


Subclinical left ventricular dysfunction in men under androgen deprivation therapy for prostate cancer, revealed by speckle-tracking-derived parameters, repolarization, and myocardial injury markers

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None.

Abstract

Objective: To analyze global left ventricular longitudinal strain (GLS), mechanical dispersion (MD), electrocardiographic repolarization, and myocardial injury markers changes during androgen deprivation therapy (ADT) and subsequent hypogonadism in men with advanced prostate cancer.

Methods: We included 31 patients 69.7 ± 7.3 years old, in sinus rhythm, with stable cardiac conditions and evaluated them by echocardiography, electrocardiography, and blood sampling for high sensitivity cardiac troponin I (hs-cTnI), and N-terminal pro-brain natriuretic peptide (NTproBNP), at ADT initiation (M0) and after 6 months of treatment (M1). Peak longitudinal strain by speckle-tracking echocardiography was assessed in 17 left ventricular segments and averaged to GLS. Standard deviation of time intervals from the start of Q/R on electrocardiogram to peak longitudinal strain in the 17 segments (MD_{SD}), and the difference between the longest and shortest time-to-peak strain intervals (MD_{delta}) were calculated as indices of MD. Fridericia corrected electrocardiographic repolarization parameters were analyzed as follows: QT interval (QTc), mean and maximum values of Tpeak-Tend interval (Tpe), and Tpe/QT ratio, Tpe dispersion (Tped).

Results: Significant impairments of the following parameters were registered between M0 and M1: GLS (%) (-16.93 ± 3.89 ; -14.43 ± 3.57 , $P < .001$), MD_{SD} (ms) (77.4 ± 21.4 ; 89 ± 27 , $P = .004$), MD_{delta} (ms) (225.3 ± 78.3 ; 259.9 ± 108.4 , $P = .02$), QTc (ms) (458.8 ± 43.4 ; 485.6 ± 45.1 , $P = .01$), maxTpe/QT (0.246 ± 0.04 ; 0.268 ± 0.04 , $P = .01$), maxTpe (ms) (105.4 ± 23.2 ; 119.5 ± 26.4 , $P = .01$), meanTpe (ms) (83.3 ± 16.8 ; 90.7 ± 19.3 , $P = .02$), and hs-cTnI (ng/mL) (4.6 ± 5.4 ; 5.4 ± 6.4 , $P = .01$). Mean serum testosterone level at M1 was 0.1 ± 0.13 ng/mL. The patients' clinical cardiologic status remained stable during follow-up.

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Conclusions: ADT and subsequent hypogonadism induce subclinical alterations in GLS, MD, electrocardiographic repolarization parameters, and hs-cTnI during the first 6 months of treatment.

KEYWORDS

brain natriuretic peptide, cardiac toxicity, left ventricular function, myocardial strain, transthoracic echocardiography

1 | INTRODUCTION

Cardio-oncology investigates the cardiotoxicity of chemotherapy, radiotherapy, and other oncological therapies such as biological therapy, monoclonal antibody therapy, and hormone therapy. Some studies¹⁻⁵ but not all⁶ suggest that androgen deprivation therapy (ADT) indicated in advanced prostate cancer,⁷ and its subsequent hypogonadism can induce cardiac electrical instability and cardiotoxicity. It is difficult to separate the deleterious cardiac effects of hypogonadism itself from those of ADT, both of them being able to damage the cardiac repolarization parameters and to increase the risk of severe ventricular arrhythmias.¹⁻⁴ However, clinical studies have indicated that, compared with orchiectomy, the use of ADT is associated with a higher risk of coronary heart disease, sudden cardiac death, and myocardial infarction.^{8,9} There are no consensus guidelines for cardiotoxicity assessment during ADT, as there are for chemotherapy,¹⁰ where longitudinal global strain (GLS) reduction of more than 15% from baseline, left ventricular ejection fraction (LVEF) decrease of more than 10% below the lower limit of normal and prolongation of corrected QT interval (QTc) on ECG suggest cardiotoxicity. GLS impairment is more sensitive than LVEF in predicting cardiac side effects of chemotherapy.¹¹ Simultaneous reduction in GLS and elevation of high sensitivity cardiac troponin improves cardiotoxicity risk assessment.^{10,12}

Mechanical dispersion reflects cardiac electrical abnormalities including both activation time and refractoriness.¹³ A prolonged mechanical dispersion assessed by the standard deviation of time-to-peak myocardial longitudinal strain intervals in the 17-segment left ventricular model (MD_{SD}), and the difference between the longest and shortest time-to-peak strain intervals (MD_{delta}) showed to be a predictive factor for ventricular arrhythmias and sudden cardiac death after myocardial infarction, in hypertrophic cardiomyopathy and long QT syndrome¹³⁻¹⁵ and could improve the cardiac evaluation of patients under oncological treatments.

