

# Speckle-tracking derived parameters of left ventricular function, repolarization and myocardial injury markers during androgen deprivation therapy

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## Research

**Keywords:** global longitudinal strain, mechanical dispersion, high sensitivity cardiac troponin, N-terminal pro-brain natriuretic peptide, Tpeak-end interval, androgen deprivation therapy

**Posted Date:** July 23rd, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-45353/v1>

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# Abstract

## Background.

Androgen deprivation therapy (ADT) and subsequent hypogonadism in patients with prostate cancer may cause cardiac toxicity. We aimed to analyse left ventricular longitudinal strain, mechanical dispersion, electrocardiographic repolarization and myocardial injury markers changes during androgen deprivation therapy in patients with advanced prostate cancer.

## Methods.

We included 31 patients with advanced prostate cancer, 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, at ADT initiation and after 6 months of treatment. Peak longitudinal strain by speckle-tracking echocardiography was assessed in 16 left ventricular segments and averaged to global longitudinal strain (GLS). Standard deviation of time intervals from the start of Q/R on electrocardiogram to peak longitudinal strain in the 16 segments ( $MD_{SD}$ ) and the difference between the longest and shortest time to peak strain intervals ( $MD_{\text{delta}}$ ) were calculated as indices of mechanical dispersion. Fridericia corrected electrocardiographic repolarization parameters were analysed: QTc interval, 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: GLS (%) ( $-16.9 \pm 3.9$ ;  $-14.4 \pm 3.6$ ,  $p < 0.001$ );  $MD_{SD}$  (ms) ( $77.4 \pm 21.4$ ;  $89.09 \pm 27$ ,  $p = 0.004$ ),  $MD_{\text{delta}}$  (ms) ( $225.3 \pm 78.3$ ;  $259.9 \pm 108.4$ ,  $p = 0.02$ ), QTc (ms) ( $458.8 \pm 43.4$ ;  $485.6 \pm 45.1$ ,  $p = 0.01$ ), maxTpe/QT ( $0.246 \pm 0.04$ ;  $0.268 \pm 0.04$ ,  $p = 0.01$ ), maxTpe (ms) ( $105.4 \pm 23.2$ ;  $119.5 \pm 26.4$ ,  $p = 0.01$ ), meanTpe (ms) ( $83.3 \pm 16.8$ ;  $90.7 \pm 19.3$ ,  $p = 0.02$ ), hs-cTnI (ng/mL) ( $4.6 \pm 5.4$ ;  $5.4 \pm 6.4$ ,  $p = 0.01$ ).

## Conclusions.

ADT and the subsequent hypogonadism induce alterations of GLS, mechanical dispersion, electrocardiographic repolarization parameters and elevation of hs-cTnI during the first 6 months of treatment.

## Background

Cardio-oncology investigates cardiotoxicity of chemotherapy, radiotherapy, and other oncological therapies as biological therapy, monoclonal antibodies therapy, and hormone therapy. Some studies [1-5] but not all [6] suggest that androgen deprivation therapy (ADT) indicated in advanced prostate cancer [7] and the subsequent hypogonadism can induce cardiac electrical instability and cardiotoxicity. It is difficult to separate the cardiac deleterious 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 indicated that, compared to 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 Q-T interval (QTc) on ECG suggest cardiotoxicity. GLS impairment is more sensitive than LVEF in predicting cardiac side effects of chemotherapy [11]. Simultaneous reduction of GLS and elevation of high sensitivity cardiac troponin improves cardiotoxicity risk assessment [10,12].

## Methods

We aimed to evaluate the cardiac effects of the 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.

We conducted a longitudinal observational analytical study and included consecutive patients with the diagnosis of advanced prostate cancer treated with ADT, in accordance with the urological and oncological recommendations. The study protocol has been 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 the 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 stable coronary disease, treated arterial hypertension, myocardial infarction more than 6 months prior to screening, NYHA class I-II heart failure, LVEF  $\geq 45\%$ , estimated glomerular filtration rate  $>30$  mL/min/1.73 m<sup>2</sup>, diabetes mellitus with glycosylated hemoglobin  $\leq 7.5\%$ , normal serum potassium, magnesium and calcium levels.

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, poor echocardiographic window.

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

All patients had blood samples, clinical, echocardiographic and electrocardiogram 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 analysed.

#### Echocardiographic assessment

Complete echocardiographic examinations were performed using a Philips iE33 system, respecting the guidelines for image acquisitions [12-14]. LVEF was measured by 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. A GLS value under -16% and a fall by more than 15% from the baseline value were considered abnormal [10,15].

