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Cardiology

The impact of radioactive iodine treatment on subclinical left ventricular dysfunction in patients treated for differentiated thyroid cancer: assessing the predictive value of presystolic wave

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ABSTRACT

Objectives: Despite strong evidence regarding the impact of radioactive iodine (RAI) on the hematopoietic, genitourinary, and gastrointestinal systems, its role in the cardiovascular system needs to be clarified. We hypothesized that the presence of a presystolic wave could be predictive for cardiovascular dysfunction in subjects receiving RAI. Thus, we investigated presystolic wave presence in differentiated thyroid cancer (DTC) patients with and without RAI therapy after undergoing total thyroidectomy.

Methods: Patients were included in the study within 1-5 years after thyroidectomy or thyroidectomy and RAI treatment. Participants were divided into three groups as follows: the first group included patients with DTC who received RAI following total thyroidectomy (Group 1; n = 33), the second group included patients with DTC who did not receive RAI following total thyroidectomy (Group 2; n = 34). The third group of age-matched subjects who underwent total thyroidectomy with suspicion of DTC and resulted in benign pathologies was also selected (Group 3; n = 37). All subjects underwent transthoracic echocardiography. The presence of a presystolic wave was assessed with Doppler imaging of the left ventricular outflow tract.

Results: Presystolic wave was more common in subjects receiving RAI (Group 1) compared to Group 2 (those without RAI) (90.9% vs. 61.8% respectively, $p = 0.003$), and its prevalence in Group 3 was 54.1%. Multiple logistic regression analysis revealed that receiving RAI (OR: 4.922, 95% CI: 1.640 – 20.022, $p = 0.004$) was independently associated with a 5-fold higher risk for the presence of a presystolic wave.

Conclusions: RAI following total thyroidectomy in patients with DTC is associated with a five-fold increase in the presence of the presystolic wave, as a proxy marker for subclinical left ventricular dysfunction.

Keywords: Differentiated thyroid cancer, radioactive iodine, echocardiography, presystolic wave

Differentiated thyroid cancer (DTC), including papillary and follicular cancer, is one of the most common endocrine malignancies that accounts for about 90% of all types of thyroid cancer. Together with the advances in screening, early diagnosis, and treatment, the prognosis of DTC has considerably im-

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proved in the last few decades. The 10-year survival rate is 85% in DTC; however, 5% of the subjects develop metastatic disease despite aggressive treatment [1].

Treatment of DTC includes surgery, radioactive iodine (RAI), and TSH suppression in the majority of the cases [2]. Partial or total thyroidectomy followed by RAI to reduce residual disease and improve prognosis is the standard of care in most patients with DTC [3]. RAI is tolerated well in general; however, several complications may occur in the hematopoietic system, salivary glands, nasolacrimal apparatus, lungs, gonads, and gastrointestinal system [4]. Although these side effects are temporary and rarely life-threatening, they may still adversely influence health-related quality of life.

Despite the accumulation of data concerning the impact of RAI on the hematopoietic, genitourinary and gastrointestinal systems, its effects on the cardiovascular system have not yet been clearly identified. Ionizing radiation has been shown to cause arterial hypertension in addition to its inhibition of nitric oxide (NO)-mediated vasodilatation, which may further promote the development of vascular inflammation and atherosclerotic vascular disease [5]. However, evidence concerning the impact of RAI on LV function is lacking.

A presystolic wave, which is a late-diastolic event detected on Doppler examination of the left ventricular outflow tract (LVOT), has been shown to be associated with subclinical left ventricular dysfunction [6, 7]. We hypothesized that the presence of a presystolic wave could be predictive for the development or progression of cardiovascular dysfunction in subjects receiving RAI.

This study aimed to investigate the presence of the presystolic wave, which is predictive for subclinical left ventricular dysfunction, in patients with DTC who were treated with RAI after thyroidectomy.

