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“Cardiotoxicity of traditional and modern antineoplastic therapies”

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The study **aims** to prospectively examine the effects of a variety of chemotherapeutic regimens on the systolic and diastolic functions of the right and left ventricles, as well as to develop a user-friendly algorithm for the echocardiographic evaluation of the right ventricle. The tasks consist of echocardiographic monitoring of standard parameters of the right and left ventricles using 2D echocardiography and tissue Doppler (TDI). Additionally, the analysis focus on examining the correlation between these parameters over time and their relationship with the biochemical marker of myocardial damage, high-sensitive troponin T (hsTnT). The study is approved by the Medical University of Varna's Commission for the Ethics of Research with approval number 84/ 27.06.2019. The research was conducted at the First Cardiology Clinic in collaboration with the Medical Oncology Clinic at the University Hospital “St. Marina” in Varna. Patients aged 18 years or older who have been diagnosed with breast, gastrointestinal, or female reproductive system cancers, scheduled to undergo systemic antitumor therapy and have provided informed consent are the subjects of this prospective observational study. Individuals diagnosed with preexisting cardiomyopathy, valve disorders, heart failure, atrial fibrillation, and chronic pulmonary diseases are ineligible to participate in the study.

The **methods** consist of clinical and echocardiographic evaluations on Day 1 (prior to the commencement of chemotherapy), as well as on the I, III, VI, IX, XII, and XVIII months. The high-sensitive troponin T is analyzed on Day 1, as well as on the I and III months, using the electrohemiluminescent immunotest “ECLIA” with the COBAS A analyzers. The observed left ventricular (LV) echocardiographic parameters include the enddyastolic volume, which is indexed for body surface area (BSA), the left ventricular ejection fraction (LVEF) by the biplane Simpson method, MAPSE, E/A, Tei index, IVRT, deceleration time (DecT), e', E/e', S', assessment of the aortic and mitral valves, and the left atrial volumes. The right ventricular (RV) parameters consist of the end-diastolic area, adjusted for BSA, the right ventricular fractional area changes (RVFAC), TAPSE, S' on the lateral tricuspid annulus, Tei Index, E/A, e', and E/e', the evaluation of the tricuspid valve, the acceleration time (AT) of pulmonary artery blood flow, and the area and volume of the right atrium. Descriptive statistics methods, correlation analysis, and generalized mixed linear and logistics regression analysis are all components of statistical methods. We utilized the “R” programming language, version 4.3.2, released on October 31, 2023.

Results: The final results involve 60 patients, 41 of whom were recruited after receiving funding under the MUV Fund “Science”, and 19 of whom were recruited prior to receiving funding. Nineteen patients were excluded from the analysis as a result of failing to

complete at least three follow-up visits. The mean age of the patients is 53 (31-74 years), and 91.7% are female. Ten percent (n = 6) of the population have type 2 diabetes, and those with hypertension are 45% of the patients (n = 27). Fifty percent (n = 30) of the patients are on ACE inhibitors or ARBs. Twenty-eight patients (45%) take beta blockers. Regarding cancer, the majority of patients, 83.3% (n = 50), are diagnosed with breast cancer, while the remaining 10 patients (16.7%) are with gastrointestinal malignancies of the colon, pancreas, or stomach. In 50% of cases, patients receive treatment with chemotherapy (CT) alone; 48% receive CT and targeted therapy, and one patient receives CT and immunotherapy with pembrolizum. The median CT duration is 106 (IQR 65, 114) days. Anthracyclins (epirubicin) are administered to 50% of the patients (n = 30), with a mean equivalent cumulative dose of doxorubicin of 128 (SD 36) mg/m2. Targeted therapy was administered to 29 patients (48%), with the majority of these patients receiving HER2-targeted therapy with trastuzumab and its modifications (n = 24; 40%). The median length of trastuzumab treatment was 447 days (IQR 353, 630). Six patients was treated with other bevacizumab, lapatinib, and ribociclib. Radiation therapy is used for breast cancer in 45% (n = 27) of the population, with nearly half receiving it in the left chest. Cardiotoxicity risk is evaluated for 45 patients who received anthracyclines and/ or trastuzumab. Out of the total, only seven patients are classified as high risk, while sixteen are assessed as moderate risk. There are no very high-risk patients. The initial dimensional and functional parameters for LV are within the normal ranges. The mean initial LVEF is 64% (SD 6); the minimum is 51%; and the maximum is 75%. The mean septal systolic tissue velocity of LV (septal S'LV) is 8.36 (SD 1.56) cm/s, and the mean systolic velocity on the lateral mitral annulus (lateral S'LV) is 9.72 (SD 2.12) cm/s. The mean initial RV indexed area is 9.14 (SD 1.72) cm2/m2. The mean right atrial indexed volume is 23 (SD 8) ml/m2. The mean RVFAC is 45 (SD 6.3)%, and the mean systolic tissue velocity S' on tricuspid annulus (S' RV) is 12.78 (2.14) cm/s. We followed the patients for a median of 446 (IQR 275, 720) days, with a median of 5 visits (IQR 4, 6). Seventy percent (n = 42) of the population is followed for a period of 12 months or longer.

