

The Effect of Brief Thyroid Functional Changes on Arterial Stiffness in Patients Who Preparing Radioactive Iodine Administration

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Background and Objectives: Abnormal thyroid function influences the cardiovascular system. In particular, brief thyroid functional change due to levothyroxine (LT4) suppression therapy and withdrawal in papillary thyroid cancer (PTC) patients can affect cardiovascular system and other biochemical markers. However, the effect of brief thyroid functional change on arterial stiffness has not been evaluated. Therefore, we evaluated the changes in arterial stiffness according to short-term thyroid hormone levels in patients who underwent total thyroidectomy and radioactive iodine (RAI) therapy for PTC. **Materials and Methods:** Patients with PTC (n=17; 15 females, mean age 52 years) who underwent total thyroidectomy and RAI therapy were enrolled in this study. The arterial stiffness was evaluated using the corrected augmentation index for heart rate (AI@75) and brachial-ankle pulse wave velocity (BaPWV). Serum thyroid hormone levels and arterial stiffness parameters were checked three times consecutively: the day before thyroidectomy (Visit 1; baseline euthyroid state), after LT4 withdrawal (Visit 2; pre-RAI hypothyroid state) and 4 weeks after RAI (Visit 3; post-RAI thyrotoxic state). Biochemical markers, which can influence the arterial stiffness, were also measured. **Results:** The heart rate, AI@75 and serum thyroid hormone levels changed significantly at each visit. BaPWV was not significantly changed. Changes in AI@75 correlated with systolic blood pressure (SBP), serum thyroid hormone levels, total cholesterol and high density lipoprotein cholesterol in univariate analysis. In multivariate analysis, SBP was the independent factor for AI@75 changes. **Conclusion:** These results suggest that brief thyroid functional changes can influence AI@75. And SBP was important factor for AI@75 change.

Key Words: Augmentation index, Arterial stiffness, Thyroid function test, Thyroid cancer

Introduction

Abnormal serum thyroid hormone levels influence the cardiovascular system. Hypothyroidism is associated with a decreased cardiac output, cardiac contractility, left ventricular compliance, as well as an increased level of total peripheral vascular resistance and risks of hypertension and atherosclerosis.¹⁾ In

contrast, thyrotoxicosis is associated with increased levels of cardiac contractility, pulse rate, cardiac output, total vascular volume and arrhythmia.¹⁾ In particular, thyroid hormones exert a direct effect on vascular endothelium and smooth muscle, causing a direct change in the vessel wall properties.²⁻⁵⁾ Therefore, thyroid hormones may be associated with changes in arterial stiffness and could increase cardiovascular risk.

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To treat differentiated thyroid cancer, patients received radioactive iodine (RAI) therapy and thyroid stimulating hormone (TSH) suppression therapy. After total thyroidectomy and thyroxine (T4) replacement, T4 was withdrawn to stimulate endogenous TSH.⁶⁾ This protocol is required for sufficient RAI uptake for diagnostic imaging or therapy. These brief changes in serum thyroid hormones can affect lipid metabolism, the cardiovascular system and atherosclerotic risk.⁷⁾ Several studies showed cardiovascular function was impaired not only in long-standing but also in short-term hypothyroidic patients.⁷⁻¹²⁾ However, the effect of acute and rapid changes in thyroid hormones on arterial stiffness has not been evaluated. Arterial stiffness is an independent predictor of cardiovascular disease risk. Recently, pulse wave velocity (PWV) and augmentation index (AI) were used as methods for noninvasive measure of arterial stiffness.¹³⁾ PWV is the aortic pulse velocity assessed by measuring the distance between two arteries and dividing by the transit time. The PWV is a marker of arterial stiffness and the best individual predictor of first major cardiovascular events.¹³⁾ Furthermore, the AI is a measurement of the arterial wave reflection and can be used to calculate the central systolic blood pressure (CBP). The CBP is associated more strongly with an increase in left ventricular mass index, vascular hypertrophy and the extent of atherosclerotic disease than is peripheral blood pressure.¹³⁻¹⁵⁾

Therefore, we evaluated the change in arterial stiffness using AI and PWV according to short-term and artificial changes in serum thyroid hormone levels of differentiated thyroid cancer patients during RAI therapy.