METHODS

Study Design and Patient Selection

Patients aged 18-65 years who had undergone thyroidectomy or thyroidectomy and RAI treatment within 1-5 years were included in this cross-sectional study. Those with known atherosclerotic cardiovascular disorders, heart failure, resistant hypertension, diabetes mellitus, moderate-severe valvular dysfunction, non-sinus rhythm, 10-year cardiovascular risk of >1%, and chronic kidney or liver disease were excluded. Written informed consent was obtained from all subjects. The study was approved by the local ethics committee and was conducted in accordance with the Helsinki Declaration.

Subjects who had undergone thyroidectomy were categorized according to RAI administration. The first group included patients who received RAI following total thyroidectomy (Group 1, n = 33), the second group included patients who did not receive RAI following total thyroidectomy (Group 2, n = 34). Additionally, a group of age-matched subjects who underwent total thyroidectomy with suspicion of DTC and resulted in benign pathologies were selected as the third group (Group 3, n = 37). Cumulative dose of RAI was retrieved from patients' charts and was 100-150 mCi.

Data Collection

All subjects underwent transthoracic echocardiography in a standardized manner by the same cardiologist experienced in cardiovascular imaging in left lateral decubitis using Vivid 5 system (GE Vingmed Ultrasound AS, Horten, Norway) with a 2.5 MHz probe. 2-D measurements were carried out according to the American Society of Echocardiography guidelines [8]. Left ventricular dimensions were measured from the parasternal long-axis view: LV ejection fraction was measured by using the modified Simpson method. Doppler measurements, mitral E and A waves were determined by placing sample volume at mitral valve closure line. Pulse Doppler flow interrogation of LVOT flow was performed just proximal to aortic valve in the apical five-chamber view. The presence or absence of a presystolic wave preceding the LVOT flow was assessed in all patients.

Demographic characteristics, physical examination data and laboratory measurements were retrieved from patient charts. The primary outcome measure of this study was the difference in the presence of presystolic wave among subjects receiving and not receiving RAI. Identifying factors associated with the presence of the presystolic wave was the secondary outcome measure of the study.

Statistical Analysis

All analyses were performed according to a significance threshold of $p < 0.05$ and with use of the SPSS software, version 25 (IBM, Armonk, NY). Data are summarized as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution (assessed with histogram and Q-Q plots). Frequency and percentage (n, %) were used to summarize categorical variables. Continuous variables were analyzed with the Student's t-test or the Mann-Whitney U test depending on normality of distribution. Categorical variable distributions were compared with Pearson or Yate's chi-square tests or the Fisher's exact test. Multiple logistic regression analysis (forward conditional method) was utilized to identify factors independently associated with the presence of presystolic wave. All factors that demonstrated univariate significance were included in the logistic regression model.

RESULTS

A total of 67 subjects with DTC and 37 subjects with non-malingnant pathology were enrolled in the study. The mean time after surgery or radiotherapy was for group 1: 36.2 ± 1.8 months, for group 2: 31.9 ± 1.7 months and for group 3: 32.5 ± 1.7 months. The groups were similar with respect to age, sex, body mass index, systolic and diastolic blood pressure. Comparison of the group 1 vs group 2, and values of group 3 in terms of other characteristics is summarized