Main findings from the assessment of the LV and RV function for a period of 18 months after the beginning of oncological treatment:

Left ventricular parameters: A significant decrease in left ventricular ejection fraction (LVEF) is noted by the XII month. The highest absolute decrease in LVEF occurs at the III and VI months, with a decline of 3.3% (95% CI -5.1, -1.5, p <0.001) and 4.3% (95% CI -6.2, -2.3, p <0.001) respectively. Out of the total number of patients, four individuals (6.7%) exhibit a minimum LVEF below 50% and a relative decrease of over 10%. This indicates a diagnosis of cardiac dysfunction produced by OT (CD-OT). There is a substantial reduction in the systolic tissue velocities for the septal S'LV until the XVIII month and for the lateral S'LV until the XII month. The median systolic velocity S'LV, which is the average of the septal and lateral S'LV, is significantly lowered by 0.44 cm/s (95% CI: -0.80, -0.09, p = 0.014) after the first month of starting OT. This decrease in the median S'LV maintains until the XII month, with a reduction of 0.94 cm/s (95% CI: -1.4, -0.52, p <0.001). Thirteen patients had a pathological drop in septal S'LV, with a value of 6 cm/s or below. Additionally, 17 patients had a pathological decline in median S' LV, with a value below 7 cm/s. The assessment of left

ventricular (LV) diastolic function reveals that in 7 patients (11.7%) LV diastolic function deteriorated from the initial normal state. Three patients had diastolic dysfunction I, two had diastolic dysfunction II, and two had diastolic dysfunction III. The risk of LV diastolic dysfunction rises during the sixth and twelfth months of OT, with ORs of 6.0 (95% CI 1.43, 25.2, p = 0.014) and 6.23 (95% CI 1.19, 32.5, p = 0.03), respectively. Radiation therapy is a major contributor to the development of diastolic dysfunction, increasing the probability by sixfold (OR 6.21, p <0.01). The Tei index from tissue Doppler (TDI) on the medial mitral annulus (LVMPI-TDI) displays an increase of 0.03 (95%CI 0.06, p = 0.041) at the III month. However, there is no significant alteration in the index after this monitoring period. The LVMPI-TDI, measured on the lateral mitral annulus, did not exhibit substantial changes during and after the OT. The LVMPI parameter, as assessed by PW Doppler, increases by 0.04 at 6 months (95% CI 0.00, 0.08, p = 0.045) and shows a marginal statistical significance at the XII month (β 0.04, 95% CI 0.08, P = 0.055). The mean value for the maximum elevated PW-LVMPI population is 0.56 (SD 0.12). This rise occurred in a median of 108 (IQR 45.8, 392.5) days.

Right ventricular parameters: We detected a significant decrease in RVFAC of 2.3% (95% CI: -3.9, -0.75, p = 0.004) as early as the first month after the initiation of OT. The maximum decrease of 3.7% (95% CI -6.9, -0.43, p = 0.026) is observed in the XVIII month. The mean of individual maximum decrease is 7.45% (95% CI 6.0, 8.9, P = 0.0000). Right ventricular systolic dysfunction was identified in 23 patients (38%), with a maximum decrease in RVFAC of ≤ 35% and a relative percentage decline of 23% (IQR 15, 29%) after a median of 153 days (IQR 50, 273 days).