We aimed to evaluate the cardiac effects of ADT and subsequent hypogonadism in patients with advanced prostate cancer by analyzing speckle-tracking-derived parameters of left ventricular function in relation to repolarization and myocardial injury markers changes.

2 | METHODS

We conducted a longitudinal observational analytical study and included consecutive patients with the diagnosis of advanced prostate

cancer treated with ADT, in accordance with urological and oncological recommendations. The study protocol was approved by the local ethics committee and was conducted according to the ethical principles stated in the Declaration of Helsinki. All patients were informed about the aim of the study and signed written informed consent before inclusion.

The patients were screened 5-7 days before beginning ADT and included if they were in sinus rhythm, had optimal echocardiographic windows and no cardiac diseases or at most chronic coronary syndrome, treated arterial hypertension, myocardial infarction more than 6 months before screening, NYHA class I-II heart failure, LVEF $\geq 45\%$, estimated glomerular filtration rate >30 mL/min/1.73 m², diabetes mellitus with glycosylated hemoglobin $\leq 7.5\%$, normal serum potassium, and magnesium and calcium levels.

The exclusion criteria were unstable angina, recent myocardial infarction, NYHA class III-IV heart failure, LVEF $<45\%$, sustained ventricular tachycardia, persistent or permanent atrial fibrillation, complete bundle branch block, diabetes mellitus with glycosylated hemoglobin $>7.5\%$, grade 4-5 chronic kidney disease, electrolyte disturbances, chronic use of drugs known to prolong QTc, life expectancy less than 6 months, and poor echocardiographic window.

No patient received drugs that prolong the QT interval during the 6-month follow-up period.

All patients had blood samples and clinical, echocardiographic, and electrocardiographic examinations at screening (M0) and after 6 months of treatment (M1).

From the blood samples, high sensitivity cardiac troponin I (hs-cTnI), N-terminal pro-brain natriuretic peptide (NTproBNP), and testosterone were analyzed.

2.1 | Echocardiographic assessment

Complete echocardiographic examinations were performed using a Philips iE33 system, following the guidelines for image acquisitions.^{12,16,17} LVEF was measured by the biplane method of disks. By tissue Doppler imaging, using the apical four-chamber view, septal and lateral early diastolic (e'), and late diastolic (a') mitral annular velocities were measured, then averaged, and E/e' ratio was calculated. Speckle-tracking imaging with the Philips Q-Lab software was used for the assessment of global longitudinal left ventricular systolic strain (GLS) and global circumferential left ventricular systolic strain (GCS), after manually optimizing the adequacy

of tracking. An acquisition was considered uninterpretable if the endocardial border was not clearly defined and the recordings needed to be rejected in more than two myocardial segments. This was an eligibility criterion, thus was checked before M0, and only patients with interpretable speckle-tracking acquisitions were included in the study.

According to current guidelines, in adults, GLS < 16% is considered abnormal, GLS > 18% normal, and GLS 16% to 18% is borderline,¹⁸ and a fall of GLS by more than 15% from the baseline value under chemotherapy suggests cardiotoxicity.¹⁰ These cutoff values were used in our study.

Mechanical dispersion was assessed using the standard deviation of time intervals from the start of Q/R on ECG to peak myocardial longitudinal strain in the 17-segment left ventricular model (MD_{SD}) and the difference between the longest and shortest time-to-peak strain intervals (MD_{Δ}) (Figure 1). Both MD_{SD} and MD_{Δ} values were corrected for heart rate using the Fridericia formula.¹⁹⁻²¹

All measurements were performed by a single experienced member of the team, blinded to the patients' data.