Table 1. Demographic features and laboratory measurements of the groups

Variables	Group 1 (n = 33)	Group 2 (n = 34)	Group 3 (n = 37)	*p* value
Age, years	44.82 ± 11.42	44.88 ± 10.46	45.38 ± 9.27	0.087
Female sex, n (%)	28 (84.8)	28 (82.4)	32 (86.5)	0.889
Smoking, n (%)	6 (18.2)	6 (17.6)	2 (5.4)	0.202
Body Mass Index, kg/m^2	29.27 ± 3.87	28.61 ± 3.91	30.13 ± 4.33	0.494
Waist circumference, cm	97.42 ± 10.71	95.21 ± 11.52	95.73 ± 9.72	0.418
Heart Rate, beats/min	82.64 ±12.49	74.97 ± 8.01	81.30 ± 13.35	**0.004**
Systolic Pressure, mmHg	132.15 ± 16.08	129.71 ± 21.89	128.97 ± 19.71	0.605
Diastolic Pressure, mmHg	79.55 ± 14.11	85.44 ± 13.95	81.92 ± 12.26	**0.032**
Fasting glucose, mg/dl	99 ± 7.62	98.32 ± 7.17	94.81 ± 8.09	**0.030**
Blood Urea Nitrogen	31.12 ± 8.99	27.58 ± 4.36	29.27 ± 6.58	0.084
Creatinine, mg /dl	0.75 (0.65 – 0.91)	0.73 (0.65 – 0.78)	0.80 (0.70 – 0.95)	0.087
Alanine transaminase	19.03 ± 5.70	19.52 ± 6.78	21.37 ± 8.23	0.746
Aspartate transaminase	19.96 ± 5.26	19.61 ± 5.30	20.40 ± 6.04	0.786
Total Cholesterol, mg/dl	192.54 ± 27.89	195.79 ± 39.30	186 ± 26.10	0.698
Leukocyte Count, ×10^3	7.17 ± 1.12	7.21 ± 1.16	6.94 ± 1.30	0.902
Hemoglobin,	13.09 ± 1.19	13.26 ± 2.01	13.43 ± 0.95	0.670
Hematocrit	39.20 ± 4.10	40.62 ± 5.08	39.27 ± 5.54	0.215
Platelet count, ×10^3	281.60 ± 68.03	273.41 ± 76.34	297.82 ± 51.25	0.645
TSH, mU/ml	1.03 (0.59 – 2.47)	0.86 (0.33 – 1.96)	1.40 (0.99 – 3.30)	0.061
fT4	1.27 ± 0.36	1.32 ± 0.24	1.54 ± 0.84	0.502

Data are given as mean ± standard deviation or median (1^{st} quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. *p* values in **bold** indicate statistical significance

Comparison was made between the group 1 and group 2.

in Table 1. Echocardiographic measurements of the study groups are presented in Table 2. E wave deceleration time (EDEC) of the subjects receiving RAI was significantly longer than that of those without RAI (189.2 ± 34.8 ms, vs 178.8 ± 33.2 ms, respectively, $p = 0.013$). Mitral E/A ratio was higher in subjects receiving RAI than that of those who had not received RAI ($p = 0.009$). Epicardial fat thickness was higher in subjects receiving RAI than that of those who had not received RAI (8.43 ± 1.75 mm vs. 7.87 ± 1.99, respectively, $p = 0.039$). Finally, presystolic wave was more common in subjects receiving RAI compared to those not receiving RAI (90.9% vs. 61.8%, respectively, $p = 0.003$) and its prevalence in Group 3 was 54.1%.

Variables with a p value < 0.05 were included in the multivariate analysis model. Multiple logistic regression analysis revealed that receiving RAI (OR: 4.922, 95% CI: 1.640 – 20.022, $p = 0.004$) was associated with a 5-fold higher likelihood of having a presystolic wave. Epicardial fat thickness (OR: 1.403, 95% CI: 1.110 – 2.265, $p = 0.005$), mitral E/A ratio (OR: 1.286, 95% CI: 1.102 – 1.719, $p = 0.003$), and heart rate (OR: 1.082, 95% CI: 1.006 – 1.128, $p = 0.032$) were also independently associated with the presence of presystolic wave (Table 3).

DISCUSSION

This study investigated whether RAI therapy in patients with DTC was associated with the presence of presystolic wave (as a proxy for cardiac function). Our findings indicate that subjects receiving RAI following total thyroidectomy more frequently exhibit presystolic wave compared to subjects with non-malignant pathology and to those who did not receive RAI following total thyroidectomy. Mitral E wave deceleration time is also prolonged in subjects who received RAI compared to those who did not receive RAI. Moreover, RAI treatment following total thyroidectomy was associated with a five-fold increase in the risk for the presence of presystolic wave.