The RVFAC intraclass-correlation coefficient for intraobserver variability is 0.79 (95%CI 0.64, 0.89, p <0.001).

Regarding systolic velocity, S 'RV, examined with a tissue Doppler on the lateral tricuspid annulus, coefficient of intraclass-correlation is very high 0.98 (95% CI 0.96, 0.99, p <0.001). The S'RV shows a significant decrease of 0.73 cm/s (95% CI -1.3, -0.17, p = 0.010) as early as the I month, and this decline continues until the XII month (-0.87 cm/s, 95% CI -1.4, -0.32, p = 0.002). In 5 patients, or 8% of the population, the relative reduction of S'RV was reported with more than 15% to a pathological value ≤ 9.5 cm/s. It is possible to determine that these patients have systolic right ventricular dysfunction due to OT, without any accompanying heart failure symptoms. Only two of these patients have an RVFAC below 35%, and none have an LVEF below 50%. Simultaneously, the LV's systolic tissue velocities in these patients are low; the maximal recorded systolic septal S'LV is 7 cm/s, and in three patients, it is ≤ 6 cm/s. The patients are assessed to have varying levels of risk for cardiotoxicity and are administered a range of anti-tumor drugs, including non-anthracycline therapy with trastuzumab, 5FU, docetaxel, and cisplatin. In relation to the parameter TAPSE, 25 patients experienced a drop to pathological levels of ≤ 16 mm at some point throughout the follow-up period, with a mean time frame of 168 days. The evaluation of the diastolic RV function shows 13 cases of new diastolic dysfunction – 6 with impaired relaxation and 9 with pseudonormal filling type. Only in two patients, diastolic disorders persist until the end of their follow-up. The analysis of the tissue Doppler RV Tei index (RVMPI-TDI) indicates a

significant deterioration only at the XVIII month from the beginning of the OT with a borderline statistical credibility (by 0.07, 95% CI 0.13, p = 0.051). In 14 (23%) patients, RVMPI-TDI has a relative increase of more than 20% to a value > 0.55, which is accompanied by a decline of the diastolic parameters of RV. Early RV diastolic tissue velocity is significantly lower in these patients (7.8 (SD 1.22) cm/s vs 10.23 (SD 2.17) cm/s, p <0.001), and the parameter E/e' is significantly elevated (7.81 (SD 2.15) vs. 5.09 (SD 0.85), p <0.001) compared to the rest of the population. The risk profile of patients with pathologically significant change in RVMPI-TDI is characterized by a higher percentage of hypertension, type 2 diabetes mellitus, dyslipidemia, and a high risk of CD-OT.

In 41 patients, we performed hsTnT monitoring. In the majority (n = 29) of them, the hsTnT examination was conducted by the III month, at a small part to the IX (n = 6) and XII months (n = 5). The median initial value is 7.1 ng/l (IQR 4.8, 9.4). The overall dynamics of the hsTnT show an ascending course and a statistically significant rise in values at the III and VI months. The median difference between the initial and maximum value of hsTnT is 1.20 ng/l (IQR 0.39, 3.30). The median relative percentage increase in hsTnT is 23% (IQR 4%, 50%). The hsTnT increase is predictive and results in a small but statistically significant decrease in septal, lateral, and median S'LV (β -0.06, 95%CI -0.11, -0.02, p = 0.005; β -0.08, 95%CI -0.14, -0.01, p = 0.031; β -0.07, 95%CI -0.12, -0.02, p = 0.008). Regarding the RV's systolic tissue velocity, there is a tendency for it to decrease in conjunction with an increase in hsTnT, although this trend does not reach statistical significance (β -0.08, 95CI -0.16, 0.01, p = 0.082).

In order to find the parameters that are suitable for monitoring patients in the conditions of OT and to detect myocardial damage, generalized estimating equations-based multivariable regression models have been prepared. We have positioned multiple parameters to predict the deterioration of LV and RV systolic function. The prognostic factors include LV and RV systolic and diastolic function parameters, oncological systemic and radiation therapy indicators, patient comorbidity, and risk characteristics. We evaluate the regression patterns step-wise to select appropriate predictors, using criteria such as the QIC (Quasi-likelihood under Independence model criterion), AGPC (Akaike-type penalized Gaussian pseudo-likelihood criterion), and SGPC (Schwarz-type penalized Gaussian pseudo-likelihood criterion), and test them with the WALD and Score tests. We form regression models with the most significant prognostic factors for the main functional parameters of RV (RVFAC and S'RV) and LV (LVEF and median S'LV).