2.2 | Electrocardiographic assessment

The following ECG parameters were measured: QT interval, between the onset of the QRS complex and the end of the T-wave measured in all leads; Tpeak-Tend wave interval (Tpe) between T-wave peak and T-wave end in the precordial leads; Tpe/QT ratio; Tpe dispersion (Tped) as the difference between the highest and lowest value of Tpe intervals. The end of the T-wave was measured by the method of the tangent to the steepest slope of the descending portion of the T-wave (Figure 1). The maximum Tpe value (maxTpe) and mean Tpe value (meanTpe) were taken into account during the data analysis. QT, Tpe, and Tped were corrected for heart rate using the Fridericia formula ($QTc = QT/RR^{1/3}$). Leads were considered uninterpretable if the T-wave amplitude was lower than 0.1 mV or if biphasic T-waves were present. The measurements were performed on a stable RR interval, with a heart rate between 50 and 90 beats/min.^{17,18}

For each patient, we compared the variations in the laboratory, echocardiographic, and ECG parameters between visits.

2.3 | Statistical analysis

Data are presented as means \pm standard deviation for numerical variables and as absolute numbers and percentages for categorical variables. Normality was checked using the Shapiro-Wilk test. For numerical variables, parametric (two-tailed Student's *t* test for dependent samples or groups), or nonparametric (Mann-Whitney) tests were used, according to the distribution of data. Linear regression and Pearson's correlation coefficient or Spearman's correlation coefficient were used to assess the correlation between different

numerical variables, according to their distribution. For comparison of categorical data proportions, chi-squared and Fischer's exact tests were used. The statistical analysis and the graphic representations of data were performed using STATISTICA version 8. A *p*-value < 0.05 was considered statistically significant.

3 | RESULTS

A total of 31 patients, 69.7 ± 7.3 years old, were included. The basic demographic characteristics and baseline cardiovascular therapy of the study group are shown in Table 1. The baseline serum testosterone level at M0 was 2.2 ± 0.2 ng/mL. It decreased significantly to 0.1 ± 0.13 ng/mL after 6 months of treatment ($P < .001$) (normal values in men: 1.75-7.81 ng/mL). Echocardiographic and ECG data are depicted in Table 2.

At M0, the mean GLS was $-16.93 \pm 3.89\%$, and 11 (35.4%) patients had abnormal baseline GLS values. Between M0 and M1, there was a reduction in GLS to a mean value of $-14.43 \pm 3.57\%$ ($P < .001$). The GLS impairment between visits (defined as percentage fall from baseline) was similar in patients with or without abnormal baseline GLS ($11.4\% \pm 23.6\%$ versus $13.8 \pm 17.1\%$, $P = .74$). Eighteen (56%) patients had a more than 15% GLS fall from M0 to M1, irrespective of the baseline GLS value. GCS did not vary significantly between visits (Table 2). Between M0 and M1, there were also statistically significant prolongations of MD_{SD} , MD_{Δ} on echocardiography, and of QTc, max Tpe/QT, maxTpe, meanTpe, Tped on ECG (Table 2).

The laboratory study demonstrated a statistically significant elevation of hs-cTnI between M0 and M1 and no significant variation of NTproBNP (Table 2).

GLS variation correlated with max Tpe variation (Figure 2) and did not correlate with other ECG or echocardiographic parameters, including LVEF, MD_{SD} , and MD_{Δ} , and neither with hs-cTnI or NTproBNP variations (Table 3). However, patients with abnormal baseline GLS values had a significantly greater increase in hs-cTnI level compared with those with normal baseline GLS values (mean variation of hs-cTnI between visits 1.8 ± 1.8 ng/mL versus 0.2 ± 1.2 ng/mL, respectively, $P = .02$).

MD_{Δ} variation presented a moderate correlation with hs-cTnI variation (Table 3, Figure 3).

The history of chronic coronary syndromes, present in 18 (58.1%) of the study group, did not influence the changes recorded in the echocardiographic, ECG, and myocardial injury parameters under ADT during the observation period (Table 4). Because of the lack of representativity, the other comorbidities did not allow us to analyze their possible contribution to the extent of cardiac changes under ADT.