Materials and Methods

Patients

Patients with suspected thyroid cancer were screened using ultrasonography and fine-needle aspiration between June 2011 and May 2012. Patients with a previous history of peripheral arterial disease were excluded. The total of 48 patients underwent screening and 31 patients were participated in this study.

Among them, fourteen patients were initially excluded: six patients were follow-up loss for personal reasons, four patients were excluded because TSH was not suppressed well. Two due to unconfirmed differentiated thyroid cancer, one because levothyroxine (LT4) was not stopped, and one due to use of recombinant human TSH during RAI therapy. Finally, 17 patients (15 females; median age, 52 years) were enrolled in this study. The medications of the subjects were not changed during the study to avoid other confounding factors.

All study participants were treated using the standard RAI protocol.⁶⁾ Dose of RAI was 100 mCi or 150 mCi. After total thyroidectomy, patients took LT4 for several weeks and then underwent LT4 withdrawal therapy over 4 weeks. During LT4 withdrawal, liothyronine (LT3) was administered for 2 weeks initially, followed by LT3 withdrawal for 2 weeks. After RAI, all patients were restarted on LT4. The laboratory test results and arterial stiffness were compared pre-operatively (Visit 1; baseline euthyroid state), the day of RAI treatment (Visit 2; pre-RAI hypothyroid state) and 4 weeks after RAI (Visit 3; post-RAI mild thyrotoxic state). All the hemodynamic and laboratory measurements were obtained on the same day. The study was conducted prospectively and approved by the Ethics Committee of Gyeongsang National University Hospital. All studies were performed after receiving informed consent from study participants.

Arterial Stiffness Measurement

To evaluate arterial stiffness, brachial-ankle PWV (BaPWV) and AI were used. PWV is the distance of traveled (ΔD) by the wave divided by the time (ΔT) for the wave to travel distance: $PWV = \Delta D / \Delta T$. In this study, BaPWV was measured using VP-1000 (Colin Co., Ltd., Komaki, Japan), an automated, noninvasive device. The four blood pressure cuffs were applied at both ankles and both upper arms, and the pressure wave was acquired simultaneously. The BaPWVs were estimated automatically from waveforms at the upper arm and ankle and patient's height.

AI can derive from pulse waveform analysis. Pulse waveform is a composite of forward wave and re-

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flected wave. In condition of central arterial stiffness, reflection wave derived faster and resulting in an augmentation of CBP (AG). Therefore, increase of the AI, meaning an increase in the central arterial stiffness. Pulse pressure (PP) was calculated by subtracting the diastolic blood pressure (DBP) from the systolic blood pressure (SBP). AG is the difference between the first and second systolic peak in the central pulse waveform. AI can calculate by followed equation: $AG/PP \times 100\%$. Because of heart rate (HR) dependency on AI, we used AI@75 which was adjusted to 75 beats in this study. The AI75 was obtained automatically using the following equation: $AI75 = AI + 0.43 \times (75 - PR)$. HEM-9000AI (Omron Healthcare Co., Ltd., Kyoto, Japan) was used to check pulse waveform analysis, which described AI and AI@75. This device can measure the CBP as non-invasive method. And reproducibility was validated from pre-

vious study. Compared to invasive technique, there was no significant difference in the result.^{16,17)}

Laboratory Tests

Thyroid function tests, AI@75 and BaPWV were evaluated three times consecutively. First examinations were performed the day before total thyroidectomy when all patients were in a euthyroid state (Visit 1). The second follow-up was performed the day of RAI therapy (Visit 2). After RAI therapy, patients were re-taking LT4 for TSH suppression therapy, and the third follow-up was performed 4 weeks later after RAI (Visit 3). Body mass index (BMI) was calculated as weight (Kg) divided by height (m) squared. Total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), C-reactive protein and glucose levels were measured at each visit.