The final predictive model for S'RV includes some echoparameters: septal S'LV below 6 cm/s, LVEF, and early diastolic tissue velocity of the RV (e'). The decline in the septal SLV ≤ 6 cm/s is a predictor of a decrease in S'RV by 1.1 cm/s (95% CI -1.9, -0.31, p = 0.007). Early diastolic tissue velocity (e') of the RV and LVEF is positively associated with the S'RV (respectively, β 0.36, 95% CI 0.25, 0.46, p 0.001, and β 0.06, 95% CI 0.01, 0.10; P = 0.012). The other two factors – the duration of CT and the time to start cardioprotective treatment – are statistically significant but do not lead to a significant change in S'RV.

From the systolic TDI velocities of the LV, the median S'LV was selected as it summarizes the indicators of the septal and lateral S'LV. In the regression model to predict the decline of the median S'LV, the most significant factors are again ultrasound indicators. Systolic tissue velocity S'RV and LVEF are unidirectionally linked to the median S'LV (respectively β 0.18, 95%CI 0.11, 0.25; p <0.001 and β 0.07, 95%CI 0.08, p <0.001). Increasing the indicator reflecting the diastolic function of LV, E/e', is associated with a decrease in the median S'LV by 0.24 cm/s (95% CI -0.30, -0.19, p <0.001).

The regression model for predicting the change in RVFAC, after the evaluation, includes as a statistically significant prognostic factor only the time from the beginning of OT (β -1.4, 95%CI -2.6, -0.25, p = 0.018), which incorporates different modalities of OT and their duration.

The final regression model for prediction of the LVEF shows that the therapy with the trastuzumab and the combined sequential therapy with anthracyclines and trastuzumab are associated with a decrease in LVEF, respectively by 2.6% (95% CI -5.2, 0.05) and 4.0% (95% CI -6.9, -1.2, p = 0.005). From echoparamters, statistical significant factor is the median S'LV ≤ 7 cm/s for decrease in LVeF by 4.3% (95% -6.6, -2.0. P <0.001). The time from starting of the OT is associated with a drop in LVEF by 1.7% (95% CI -2.9, -0.53, p = 0.004).

None of the regression models include factors such as risk of CD-OT, age, comorbidities, radiation, or endocrine therapy, which is valid for the specific population studied. The regression models and analysis of the individual indicators for right ventricular and left ventricular function indicate a decline after the onset of the OT and a correlation between them. The earliest decrease, in the first month, is found for the parameters of RV, RVFAC, and S'RV. At the same time, S'RV is a prognostic factor for reducing the median S'LV. S'RV, in turn, is a predictor of a decrease in LVEF. This enables the inclusion of these indicators in the ultrasound functional cardiac evaluation of patients undergoing systemic OT.

The algorithm given for assessing the right and left ventricles involves measuring S'RV, e''RV, septal, lateral, and median S'LC, as well as E/e' of the LV, LVEF, and RVFAC at each stage of follow-up. Furthermore, the tissue Doppler parameters, including the systolic and diastolic velocities of the left ventricle (LV) and right ventricle (RV), exhibit minimal variability and do not necessitate the use of highly specialized equipment. As per the guidelines of the European Cardiology Society, if it is not possible to monitor the deformation indices of the left ventricle (LV) and right ventricle (RV), they can be substituted with the systolic tissue Doppler imaging (TDI) velocities of the LV and RV. These indicators can be effectively monitored in clinical practice.

Contributions:

1. A particular study has demonstrated a change in the systolic and diastolic function of RV due to cancer therapy, which includes anthraciclin-based, non-anthraciclin-based regimens and HER2-targeted therapy.
2. The parameter systolic tissue velocity S'RV, which undergoes an early decrease, has low variability and even predicts LV systolic dysfunction.

3. We have prepared regression predictive models to identify the most significant indicators for monitoring the LV and RV function in patients undergoing OT.