Patients remained in a stable cardiac condition during the first 6 months of ADT, and no severe ventricular arrhythmias or signs and symptoms of new-onset or worsening heart failure were recorded during this follow-up period.

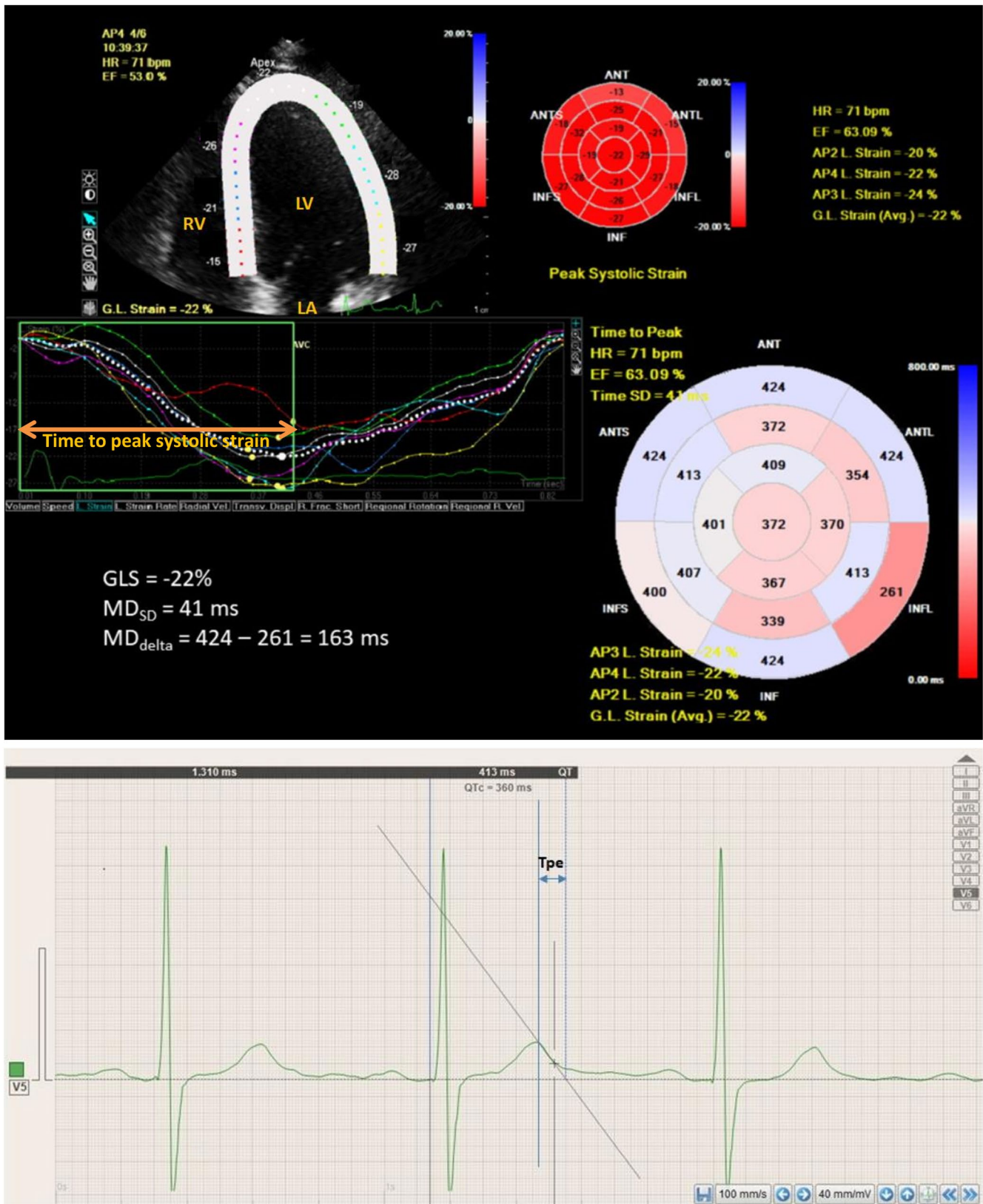


FIGURE 1 Example of measurement of the longitudinal strain derived mechanical dispersion (top) and electrocardiographic parameters of repolarization (bottom); RV, right ventricle; LA, left atrium; LV, left ventricle; GLS, global longitudinal strain; MD, mechanical dispersion