Mechanical dispersion was assessed using standard deviation of time intervals from the start of Q/R on ECG to peak myocardial longitudinal strain in the 16 segment left ventricular model ( $MD_{SD}$ ) and the difference between the longest and shortest time to peak strain intervals ( $MD_{\Delta}$ ) (Fig. 1). Both  $MD_{SD}$  and  $MD_{\Delta}$  values were corrected for heart rate using Fridericia formula [16-18].

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

#### 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 ( $T_{pe}$ ) between T wave peak and T wave end in the precordial leads;  $T_{pe}/QT$  ratio;  $T_{pe}$  dispersion ( $T_{ped}$ ) as the difference between the highest and lowest value of  $T_{pe}$  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 (Fig. 1). Maximum  $T_{pe}$  value ( $maxT_{pe}$ ) and mean  $T_{pe}$  value ( $meanT_{pe}$ ) were taken into account during the data analysis. QT,  $T_{pe}$  and  $T_{ped}$  were corrected for heart rate using Fridericia formula ( $QT_c = QT/RR^{1/3}$ ). 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 [14,15].

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

## 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 Shapiro-Wilk test. For numerical variables, parametric (two-tailed Student's t-test for dependent samples or for groups) or non-parametric (Mann-Whitney) tests were used, according to the distribution of data. Linear regression and Pearson correlation coefficient or Spearman correlation coefficient were used to examine 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.

## Results

A total of 31 patients 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  $2.2 \pm 0.2$  ng/mL. It decreased significantly to  $0.1 \pm 0.13$  ng/mL after the 6 months treatment ( $p < 0.001$ ) (normal values in men: 1.75-7.81 ng/mL).

Echocardiographic and ECG data are depicted in Table 2.

At M0 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 of GLS to a mean value of  $-14.43 \pm 3.57\%$  ( $p < 0.001$ ). 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  $13.8 \pm 17.1\%$ ,  $p = 0.74$ ). 18 (56%) patients had a more than 15% GLS fall from M0 to M1 irrespective of the baseline GLS value. Patients with abnormal baseline GLS values had a significantly greater increase in hs-cTnI level (mean variation between visits  $1.8 \pm 1.8$  ng/mL versus  $0.2 \pm 1.2$  ng/mL, respectively,  $p = 0.02$ ).

Between M0 and M1 there were also statistically significant prolongations of  $MD_{SD}$  and  $MD_{delta}$ , and of QTc, max Tpe/QT, maxTpe, meanTpe, Tped on ECG (Table 2).

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 (Fig. 2) and did not correlate with other ECG or echocardiographic parameters, including LVEF,  $MD_{SD}$  and  $MD_{delta}$ , and neither with hs-cTnI, NTproBNP variations (Table 3).

$MD_{\text{delta}}$  variation presented a moderate correlation with hs-cTnI variation (Table 2, Fig. 3).

Patients remained in 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.

## Discussion

We observed in our patients a statistical significant reduction of GLS from  $-16.93 \pm 3.89$  at M0 to  $-14.43 \pm 3.57$  at M1 ( $p < 0.001$ ) 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 al. [19] studied 49 patients  $71.5 \pm 6.7$  years old with prostate cancer, treated with radiotherapy and ADT versus 32 patients,  $71.9 \pm 7$  years old treated with prostatectomy and described the reduction of GLS, GCS and radial strain after 6 months of treatment only in patients who received ADT. Post HK et al. [20] demonstrated in 3 patients  $66 \pm 7$  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.

To the best of our knowledge, this study is the first attempt to assess speckle-tracking derived mechanical dispersion in patients on ADT. Mechanical dispersion reflects cardiac electrical abnormalities including both activation time and refractoriness. A prolonged mechanical dispersion assessed by  $MD_{\text{SD}}$  and  $MD_{\text{delta}}$  showed to be a predictive factor for ventricular arrhythmias and sudden cardiac death after myocardial infarction, in hypertrophic cardiomyopathy and in long Q-T syndrome [21–23]. In our patients we observed a statistically significant prolongation of mechanical dispersion that did not correlate with the impairment of GLS, but moderately correlated with the significant elevation of hs-cTnI after 6 months of ADT. There are studies demonstrating that the GLS reduction associated with hs-cTn elevation predict the occurrence of heart failure under anthracycline therapy [24]. At the same time, there are no studies regarding the correlation between the variation of mechanical dispersion and the variation of hsTn under chemotherapy or ADT. In our patients hs-cTnI elevation did not correlate with GLS impairment during 6 months of 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 to develop 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 on ECG a statistical significant prolongation of QTc interval, maxTpe/QT ratio, maxTpe, and mean Tpe 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. This data are in line with the knowledge that LVEF is not sensitive to subtle cardiac changes [17]. 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 is difficult to separate the deleterious effects of ADT from those of the hypogonadism itself on cardiac cells repolarization. Both of them can modify the myocardial transmembrane repolarization K currents and may induce torsade de points 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 summary, during the first 6 months, ADT and hypogonadism induce an impairment of GLS on echocardiography which correlates with the prolongation of maxTpe interval on ECG, a prolongation of the mechanical dispersion, correlated with elevation of hs-cTnl and a prolongation of QTc interval, mean Tpe interval, max Tpe/QT ratio, but no variation of NTproBNP and LVEF. Patients with a baseline abnormal GLS value had a greater increase in hs-cTnl 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 months 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 rising from the small number of patients analysed and the short duration of follow-up. Also, we cannot separate the cardiac effects of the treatment from those of the hypogonadism itself because of the study design. Additional research is needed to assess the long-term arrhythmic and heart failure risk effects of ADT versus hypogonadism in patients with prostate cancer.

