International Urology and Nephrology (2019) 51:1107–1112
https://doi.org/10.1007/s11255-019-02184-4

UROLOGY - ORIGINAL PAPER

Androgen-deprivation therapy impairs left ventricle functions in prostate cancer patients

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Received: 25 April 2019 / Accepted: 26 May 2019 / Published online: 4 June 2019

Abstract

Background Androgen-deprivation therapy (ADT) is a treatment option for locally advanced and metastatic prostate cancer (PCA). The aim of the study was to evaluate the effect of ADT on left ventricular (LV) functions assessed by speckle-tracking echocardiography (STE) in prostate cancer (PCA) patients.

Methods Forty-nine consecutive PCA patients (mean age 71.5 ± 6.7 years) who would be treated with radiotherapy and ADT and 32 consecutive PCA patients (mean age 71.9 ± 7.0 years) who would be treated with radical or partial prostatectomy and 42 age-matched healthy men (mean age 70.5 ± 9.1 years) were included in our study. The left ventricular functions were assessed by both conventional echocardiography and STE at baseline and 6 months later.

Results There were not any significant difference in characteristics of the patients and controls. There were not any significant differences in conventional echocardiographic measures at baseline and at 6th month among the PCA patients and controls. Although there were not any significant differences in STE measures at baseline among the PCA patients and controls, the strain measures of the PCA patients receiving ADT decreased significantly at the 6th month and were significantly lower compared to strain measures of PCA patients undergoing prostatectomy and controls. There was not any statistically significant difference in baseline and 6th-month strain measures of the PCA patients undergoing prostatectomy.

Conclusions ADT might be associated with decrease in LV longitudinal, circumferential, and radial strain measures in patients with PCA. STE might be useful for early identification of LV subclinical impairment in PCA patients treated with ADT.

Keywords Androgen-deprivation therapy · Echocardiography · Prostate cancer · Testosterone

Introduction

Testosterone has a great number of effects on the cardiovascular system [1, 2], including a substantial impact on cardiomyocyte anabolism by inhibition of apoptosis and upregulation of protein synthesis. This pathophysiology means that testosterone can improve the systolic and diastolic functions of the left ventricle (LV). Recent clinical studies have confirmed that the use of testosterone supplementation improves exercise capacity and symptoms with no effect on the LV ejection fraction (EF) in heart failure patients with a reduced EF [3, 4]. An increasing number

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of studies have also demonstrated a relationship between low testosterone levels and cardiovascular mortality and morbidity in men [4–6]. Conversely, the overuse of anabolic androgens at supraphysiological levels is associated with LV systolic and diastolic dysfunctions, as well as myocardial hypertrophy [7, 8].

Prostate cancer (PCA) is the most common cancer in men [9] and has acceptable survival rates even in patients with advanced disease with different treatment regimens including androgen-deprivation therapies (ADT). Androgens regulate the development, proliferation, cell cycle and major physiological functions of PCA cells [10]. With ADT, the aim is to lower and maintain testosterone levels at the castrated levels (< 20 ng/dl) [11, 21]. Even though this treatment modality increases the overall survival rates of PCA patients, it also has some side effects affecting different organ systems in the body [13]. Recent studies have shown that ADT is associated with the cardiovascular mortality and morbidity [14, 15]. Moreover, the low serum testosterone level causes the decrease of the exercise capacity and the increase of the clinical symptoms in patients with congestive heart failure [3, 16].

The aim of the present study was to evaluate the effect of ADT on LV functions in PCA patients.