TABLE 1 Baseline characteristics of the study group

	Total (n = 31)
Age (years)	69.7 ± 7.3
Cardiovascular risk factors and comorbidities	
Body mass index > 27 kg/m ²	8 (25.8%)
Diabetes mellitus	7 (22.5%)
Grade 3 chronic kidney disease	5 (16.1%)
Hypertension	22 (70.9%)
Stable coronary artery disease	18 (58.0%)
Old myocardial infarction	5 (16.1%)
Heart failure NYHA class II	3 (9.7%)
Left ventricular ejection fraction (%)	60.7 ± 4.9
Cardiovascular drugs	
Betablockers	16 (51.6%)
Angiotensin-converting enzyme inhibitors	19 (61.3%)
Aspirin	14 (45.1%)
Statins	11 (35.4%)
Calcium channels blockers	7 (22.5%)

Abbreviation: NYHA, New York Heart Association classification of heart failure.

4 | DISCUSSION

ADT is the cornerstone of the treatment in patients with advanced prostate cancer, and there are concerns about the cardiovascular safety of these drugs. Some reported data show that the use of ADT is associated with a higher risk of coronary artery disease, sudden cardiac death, and myocardial infarction, compared with orchiectomy alone.^{3,6} Tsai HK et al⁵ studied 3262 patients with prostate cancer from the Cancer of the Prostate Strategic Urologic Research Endeavor database. 1015 patients received ADT for 1.0–32.9 months, associated with prostatectomy. The 5-year cumulative incidence of cardiovascular death was 5.5% (95% CI = 1.2% to 9.8%) in patients older than 65 years receiving ADT and 2% (95% CI = 1.1% to 3.0%) in those treated with prostatectomy only. However, according to other scientific data, a low serum testosterone level by itself is associated with QTc interval prolongation on ECG, accelerated ischemic heart disease, higher risk of myocardial infarction, and cardiovascular death.⁹ We observed in our patients a statistically significant reduction in GLS from $-16.93 \pm 3.89\%$ at M0 to $-14.43 \pm 3.57\%$ at M1 ($P < .001$) after 6 months of treatment with ADT. Moreover, 18 (56%) patients had a more than 15% GLS reduction from baseline, which is considered a sign of cardiotoxicity in patients under chemotherapy.⁹ Our results are in agreement with other data in the literature. Kanar BG et al²² studied 49 patients 71.5 ± 6.7 years old with prostate cancer, treated with radiotherapy and ADT versus 32 patients, 71.9 ± 7 years old treated with prostatectomy alone and described the reduction in GLS, GCS, and radial strain after 6 months of treatment only in patients who received ADT. Post HK et al²³ demonstrated in 3 patients 66 ± 7 years old

with prostate cancer receiving ADT that GLS decreased from the resting value during exercise, compared to 4 age-matched healthy subjects in whom GLS increased during exercise. In addition, in our patients, neither the baseline GLS value nor the chronic coronary syndrome associated with a greater extent of GLS alteration.

To the best of our knowledge, this study is the first attempt to assess speckle-tracking-derived mechanical dispersion in patients on ADT. In our patients, we observed a statistically significant prolongation of mechanical dispersion that moderately correlated with the significant elevation of hs-cTnI after 6 months of ADT. Studies are pointing to an association between left ventricular systolic impairment revealed by an altered GLS and a rise in myocardial injury markers expressed by hs-cTn elevation in patients who develop heart failure under anthracycline therapy.²⁴ In our study, mechanical dispersion prolongation, and not GLS reduction correlated with hs-cTnI elevation after 6 months of ADT. This fact might suggest that cardiac changes under ADT could be more subtle than under chemotherapy. Temporal inhomogeneity of the ventricular deformation assessed by mechanical dispersion parameters could be more sensitive than the amplitude of the systolic strain assessed by GLS in detecting such subtle cardiac changes under ADT. However, hs-cTnI elevation between M0 and M1 was more pronounced in patients with an abnormal GLS at admission demonstrating that a previous subclinical cardiac dysfunction may be associated with a higher probability of developing cardiac toxicity. This finding is consistent with other studies that showed that patients with previous cardiovascular diseases had a higher risk of cardiac side effects on ADT.²⁵ We observed a statistically significant prolongation of QTc interval, maxTpe/QT ratio, maxTpe, and mean Tpe on ECG after 6 months of treatment. These findings are in line with the results of other studies demonstrating the prolongation of QTc interval on ECG related to arrhythmic effects in patients on ADT with hypogonadism.^{3,8} We found a correlation between the prolongation of max Tpe and the alteration of GLS, suggesting a deleterious effect on both mechanical and electrical cardiac activity.