## Conclusions

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-cTnl. The hs-cTnl increase is more pronounced in patients with an abnormal baseline GLS value. The assessment of the mechanical dispersion in addition to the traditional parameters of arrhythmic risk might have an additive value for cardiotoxicity evaluation.

## List Of Abbreviations

ADT - androgen deprivation therapy

GLS - global longitudinal left ventricular systolic strain

GCS - global circumferential left ventricular systolic strain

hs-cTnI - high sensitivity cardiac troponin I

LVEF - left ventricular ejection fraction

MD<sub>SD</sub> - standard deviation of time intervals from the start of Q/R on ECG to peak myocardial longitudinal strain

MD<sub>delta</sub> - difference between the longest and shortest time to peak strain intervals

NTproBNP - N-terminal pro-brain natriuretic peptide

T<sub>pe</sub> - T<sub>peak</sub>-T<sub>end</sub> wave interval

T<sub>ped</sub> - T<sub>peak</sub>-T<sub>end</sub> wave interval dispersion

## Declarations

### Ethics approval and consent to participate

This study has been approved by the Theodor Burghele Clinical Hospital ethics committee (No.2/2017). All participants were informed about the aim of the study and signed the written informed consent before inclusion.

### Consent for publication

Not applicable

### Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

### Competing interests

The authors declare that they have no competing interests.

### Funding

None.

### Authors' contributions

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. All authors have read and approved the final manuscript.

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## Tables

**Table 1. Baseline characteristics of the study group**

	<b>Total (n=31)</b>
Age (years)	69.7±7.3
<b>Cardiovascular risk factors and comorbidities</b>	
Body mass index > 27 kg/m <sup>2</sup>	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
<b>Cardiovascular drugs</b>	
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%)

NYHA=New York Heart Association classification of heart failure

**Table 2. Variations of the measured parameters between visits in the study group**

Parameter	M0	M1	p
<b>Echocardiographic parameters</b>			
E/A ratio	0.89 ± 0.35	0.89 ± 0.28	0.96
E/e' ratio	9.14 ± 2.61	9.82 ± 2.32	0.09
DTE (ms)	243.80 ± 60.04	229.67 ± 53.06	0.15
IVRT (ms)	111.03 ± 24.20	111.74 ± 22.28	0.82
GLS (%)	-16.93 ± 3.89	-14.43 ± 3.57	<0.001
GCS (%)	-17.70 ± 5.38	-16.71 ± 4.81	0.27
LVEF (%)	60.69 ± 4.96	59.83 ± 5.62	0.33
MD <sub>SD</sub> (ms)	77.39 ± 21.43	89.09 ± 26.99	0.004
MD <sub>delta</sub> (ms)	225.32 ± 78.29	259.92 ± 108.37	0.02
<b>Electrocardiographic parameters</b>			
QTc (ms)	458.8 ± 43.3	476.9 ± 39.7	0.03
mean Tpe (ms)	83.3 ± 16.8	90.7 ± 19.3	0.02
max Tpe (ms)	105.4 ± 23.2	119.5 ± 26.4	0.01
Tped (ms)	39.67 ± 18.43	49.98 ± 19.92	0.03
mean Tpe/QT ratio	0.199 ± 0.04	0.206 ± 0.04	0.36
max Tpe/QT ratio	0.246 ± 0.04	0.268 ± 0.05	0.01
<b>Myocardial injury markers</b>			
hs-cTnI (ng/L)	4.64 ± 5.37	5.40 ± 6.35	0.01
NTproBNP (pg/mL)	366.69 ± 576.86	343.66 ± 326.38	0.74