Table 1. Change of biochemical results and hemodynamic parameters (n=17)

Variables	Visit 1	Visit 2	Visit 3	*p value	†p value	‡p value
TSH (mIU/L)	2.1±0.9	76.1±23.0	0.5±0.9	<0.001	0.002	<0.001
T3 (ng/dL)	108.0±17.4	21.5±3.8	147.3±42.0	<0.001	0.006	0.001
fT4 (ng/dL)	1.2±0.2	0.1±0.1	2.4±0.9	<0.001	<0.001	<0.001
SBP (mmHg)	128.7±16.8	121.4±17.7	132.5±18.5	0.097	0.286	0.297
DBP (mmHg)	78.9±11.7	77.6±10.7	78.2±12.7	0.736	0.831	0.811
HR (bpm)	72.7±10.3	69.8±10.3	82.1±11.3	0.155	0.001	<0.001
CBP (mmHg)	134.2±20.4	125.7±19.9	137.1±19.8	0.109	0.722	0.517
AI (%)	81.2±13.3	75.5±12.3	83.4±12.4	0.070	0.622	0.054
AI@75 (%)	80.2±11.4	73.2±10.1	86.4±11.2	0.039	0.019	0.021
BaPWV, Rt (m/s)	13.8±2.9	13.6±2.5	13.7±2.4	0.722	0.906	0.692
BaPWV, Lt (m/s)	13.9±2.7	13.8±2.4	13.8±2.2	0.981	0.687	0.607
TC (mg/dL)	167.4±23.8	244.6±44.5	174.2±46.3	0.001	0.865	0.322
HDL-C (mg/dL)	51.2±13.6	63.2±15.2	48.0±11.7	0.004	0.878	0.685
LDL-C (mg/dL)	110.1±28.5	154.5±41.2	112.0±46.4	0.019	0.239	0.784
TG (mg/dL)	106.9±69.7	194.1±139.6	151.8±110.9	0.002	0.239	0.135
Glu (mg/dL)	112.2±32.7	107.3±36.4	106.6±19.0	0.451	0.593	0.499
Hb (mg/dL)	13.0±1.1	13.4±1.3	12.6±1.2	0.038	0.180	0.195
Cr (mg/dL)	0.73±0.1	0.69±0.1	0.68±0.1	0.348	0.093	0.041
CRP (mg/dL)	0.44±0.3	0.51±0.6	0.68±0.6	0.959	0.125	0.120

Values are means±standard deviation. Statistical significance was evaluated using generalized estimating equation analysis. Visit 1 reflects baseline euthyroid state. Visit 2 reflects pre-RAI hypothyroid state. Visit 3 reflects post-RAI thyrotoxic state.

*p value compared Visit 1 to Visit 2

†p value compared Visit 1 to Visit 3

‡p value compared to continuous data from Visit 1 to Visit 3

AI: augmentation index, AI@75: corrected augmentation index for heart rate, BaPWV: brachial–ankle pulse wave velocity, CBP: central systolic blood pressure, Cr: creatinin, CRP: C-reactive protein, DBP: diastolic blood pressure, fT4: free thyroxine, Glu: glucose, Hb: hemoglobin, HDL-C: high density lipoprotein cholesterol, HR: heart rate, LDL-C: low density lipoprotein cholesterol, Lt: left, RAI: radioactive iodine, Rt: right, SBP: systolic blood pressure, T3: triiodothyronine, TC: total cholesterol, TG: triglyceride, TSH: thyroid stimulating hormone