LVEF did not significantly vary between M0 and M1. These data are in line with the knowledge that LVEF is not sensitive to subtle cardiac changes.²⁰ At the same time, NTproBNP did not significantly vary after 6 months of ADT. In contrast, there are studies reporting elevation of NTproBNP under chemotherapy, related to asymptomatic cardiac events.^{26–28} In clinical practice, it is difficult to separate the deleterious effects of ADT from those of hypogonadism itself on cardiac cell repolarization. Both of them can modify the myocardial transmembrane repolarization K currents and may induce torsade de pointes and sudden cardiac death.^{3,29,30} However, some clinical trials and registry data suggest that the risk is greater in patients who receive ADT.^{3,5,6,29} In our study, as there was no group treated with orchiectomy alone, we could not differentiate between a potential cardiotoxic drug effect and effects of hypogonadism itself on the assessed parameters.

In summary, during the first 6 months, ADT and subsequent hypogonadism induced statistically significant changes in some of the

TABLE 2 Variations in the measured parameters between visits in the study group

Parameter	M0	M1	P
Echocardiographic parameters			
SBP during assessment (mm Hg)	141 ± 18	138 ± 15	.24
DBP during assessment (mm Hg)	83 ± 9	80 ± 9	.10
HR during assessment (beats/minute)	72 ± 13	71 ± 11	.54
E/A ratio	0.89 ± 0.35	0.89 ± 0.28	.96
E/e' ratio	9.14 ± 2.61	9.82 ± 2.32	.09
DTE (ms)	243.80 ± 60.04	229.67 ± 53.06	.15
IVRT (ms)	111.03 ± 24.20	111.74 ± 22.28	.82
GLS (%)	-16.93 ± 3.89	-14.43 ± 3.57	<.001
GCS (%)	-17.70 ± 5.38	-16.71 ± 4.81	.27
LVEF (%)	60.69 ± 4.96	59.83 ± 5.62	.33
MD _{SD} (ms)	77.39 ± 21.43	89.09 ± 26.99	.004
MD _{delta} (ms)	225.32 ± 78.29	259.92 ± 108.37	.02
Electrocardiographic parameters			
QRS (ms)	118.0 ± 24.6	114.4 ± 16.6	.50
QTc (ms)	458.8 ± 43.3	476.9 ± 39.7	.03
mean Tpe (ms)	83.3 ± 16.8	90.7 ± 19.3	.02
max Tpe (ms)	105.4 ± 23.2	119.5 ± 26.4	.01
Tped (ms)	39.67 ± 18.43	49.98 ± 19.92	.03
mean Tpe/QT ratio	0.199 ± 0.04	0.206 ± 0.04	.36
max Tpe/QT ratio	0.246 ± 0.04	0.268 ± 0.05	.01
Myocardial injury markers			
hs-cTnI (ng/L)	4.64 ± 5.37	5.40 ± 6.35	.01
NTproBNP (pg/mL)	366.69 ± 576.86	343.66 ± 326.38	.74

Abbreviations: DBP, diastolic blood pressure; DTE, early mitral flow deceleration time; GCS, global circumferential strain; GLS, global longitudinal strain; HR, heart rate; hs-cTnI, high sensitivity cardiac troponin I; IVRT, isovolumic relaxation time; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-brain natriuretic peptide; QTc, Fridericia corrected QT interval; SBP, systolic blood pressure; Tpe, Tpeak-end interval; Tped, Tpeak-end interval dispersion.