DTE - early mitral flow deceleration time, IVRT – isovolumic relaxation time, GLS – global longitudinal strain, GCS – global circumferential strain, LVEF – left ventricular ejection fraction, QTc – Fridericia corrected QT interval, Tpe – Tpeak-end interval, Tped – Tpeak-end interval dispersion, hs-cTnI - high sensitivity cardiac troponin I, NTproBNP - N-terminal pro-brain natriuretic peptide

**Table 3. Correlation coefficients (a) and statistical significance of correlations between variations of the parameters measured**

Parameter	LVEF		GLS		GCS		MD <sub>SD</sub>		MD <sub>delta</sub>	
	Corr. coef. <sup>a</sup>	p								
<b>Myocardial injury markers</b>										
hs-cTnI	-0.13	0.47	0.04	0.83	-0.01	0.96	0.30	0.10	0.40	0.02
NTproBNP	-0.12	0.52	-0.13	0.50	-0.14	0.47	-0.28	0.13	-0.16	0.39
<b>Electrocardiographic indices of repolarization</b>										
QTc	-0.21	0.25	0.16	0.38	0.23	0.23	0.02	0.93	-0.06	0.74
Mean Tpe	0.17	0.35	0.29	0.11	0.11	0.57	0.05	0.80	-0.20	0.28
Max Tpe	0.12	0.51	0.40	0.02	0.31	0.10	0.10	0.95	-0.04	0.81
Tped	0.07	0.69	-0.24	0.19	0.01	0.94	0.31	0.08	0.10	0.58
Mean Tpe/QT	0.28	0.12	0.07	0.71	-0.07	0.72	0.05	0.77	-0.19	0.31
Max Tpe/QT	0.16	0.40	0.23	0.21	0.34	0.06	-0.07	0.69	-0.16	0.38

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

<sup>a</sup> Pearson's r for normally distributed variables and Spearman's rho for non-normally distributed variables ; variations of LVEF, MD<sub>delta</sub>, hs-cTnI and NTproBNP had a non-normal distribution.