Statistical Analyses

Statistical analysis was performed using the Statistical Package for Social Science (SPSS, Version 19.0 for Windows, SPSS, Inc., Chicago, IL, USA) and SAS 9.3 (SAS Institute Inc.). The changes in thyroid hormone, arterial stiffness parameters and laboratory findings at each visit were examined using generalized estimating equation (GEE) analysis. Spearman's (for TSH, total cholesterol, triglyceride and glucose levels) or Pearson's correlation analysis was used for the correlation among the changes in AI@75, thyroid hormone levels and other measures at respective first and second phases. To evaluate which factors affected the changes in AI@75 during the three visits, univariate analysis was performed using GEE analysis. Finally, multivariate GEE analysis was used to identify independent factors for the AI@75 changes. TSH, TC and HDL-C, as the significant factors from the univariate analysis, and age and hypertension, as the associated factors of AI, were included in the multi-

variate analysis. A p value <0.05 was considered indicative of statistical significance.

Results

Patient Characteristics

A total of 17 patients were included in this study (15 females, median age 52 years). Patient's median height, weight and BMI were 156.2 cm, 60 kg and 24.3 kg/cm². Five patients had hypertension. Among them, four patients were taking a calcium channel blocker, three patients three patients ARB (angiotensin receptor blockers), one patient a beta blocker and one patient statins. Medications were not changed during the study period.

Biochemical and Hemodynamic Parameter Changes

When analyzing the consecutive three data, the TSH, free T4 (fT4) and T3 levels changed significantly during the study period (Table 1). Regarding hemody-

Table 2. The correlation analysis for changes of hemodynamic and biochemical parameters according to changes in AI@75, TSH, and fT4 (n=17)

Changes in variables	Δ AI@75		Δ TSH		Δ fT4	
	1 st phase	2 nd phase	1 st phase	2 nd phase	1 st phase	2 nd phase
Δ TSH	0.119	0.442*	—	—	—	—
Δ fT4	0.040	-0.092	—	—	—	—
Δ T3	-0.228	-0.119	—	—	—	—
Δ Heart rate	-0.570*	-0.056	0.021	-0.148	0.102	-0.242
Δ SBP	0.502*	0.234	0.591*	0.529*	-0.099	-0.898*
Δ DBP	0.437	0.219	0.580*	0.511*	0.218	-0.115
Δ CBP	0.740*	0.489*	0.528*	0.634*	0.183	-0.049
Δ TC	-0.062	-0.079	0.291	0.396	0.376	-0.293
Δ LDL-C	-0.042	-0.049	0.209	0.236	-0.230	-0.422
Δ HDL-C	-0.371	-0.232	0.537*	0.234	0.302	-0.071
Δ TG	0.449	0.209	-0.0182	0.022	0.064	0.193
Δ Glucose	-0.100	-0.240	0.118	-0.343	0.118	-0.547*
Δ Creatinin	-0.242	-0.026	-0.254	-0.163	0.280	-0.402
Δ CRP	-0.027	0.163	0.147	0.299	-0.173	-0.047

All values are correlation coefficients (r) of correlation analysis. Univariate analysis was performed using Spearman's or Pearson's correlation analysis. The changes in variables were obtained by subtracting the pre-radioactive iodine (RAI) therapy values from the baseline values (1st phase) and the post-RAI therapy values from the pre-RAI values (2nd phase).

AI: augmentation index, AI@75: corrected augmentation index for heart rate, CBP: central systolic blood pressure, CRP: C-reactive protein, DBP: diastolic blood pressure, fT4: free thyroxine, HDL-C: high density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, PWV: pulse wave velocity, SBP: systolic blood pressure, T3: triiodothyronine, TC: total cholesterol, TG: triglyceride, TSH: thyroid stimulating hormone