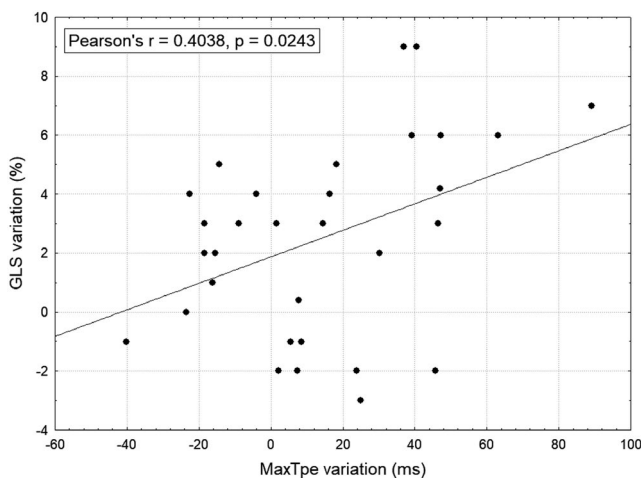
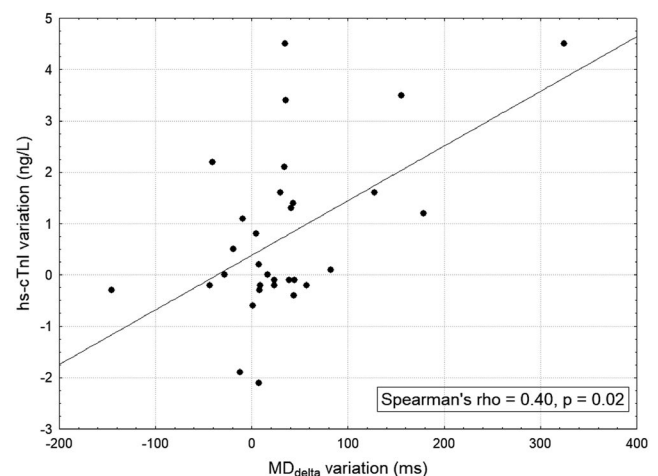
**FIGURE 2** Scatterplot of GLS variation against maxTpe variation; GLS, global longitudinal strain; maxTpe, maximum T peak-Tend interval**FIGURE 3** Scatterplot of MDdelta variation against hs-cTnI variation; MD, mechanical dispersion; hs-cTnI, high sensitivity cardiac troponin I

TABLE 3 Correlation coefficients (^a) and statistical significance of correlations between variations of the parameters measured

Parameter	LVEF		GLS		GCS		MD _{SD}		MD _{delta}	
	Corr. coef. ^a	P	Corr. coef. ^a	P	Corr. coef. ^a	P	Corr. coef. ^a	P	Corr. coef. ^a	P
Myocardial injury markers										
hs-cTnI	-0.13	.47	0.04	.83	-0.01	.96	0.30	.10	0.40	.02
NTproBNP	-0.12	.52	-0.13	.50	-0.14	.47	-0.28	.13	-0.16	.39
Electrocardiographic indices of repolarization										
QTc	-0.21	.25	0.16	.38	0.23	.23	0.02	.93	-0.06	.74
Mean Tpe	0.17	.35	0.29	.11	0.11	.57	0.05	.80	-0.20	.28
Max Tpe	0.12	.51	0.40	.02	0.31	.10	0.10	.95	-0.04	.81
Tped	0.07	.69	-0.24	.19	0.01	.94	0.31	.08	0.10	.58
Mean Tpe/QT	0.28	.12	0.07	.71	-0.07	.72	0.05	.77	-0.19	.31
Max Tpe/QT	0.16	.40	0.23	.21	0.34	.06	-0.07	.69	-0.16	.38

Abbreviations: GCS, global circumferential strain; GLS, global longitudinal strain; hs-cTnI, high sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-brain natriuretic peptide; QTc, Fridericia corrected QT interval; Tpe, Tpeak-end interval; Tped, Tpeak-end interval dispersion.

^aPearson's r for normally distributed variables and Spearman's rho for nonnormally distributed variables; variations in LVEF, MD_{delta}, hs-cTnI, and NTproBNP had a nonnormal distribution.