## Figures

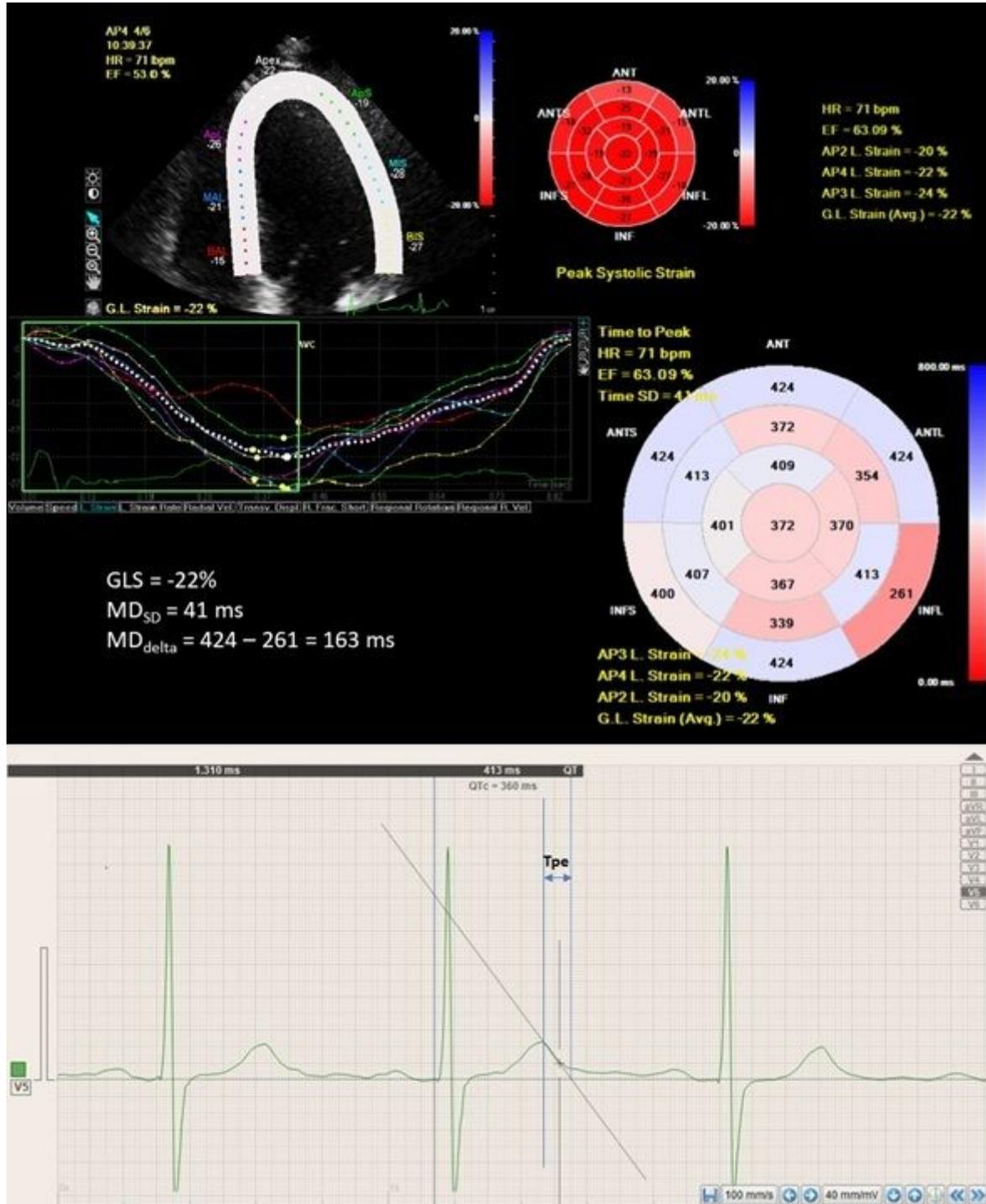


Figure 1

Example of measurement of longitudinal strain derived mechanical dispersion (top) and electrocardiographic parameters of repolarization (bottom)

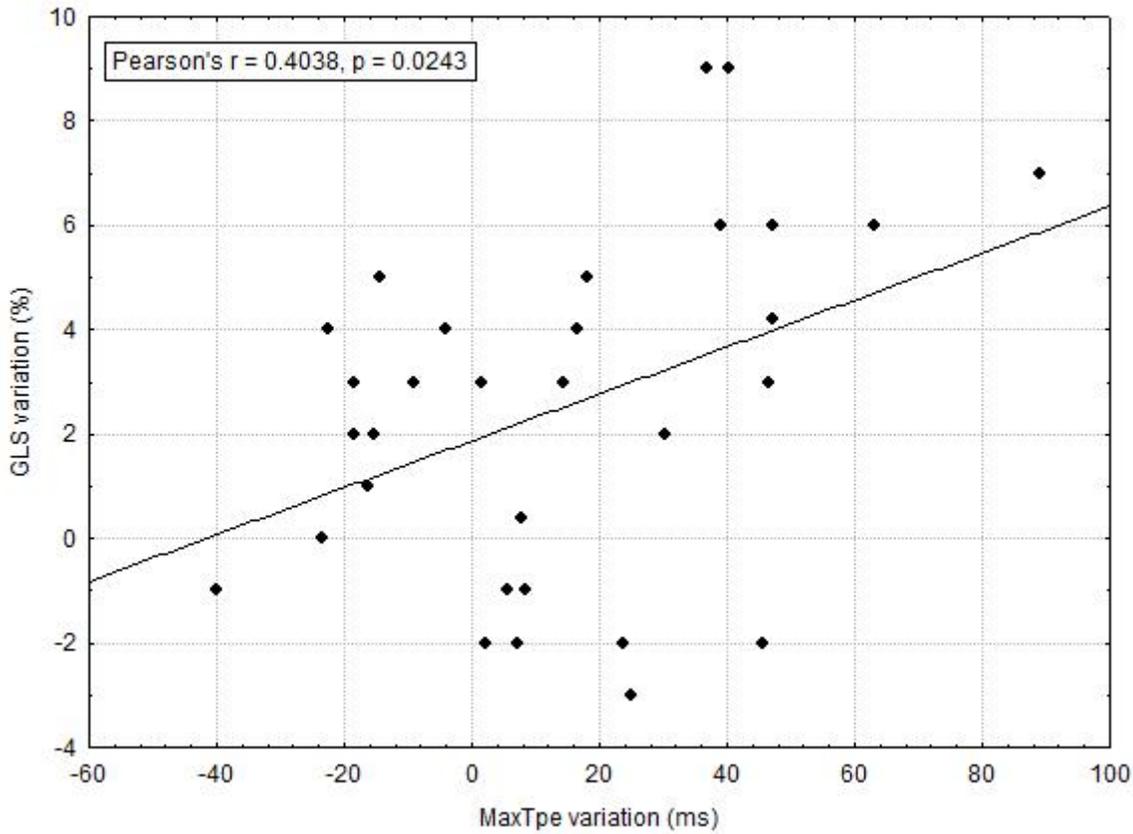


Figure 2

Scatterplot of GLS variation against maxTpe variation