Materials and methods

Study population

Overall, 81 patients with PCA and 42 age-matched healthy men were consecutively enrolled in our study. The diagnosis, classification and treatment of the patients were managed according to the PCA diagnosis and management guidelines of European Association of Urology and American Society of Clinical Oncology for PCA [11, 12]. PCA patients had local or locally advanced diseases, and were either treated with radical prostatectomy or radiotherapy (intensity-modulated radiotherapy) combined with ADT. According to the treatment modalities, 49 patients were planned to be treated with radiotherapy and ADT while 32 patients were planned to be treated with radical or partial prostatectomy. The treatment regimen for ADT consisted of an androgen receptor antagonist (bicalutamide 50 mg for 1 month) and a gonadotropin-releasing hormone antagonist (leuprolide acetate 22.5 mg s.c. repeated every 12 weeks) for at least 6 months. Patients were excluded if they had a history of coronary heart disease, atrial fibrillation, congestive heart failure, congenital heart disease, atrioventricular conduction disturbance, moderate or high-grade valvular stenosis or valvular insufficiency.

Clinical, laboratory and echocardiographic evaluations were performed on all participants at baseline evaluation. None of the patients had signs or symptoms of congestive heart failure at baseline examination. The echocardiographic evaluations of the PCA patients were repeated at the 6 months.

Our study was approved by the Ethical Committee based on the Declaration of Helsinki and informed consent was obtained from each participant after the process of the study was clearly explained.

Echocardiographic evaluation

The two-dimensional (2D) echocardiographic evaluations of the LV's systolic and diastolic functions were performed with an ultrasound system (Epic, Philips Healthcare Medical Systems, Andover, MA, USA) in accordance with the guidelines of the American and European Societies of Echocardiography for cardiac chamber quantification and diastolic dysfunction evaluation [17, 18]. Standard echocardiographic views were obtained with a 3.5 MHz transducer in all participants.

Two independent experienced cardiologists performed STE post-processing analysis using the Philips QLAB offline software program (Philips Healthcare Medical Imaging System, Andover, MA, USA). They recorded three consecutive cardiac cycles in the DICOM format for each view, with a frame rate above 50 per second, which seems to be the best compromise between appropriate spatial and temporal resolutions of the heart chambers. The region of interest (ROI) was obtained by tracing the endocardial border of the LV in a still frame at end-systole in STE post-processing analyses [19]. The ROI was adjusted to cover at least 90% of the myocardial wall thickness. If the first tracking was considered suboptimal, other retracings were performed either manually or semi-automatically. The longitudinal strain curves of 6 LV segments [the basal, mid, and apical segments of the LV lateral wall and inter ventricular septum (IVS)], and the longitudinal strain curves of the LV lateral wall were analyzed using the same method. LV longitudinal strain analysis measured the global longitudinal strain (GLS), systolic strain rate (SRS), early diastolic strain rate (SRE), and late diastolic strain rate (SRA) using the apical views (4-, 3-, and 2-chamber). In addition, LV global circumferential strain (GCS) and global radial strain (GRS) were analyzed using short-axis views at the basal, midpapillary, and apical levels as recommended [20, 21]. Systolic strain is the systolic displacement of the tracking segment of the myocardium as a percentage. It is a negative value; the more negative the value is, the greater the deformation and LV function [22].

The same echocardiography machine and same software were used for pre- and post-studies. The two cardiologists who performed echocardiographic examinations were experienced in STE and the LV GLS analysis revealed the intraobserver variability as 7.9% and the interobserver variability 12.3%.

Statistical analysis

All statistical variables were analyzed with the Statistical Package for the Social Sciences (SPSS 22.0 for Mac; Inc., Chicago, IL, USA) software. The disturbances of variables were examined with analytic Kolmogorov–Smirnov or Shapiro–Wilk's tests. Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and percentages. Kruskal–Wallis or ANOVA test was used to compare continuous parameters among the three groups while Wilcoxon or paired samples *t* test was used to compare the continuous parameters before and after treatment. Post hoc analyses were performed using Bonferroni test when an overall statistically significance was determined. A *p* value of < 0.05 was considered statistically significant. Intra- and interobserver variabilities were evaluated using the intraclass correlation coefficient.

Results

The study included 81 patients with PCA and 42 age-matched healthy men.