* p <0.05

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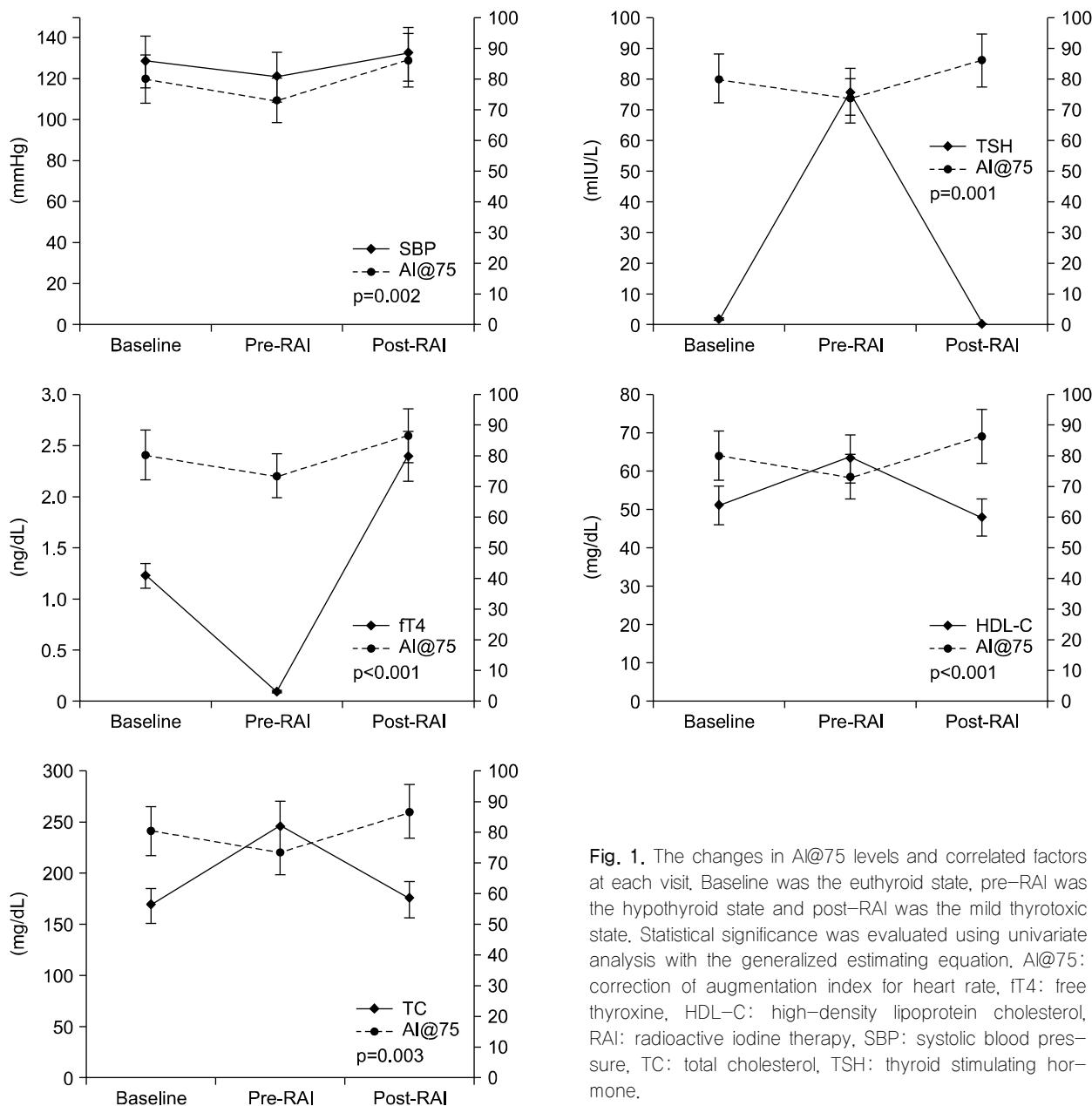


