This work can serve as a basis for conducting additional studies in the cardio-oncology in order to optimize the **complex approach** to **patients on OT in our country.**

This gives me grounds **to vote in favor** of the award **of the educational and scientific degree "Doctor"** in the doctoral program "Cardiology" at a professional direction "Medicine" **to Svetoslava Elefterova Slavcheva MD**, a full-time doctoral student at First Department of "Internal Medicine" of the Faculty of Medicine at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

21.02.2025

Prof. Nikolay Runev, MD, PhD