Forty-nine PCA patients, who were treated with radiotherapy and ADT, had castrated testosterone levels (< 20 ng/dl) at the 3rd month after the initiation of ADT. The remaining 32 PCA patients were treated with radical or partial prostatectomy and did not receive any ADT treatment. The clinical and laboratory characteristics of the PCA patients and controls are shown in Table 1. PCA patients had higher prostate-specific antigen levels compared to healthy controls.

The conventional echocardiographic measurements of the PCA patients and the healthy controls are shown in Table 2. There were not any significant differences in conventional echocardiographic measures at baseline and at 6th month among the PCA patients and controls.

The STE measurements of the PCA patients and controls are shown in Table 3. There were not any significant differences in strain measures at baseline among the PCA patients and controls. The strain measures of the PCA patients receiving ADT decreased at the 6th month while there were not any significant differences in the strain measures obtained at baseline and at 6th month in PCA patients undergoing prostatectomy. The strain measures of the PCA patients receiving ADT at the 6th month were significantly lower than those of PCA patients undergoing prostatectomy and controls while there were not any significant differences in strain measures obtained at the 6th month between the PCA patients undergoing prostatectomy and controls.

Discussion

ADT is a frequently used treatment modality for the management of patients with PCA. We conducted a prospective study to evaluate the potential effect of medical castration on the LV systolic using conventional and advanced echocardiography techniques. Although there were not any significant differences in conventional measures of LV systolic function among the PCA patients receiving ADT, PCA patients undergoing prostatectomy and healthy controls; the STE analyses detected a decrease in strain measurements in the patients receiving the ADT, suggesting that ADT might induce a subclinical LV systolic dysfunction without a significant decrease in the EF in patients with PCA. To the best of our knowledge, our study

Table 1 Clinical and laboratory characteristics of the patients with prostate cancer and healthy control group

	PCA patients receiving ADT (*n* = 49)	PCA patients undergoing prostatectomy (*n* = 32)	Healthy control group (*n* = 42)	*p* value
Age (years)	71.5 ± 6.7	71.9 ± 7.0	70.5 ± 9.1	0.23
Body mass index (kg/m^2)	24.7 ± 7.3	24.1 ± 7.0	25.2 ± 6.8	0.27
Hypertension (%)	19(38.7%)	12(37.5%)	16(38.1%)	0.19
Diabetes mellitus (%)	18(36.7%)	11(34.4%)	12(28.5%)	0.11
COPD (%)	11(22.4%)	8(25.0%)	9(21.4%)	0.22
Smoking (%)	23(46.9%)	15(46.9%)	19(45.2%)	0.15
Hemoglobin (g/dl)	13.7 ± 2.3	13.5 ± 2.2	14.0 ± 2.5	0.29
Creatinine (mg/dl)	0.91 ± 0.5	0.93 ± 0.6	0.89 ± 0.7	0.21
Prostate-specific antigen (ng/ml)	11.4 ± 7.9	9.2 ± 2.8	2.4 ± 0.8	**< 0.001**

Bold values indicate statistical significance $P < 0.05$

ADT androgen-deprivation therapy, *COPD* chronic obstructive pulmonary disease, *PCA* prostate cancer

Table 2 Conventional echocardiographic measurements of the prostate cancer patients and controls

	PCA patients receiving ADT ($n=49$)			PCA patients undergoing prostatectomy ($n=32$)			Healthy control group ($n=42$)		
	Baseline	At the 6th month	P1	Baseline	At the 6th month	P2		P3	P4
LV EDD (mm)	47.3 ± 7.8	46.8 ± 8.3	0.28	48.2 ± 8.1	47.5 ± 8.9	0.23	45.2 ± 3.3	0.21	0.19
LV ESD (mm)	31.5 ± 4.3	30.2 ± 4.0	0.31	30.6 ± 4.5	29.5 ± 4.2	0.28	29.4 ± 4.2	0.25	0.27
IVST (mm)	8.9 ± 2.0	8.8 ± 2.2	0.63	8.4 ± 1.9	8.3 ± 1.8	0.61	7.9 ± 1.8	0.37	0.41
PWT (mm)	8.4 ± 1.7	8.2 ± 1.6	0.51	8.0 ± 1.6	8.1 ± 1.8	0.62	7.4 ± 0.9	0.42	0.57
LV EF (%)	60.8 ± 4.7	59.7 ± 4.4	0.34	61.1 ± 4.1	60.6 ± 4.3	0.46	62.4 ± 3.8	0.29	0.37
E/*A* ratio	0.66 ± 0.2	0.64 ± 0.2	0.27	0.71 ± 0.2	0.68 ± 0.2	0.22	0.75 ± 0.2	0.18	0.25
E/*e′* ratio	18.0 ± 4.8	18.2 ± 4.4	0.37	17.1 ± 4.5	16.9 ± 4.2	0.29	16.6 ± 4.1	0.28	0.19