Exposure to radiation has been established to increase reactive oxygen species, chemokines and cytokines in tissues, subsequently leading to the stimulation of inflammation [9]. Reactive oxygen species are associated with cardiac fibrosis, apoptosis and myocardial hypertrophy [10, 11]. Stimulated cytokines promote molecular and phenotypic changes in myocardial cells which may lead to contractile dysfunction [12]. However, although RAI may be expected to trigger such effects, it has been shown that there is a need for relatively high-dose radiation ex-

Table 2. Comparison of transthoracic echocardiography measurements among the groups

Variables	Group 1 (RAI (+) (n = 33)	Group 2 RAI (-) (n = 34)	Group 3 (n= 37)	p value
LVEF, %	60.2 ± 10.7	59.4 ± 9.9	59.6 ± 10.2	0.347
LVED diameter, mm	47.1 ± 8.6	47.7 ± 8.4	48.1 ± 9.2	0.402
LVES diameter, mm	33.6 ± 5.6	30.2 ± 5.1	29.5 ± 4.9	0.097
LA diameter, mm	42.9 ± 7.2	43.6 ± 7.6	44.2 ± 7.9	0.198
E peak rate, cm/sec	78.9 ± 16.8	77.1 ± 16.2	76.8 ± 16.4	0.326
A peak rate, cm/sec	60.7 ± 9.9	62.3 ± 10.8	62.4 ± 10.6	0.114
Mitral E deceleration time, msec	189.2 ± 34.8	178.8 ± 33.2	176.2 ± 31.8	**0.013**
Mitral E/A ratio	1.43 (1.02 – 2.09)	1.22 (0.72- 1.61)	1.24 (0.75 – 1.59)	**0.009**
Presystolic wave, n (%)	30 (90.9%)	21 (61.8%)	20 (54.1%)	**0.003**
Epicardial fat thickness, mm	8.43 ± 1.75	7.87 ± 1.99	7.82 ± 2.41	**0.039**
Aortic Velocity	103.09 ± 17.10	108.12 ± 17.84	120.68 ± 19.36	0.106

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. p values in **bold** indicate statistical significance. Comparison was made between the group 1 and group 2.

Table 3. Univariate and multivariable analyses to detect parameters associated with the presence of presystolic wave

	Univariate		Multivariable	
	OR (%95 CI)	*p* value	OR (95 %CI)	*p* value
RAI treatment	6.190 (1.567 – 24.451)	**0.009**	4.922 (1.640 – 20.022)	**0.004**
Male sex	0.738 (0.243 – 2.236)	0.591		
Age	1.021 (0.982 – 1.061)	0.302		
LVEF	0.922 (0.827 – 1.046)	0.288		
LVED diameter	1.006 (0.989 – 1.012)	0.902		
LVES diameter	0.756 (0.402 – 1.308)	0.195		
LA diameter	1.011 (0.662 – 2.034)	0.624		
E peak rate	1.289 (1.085 – 2.106)	**0.021**	1.032 (0.992 – 1.907)	0.148
A peak rate	1.108 (0.902 – 2.644)	0.402		
Mitral E deceleration time	1.062 (1.008 – 1.640)	**0.003**	1.003 (0.982 – 1.548)	0.098
Mitral E/A ratio	1.361 (1.189 – 1.905)	**<0.001**	1.286 (1.102 – 1.719)	**0.003**
Epicardial fat thickness	1.398 (1.120 – 1.745)	**0.003**	1.403 (1.110 – 2.265)	**0.005**
Aortic Velocity	1.001 (0.979 – 1.022)	0.959		
Body mass index	1.013 (0.914 – 1.122)	0.804		
Fasting glucose	1.053 (0.994 – 1.115)	0.080		
Alanine transaminase	1.062 (0.991 – 1.137)	0.087		
Aspartate transaminase	1.100 (1.008 – 1.201)	**0.032**	0.982 (0.786 – 1.724)	0.663
LDL cholesterol	1.003 (0.994 – 1.013)	0.491		
HDL cholesterol	1.013 (0.975 – 1.053)	0.502		
Leukocyte count	1.128 (0.791 – 1.608)	0.507		
Hemoglobin	1.231 (0.915 – 1.656)	0.170		
Platelet count	0.999 (0.993 – 1.005)	0.711		
TSH	1.206 (0.935 – 1.555)	0.149		
fT4	0.536 (0.249 – 1.153)	0.110		
Heart Rate	1.050 (1.009 – 1.092)	**0.017**	1.082 (1.006 – 1.128)	**0.032**
Systolic pressure	1.004 (0.982 – 1.026)	0.731		
Diastolic pressure	0.998 (0.968 – 1.029)	0.881		

p values in **bold** indicate statistical significance. Variables with a *p* value <0.05 were included in the multivariate analysis model.