Parameter	With chronic coronary syndromes (n = 18; 58.1%)	Without chronic coronary syndromes (n = 13; 41.9%)	P
Echocardiographic parameters			
GLS (%)	2.35 ± 3.25	2.7 ± 3.48	.77
GCS (%)	0.73 ± 3.41	1.30 ± 6.42	.75
LVEF (%)	-1.85 ± 5.48	0.50 ± 3.89	.19
MD _{SD} (ms)	8.12 ± 16.93	16.65 ± 26.10	.27
MD _{delta} (ms)	15.50 ± 65.28	61.04 ± 92.94	.12
Electrocardiographic parameters			
QTc (ms)	16.26 ± 38.62	20.60 ± 51.70	.79
mean Tpe (ms)	6.29 ± 16.10	8.87 ± 18.95	.68
max Tpe (ms)	11.42 ± 30.72	17.56 ± 28.90	.57
Tped (ms)	5.78 ± 26.95	16.56 ± 23.16	.25
mean Tpe/QT ratio	0.006 ± 0.034	0.007 ± 0.051	.95
max Tpe/QT ratio	0.020 ± 0.044	0.024 ± 0.053	.85
Myocardial injury markers			
hs-cTnI (ng/L)	0.49 ± 1.63	1.10 ± 1.55	.30
NTproBNP (pg/mL)	-71.17 ± 515.77	43.63 ± 72.11	.43

Abbreviations: GCS, global circumferential strain; GLS, global longitudinal strain; hs-cTnI, high sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-brain natriuretic peptide; QTc, Fridericia corrected QT interval; Tpe, Tpeak-end interval; Tped, Tpeak-end interval dispersion.

TABLE 4 The extent of the measured parameters' variations in patients with and without chronic coronary syndromes

echocardiographic parameters, ECG parameters, and myocardial injury markers as follows: impairment of GLS on echocardiography, which correlated with the prolongation of maxTpe interval on ECG; prolongation of the mechanical dispersion correlated with elevation of hs-cTnI; prolongation of QTc interval, mean Tpe interval, and max

Tpe/QT ratio; and no variation of NTproBNP and LVEF. Patients with a baseline abnormal GLS value had a greater increase in hs-cTnI level, suggesting that baseline subclinical cardiac dysfunction might be associated with a higher probability of cardiotoxicity. By understanding these effects, we will be able to improve the monitoring strategy

of the patients, to prevent arrhythmic events and left ventricular function impairment.

Our patients' clinical cardiological status under ADT remained stable during the 6-month follow-up period, consistent with other reports that did not register any clinical change in the first months of treatment.³⁰ This study has limitations arising from the research design and also the methodology used. This was a single-center research, with relatively restrictive inclusion and exclusion criteria meant to minimize potential confounder factors' effects on the ECG and echocardiographic parameters assessed; thus, a small number of patients analyzed and a relatively short duration of follow-up. The anti-androgen treatment inhomogeneity in the study group, with various agents from different ADT classes and also combined medical therapies, did not allow us to compare the effects of the different ADT agents. Further research is needed on larger cohorts and with longer follow-up periods to assess the long-term arrhythmic and heart failure risk and to design a diagnosis and management strategy for potential cardiovascular deleterious effects of hypogonadism and ADT in patients with prostate cancer. Regarding the methodology, potential limitations for widespread use of the strain-derived parameters in clinical practice arise from the influence of acoustic window quality on proper endocardial border delineation, the possibility of important intra- and inter-observer variability. Additionally, as there are significant differences between vendors regarding the range of normal values for GLS assessed by speckle-tracking echocardiography, we might expect the same for mechanical dispersion.

In conclusion, ADT and the subsequent hypogonadism induce subtle cardiac changes in the first 6 months of treatment, expressed by the alteration of GLS, electrocardiographic repolarization parameters, and elevation of hs-cTnI. The hs-cTnI increase is more pronounced in patients with an abnormal baseline GLS value. The assessment of mechanical dispersion in addition to the traditional parameters of arrhythmic risk might have additive value for cardiotoxicity evaluation.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

ACDG, VJ, ITN, and GSG participated in the study conception and design. ACDG, AC, ASH, and GSG organized the database. ACDG, ASH, GDR, ASCR, ITN, and GSG contributed to data acquisition and interpretation. AC performed the statistical analysis. ACDG, AC, ASH, and GDR drafted the manuscript. VJ, ITN, ASCR, and GSG performed a critical revision for important intellectual content.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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