Fig. 1. The changes in AI@75 levels and correlated factors at each visit. Baseline was the euthyroid state, pre-RAI was the hypothyroid state and post-RAI was the mild thyrotoxic state. Statistical significance was evaluated using univariate analysis with the generalized estimating equation. AI@75: correction of augmentation index for heart rate, fT4: free thyroxine, HDL-C: high-density lipoprotein cholesterol, RAI: radioactive iodine therapy, SBP: systolic blood pressure, TC: total cholesterol, TSH: thyroid stimulating hormone.

namic parameters, HR was decreased in the hypothyroid state and increased in the thyrotoxic state. The SBP and DBP tended to decrease in the hypothyroid state and to increase in the thyrotoxic state. However, SBP, DBP and CBP did not show statistical significance. Regarding arterial stiffness parameters, AI did not show a significant difference. The level of AI@75, as a parameter corrected by HR, changed significantly during the study period (Visit 1; Visit 2; Visit 3, 80.2 ± 11.4 ; 73.2 ± 10.1 ; 86.4 ± 11.2 , respectively, $p=0.021$). The left and right BaPWVs did

not change significantly. Among the biochemical markers, only creatinine showed significant changes ($p=0.041$). Similarly to blood pressure, the lipid profiles, which included TC, LDL-C, HDL-C and TG, tended to change according to thyroid function, but without statistical significance (Table 1).

When the patients became euthyroid state (Visit 1) to brief hypothyroid state (Visit 2), lipid profiles and hemoglobin (Hb) were represent statistical significance (TC; HDL-C; LDL-C; TG; Hb, $p=0.001$; $p=0.004$; $p=0.019$; $p=0.002$; $p=0.038$). But, HR did not show

statistically significance. When analyzing the statistical results of the euthyroid (Visit 1) to mild thyrotoxic state (Visit 3), there were no differences compared to the continuous results, except creatinin. Although there were exist some minor difference about results, AI@75 had statistically significance in all results.

Factors Related to the Change in Arterial Stiffness

To determine the factors correlated with changes in arterial stiffness parameters, correlation analysis was performed using the changes (1st phase, the Δ indicates the Visit 2 values minus Visit 1 values; 2nd phase, the values of Visit 3 to Visit 2; Table 2). The factors that correlated statistical significantly with Δ AI@75 in the 1st phase were Δ HR, Δ CBP and Δ SBP. In the 2nd phase, Δ AI@75 was the factor that correlated with Δ TSH and Δ CBP. According to Δ TSH, the changes in SBP, DBP, CBP and HDL-C were correlated significantly (Table 2). When including the concept of time variation in the same patient, we performed univariate analysis using GEE for AI@75 (Fig. 1). Among the parameters, changes in SBP, TSH, fT4, HDL-C and TC were significantly associated with changes in AI@75 with time variation. SBP and fT4 were positive correlated with AI@75. Conversely, TSH, HDL-C and TC were negative correlated with AI@75 (Fig. 1). Multivariate analysis was performed to determine the independent factors for AI@75; thus, TSH, SBP, TC and HDL-C were selected as the significant factors for univariate analysis. In addition, age and presence of hypertension as conventional factors potentially affecting AI@75 were included in the multivariate analysis. The results showed that the change in SBP was significant factor that affected the change in AI@75 ($p=0.010$; Table 3). Changes in TC, HDL-C, age and hypertension were not statistically significant.

Discussion

In this study, we found that short-term changes in serum thyroid hormones might affect the change of AI@75. LT4 withdrawal caused a significant change in TSH, T3 and fT4 levels, and AI@75 was decreased more at hypothyroid state (Visit 2) than at euthyroid

Table 3. Multivariate analysis for changes in AI@75

Variables	Δ AI@75		
	β	95% CI	p value
TSH	-0.015	-0.066-0.037	0.577
SBP	0.132	0.032-0.233	0.010
TC	-0.012	-0.057-0.033	0.598
HDL	-0.085	-0.224-0.055	0.233
Age	-0.030	-0.163-0.104	0.663
Hypertension	-9.656	-26.715-7.402	0.267

Multivariate analysis was conducted using generalized estimating equation. AI@75: correction of augmentation index for heart rate, CI: confidence interval, HDL: high density lipoprotein, SBP: systolic blood pressure, TC: total cholesterol, TSH: thyroid stimulating hormone

state (Visit 1). The change in AI@75 was associated with TSH, fT4, TC, HDL-C and SBP in the univariate analysis. The change in SBP was an independent factor for AI@75 change.