PCA prostate cancer, *ADT* androgen-deprivation therapy, *LV* left ventricle, *EDD* end diastolic diameter, *ESD* end systolic diameter, *IVST* interventricular septum thickness, *PWT* posterior wall thickness, *EF* ejection fraction, *E* transmitral peak E velocity, *A* transmitral peak A velocity, *e′* lateral mitral annulus early velocity

P1 statistical difference in the conventional echocardiographic measurements at baseline and 6th month in PCA patients receiving ADT; *P2* statistical difference in the conventional echocardiographic measurements at baseline and 6th month in PCA patients undergoing prostatectomy; *P3* statistical difference in conventional echocardiographic measurements at baseline among the PCA patients receiving ADT, PCA patients undergoing prostatectomy and controls; *P4* statistical difference in conventional echocardiographic measurements at 6th month among the PCA patients receiving ADT, PCA patients undergoing prostatectomy and controls

Table 3 Speckle-tracking echocardiographic measurements of prostate cancer patients and controls

	PCA patients receiving ADT ($n=49$)			PCA patients undergoing prostatectomy ($n=32$)			Healthy control group ($n=42$)		
	Baseline	At the 6th month	P1	Baseline	At the 6th month	P2		P3	P4
LV GLS (− %)	23.9 ± 2.9	17.4 ± 3.8[a,b]	**<0.001**	24.8 ± 3.2	24.3 ± 3.9	0.36	24.8 ± 2.9	0.21	**< 0.001**
LV GCS (%)	28.8 ± 3.6	21.1 ± 3.7[a,b]	**<0.001**	27.9 ± 3.5	29.7 ± 3.3	0.17	30.1 ± 3.0	0.19	**< 0.001**
LV GRS (%)	39.6 ± 4.0	26.5 ± 3.3[a,b]	**< 0.001**	38.2 ± 3.9	38.7 ± 4.2	0.35	41.3 ± 3.8	0.27	**< 0.001**
LV GSRS (− 1/s)	2.4 ± 0.1	1.4 ± 0.1[a,b]	**0.02**	2.5 ± 0.2	2.8 ± 0.3	0.26	2.9 ± 0.4	0.13	**0.01**
LV GSRE (1/s)	2.5 ± 0.2	1.2 ± 0.1[a,b]	**0.01**	2.3 ± 0.2	2.2 ± 0.2	0.40	2.5 ± 0.3	0.41	**0.01**
LV GSRA (1/s)	2.6 ± 0.2	1.9 ± 0.1[a,b]	**0.04**	2.7 ± 0.2	2.8 ± 0.2	0.52	2.6 ± 0.2	0.37	**0.02**

Bold values indicate statistical significance $P < 0.05$

PCA prostate cancer, *ADT* androgen-deprivation therapy, *LV* left ventricle, *GLS* global longitudinal strain, *GCS* circumferential strain, *GRS* global radial strain, *GSRS* global systolic strain rate, *GSRE* global early diastolic strain rate, *GSRA* global late diastolic strain rate

P1 statistical difference in the speckle-tracking echocardiographic measurements at baseline and 6th month in PCA patients receiving ADT; *P2* statistical difference in the speckle-tracking echocardiographic measurements at baseline and 6th month in PCA patients undergoing prostatectomy; *P3* statistical difference in the speckle-tracking echocardiographic measurements at baseline among the PCA patients receiving ADT, PCA patients undergoing prostatectomy and controls; *P4* statistical difference in the speckle-tracking echocardiographic measurements at 6th month among the PCA patients receiving ADT, PCA patients undergoing prostatectomy and controls

Post hoc analysis:

[a]Statistically difference between PCA patients receiving ADT and PCA patients undergoing prostatectomy

[b]Statistically difference between PCA patients receiving ADT and controls

is the first to demonstrate a subclinical LV dysfunction using STE in PCA patients treated with ADT.