posure (30 Gy) in order to result in myocardial fibrosis. Nonetheless, radiation exposure may also complicate contractile function by accelerating the development of atherosclerosis through sustained inflammatory response, structural damage to the epicardial arteries or ultrastructural damage to capillary networks [13].

A presystolic wave, an easy-to-identify echocardiographic parameter, can be described as a late diastolic wave which can be observed through Doppler assessment of the LVOT. Kul *et al*. [7] have reported in their study enrolling 129 type 2 diabetic patients that presence of echocardiographic presystolic wave was related to subclinical LV dysfunction. Similarly, the study by Saylik *et al*. [14] revealed that echocardiographic presystolic waves were associated with subclinical LV dysfunction, as measured by myocardial performance index, LV global longitudinal strain, and conventional Doppler. The role of the presence of presystolic wave was also assessed in hypertensive patients and it was determined that presystolic waves were an independent predictor associated with subclinical LV dysfunction in this patient subset [6]. Several studies have also reported an association between the presence of presystolic wave and arterial stiffness, systemic hypertension, and non-dipping [15-17]. There are also studies investigating potential relationships between coronary artery disease and the lack of presystolic waves. The absence of presystolic wave was found to be predictive for extensive coronary artery disease and higher Syntax score [18, 19]. Another study conducted by Saylik *et al*. [20] revealed that presystolic wave was a common occurrence among subjects with subclinical hypothyroidism and that presystolic waves were independently associated with subclinical LV dysfunction in subjects with subclinical hypothyroidism.

Current knowledge concerning the impact of radioiodine treatment on cardiovascular function is limited. A recent study conducted by Stanciu *et al*. [21] have investigated cardiovascular effects of radioiodine treatment in DTC in subjects with type 2 diabetes. The study revealed that cumulative 131I dosage was inversely correlated with systolic function in patients with type 2 diabetes but not in those without type 2 diabetes [21]. Although we did not assess diabetes in the present study, our results showed that fasting blood glucose levels were similar among DTC patients with and without RAI therapy. Considering that the RAI recipients were found to have a significantly higher likelihood of presystolic waves, it appears that the potential relationship between RAI and subclinical LV dysfunction (as determined by presystolic wave) was not associated with glucose levels. It should be also noted that the study conducted by Stanciu *et al*. [21] investigated the association between overt LV dysfunction as quantified by the measurement of the ejection fraction.

The present study is unique for addressing the impact of RAI on subclinical LV function through the utilization of a simple, feasible and readily available technique. Although there were no significant differences in LV ejection fraction among subjects with or without RAI in our groups, presystolic wave was more common among subjects who had received RAI, indicating the presence of subclinical systolic dysfunction in this patient subset.

Limitations

There are some limitations to be mentioned. The sample size is relatively small to reach a definitive conclusion regarding the role of RAI therapy on LV function. In addition, although the presystolic wave is largely accepted to be a proxy to detect subclinical LV dysfunction, the lack of longitudinal follow-up is another limitation.

CONCLUSION

In conclusion, RAI therapy following total thyroidectomy in patients with DTC was found to be associated with a five-fold higher likelihood for the presence of presystolic wave, which was utilized as a proxy for subclinical LV dysfunction. Subjects undergoing RAI subsequent to thyroid surgery may benefit from periodic transthoracic echocardiography for early detection of possible LV dysfunction.

Authors' Contribution

Study Conception: AV; OD; Study Design: AV, OD; Supervision: BS, OD; Funding: N/A; Materials: HB, SV; Data Collection and/or Processing: BS, SV; Statistical Analysis and/or Data Interpretation: OD, AV; Literature Review: OD, AV; Manuscript Preparation: AV, SV and Critical Review: AV, BS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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