A great number of clinical trials have currently demonstrated an effect of androgen deficiency on LV functions in patients with congestive heart failure. Ayaz et al. have shown that surgical castration modified the myofilament and calcium-handling proteins and resulted in diastolic dysfunction without a decrease in LV EF in the aging mouse heart at long-term follow-up [23]. Yoshihisa et al. revealed an association between decreased serum testosterone level and myocardial damage, lower exercise capacity and higher mortality in men with heart failure, but they found no statistically significant difference in LV EF [16]. The meta-analysis by Toma et al. revealed that, when compared to a placebo, testosterone supplementation therapy improved exercise capacity without increasing the LV EF in patients with congestive heart failure [3]. Similarly, Kang et al. performed surgical castration in rats with isoproterenol-induced heart failure and found that the EF was higher in the rat group that received testosterone than in the group that received a placebo [24].

Although testosterone has numerous impact on myocytes in cardiac and skeletal muscles, the mechanisms through which it affects cardiorespiratory indexes is still unclear [1]. A low serum testosterone level might cause the decrease of the dissociation for contraction and calcium (Ca^{2+}) transients [23, 25]. Even though Na^{+}/Ca^{2+} exchanger and sarco(endo) plasmic reticulum Ca^{2+}-ATPase type 2 (SERCA2) protein levels were unaffected, phospholamban protein was higher in the low testosterone level. Higher levels of phospholamban protein could prolong Ca^{2+} uptake into the sarcoplasmic reticulum and help explain prolonged Ca^{2+} transient dissociation in myocytes [25–27]. Furthermore, there might be a marked decrease in phosphorylation of essential myosin light chain in the low testosterone level [25–27]. Therefore, changes in myofilaments may contribute to changes in contractile function. These may explain the decrease in strain measurements in ADT receiving PCA patients in our study.

Study limitations

This clinical research had several limitations. First of all, our study population was small. Second, our results should be compared with cardiac magnetic resonance imaging, because it is still the gold standard non-invasive imaging method for diagnosis LV mechanical dysfunction, as it has a higher spatial resolution than echocardiography [28]. However, echocardiography is still the most common method for the evaluation of LV systolic and diastolic functions because of its cost effectiveness, easy accessibility, ability to assess more than ventricular function and absence of exposure to radiation and contrast agents. Technical expertise, good echocardiographic images, and necessary software upgrades are important for strain analysis. PCA patients receiving ADT also received radiotherapy which might also have an adverse effect on LV functions. The concept of ADT having negative effect on cardiovascular system is not new and there are ongoing studies exploring the affect of ADT on LV functions in PCA patients (such as NCT03275181 clinicaltrials.gov). Our findings need to be supported by large-scale and multi-centre clinical studies.

Conclusion

ADT might decrease strain measures and cause impairment in longitudinal, circumferential and radial LV myocardial function while there was not any significant change in LV EF. STE might be useful for early identification of subclinical LV impairment in PCA patients treated with ADT.

Author contributions All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by BGK, MS, EŞ, OO and IT. The first draft of the manuscript was written by BGK, BO and MKT and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Funding No grant received.

Compliance with ethical standards

Conflict of interest There is no conflict of interest. We confirm that all the authors of this submission have understood and approved the journal's licensing policy.

Human/animal rights statement Our research involving human participants.

Ethical approval Our study was approved by the local Ethics Committee regarding Helsinki Declaration and written informed consent was obtained from all participants.

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