Changes in serum thyroid hormones can influence the cardiovascular system.¹⁾ In general, thyroid hormones decrease peripheral vascular resistance and blood pressure and increase HR, left ventricular contractility and blood volume. Long-standing hypothyroidism exacerbates cardiovascular disease and negatively affects lipid profiles.^{1,7,18-20)} Furthermore, short-term hypothyroidism caused by LT4 withdrawal could be associated with adverse cardiovascular effects resulting from reduced heart rate, preload of the left ventricle and left ventricular diastolic function, and increased blood pressure.⁷⁻¹²⁾ A number of studies have evaluated the relationship between thyroid hormones and arterial stiffness.^{2,21-29)} Although several discrepancies existed, many studies showed that arterial stiffness, according to AI and BaPWV, was lower in thyrotoxic patients than in the control group.^{5,18,22,23)} In addition, Nagasaki et al.^{2,24)} proved LT4 treatment reduced BaPWV in subclinical hypothyroidic patients. The previous studies on long-standing hypothyroidic patients have suggested several mechanisms responsible for the change in arterial stiffness according to thyroid hormone changes. First, thyroid hormone deficiency can cause vascular endothelial dysfunction, directly or indirectly. Serum fibrinogen and fibronectin and vascular inflammation caused by norepinephrine

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were suggested as factors for endothelial dysfunction.^{4,18,26,28)} The second mechanism included activation of the renin–angiotensin–aldosterone system caused by hypothyroidism, which was related to carotid artery wall thickening in low TSH level patients.^{3,30)} The third mechanism involves hypothyroidism–induced dyslipidemia, which can exacerbate atherosclerosis and increase arterial wall resistance.^{20,30)}

However, studies regarding the effect of LT4 withdrawal on arterial stiffness are lacking. Chang et al.³¹⁾ showed that short-term changes in thyroid functions did not affect endothelial function, which was assessed by flow-mediated dilation. Our study is the first to observe changes in AI and BaPWV during a brief LT4 withdrawal. In the current study, the pattern of AI@75 change was different from the results of long-standing hypothyroidism or hyperthyroidism. The first possible explanation for the unexpected findings is the duration of T4 withdrawal. The previous studies examined LT4 withdrawal over a 5–6–week period.^{9,11)} However, in this study, the mean period from the operation to RAI therapy was 120 days. Additionally, the patients were started on LT4 therapy, using a suppressive dose immediately after total thyroidectomy, and on T3, as a LT4 substitute for 14 days, after which they did not take any thyroid hormone for 14 days until the RAI administration. The longer period of mild thyrotoxicosis than of thyroid hormone withdrawal may have affected the AI@75 changes. The second possible explanation was the relationship between SBP and AI@75. In the multivariate analysis, the SBP change was only independent factor for the AI@75 change. SBP changes also showed a different pattern in the current study. Although the LT4 withdrawal phase was during the hypothyroidic period, SBP was lower than the baseline value. We hypothesized that the change in SBP may be associated with low salt intake. Typically, Koreans use sea salt in most pickled foods. Therefore, with a strict low-iodine diet, patients consume lower amounts of sun-dried salt. The low-salt diet is associated with decreased blood pressure. Furthermore, the report by Chang et al.³¹⁾ showed decreases in SBP and DBP during the LT4 withdrawal phase. Because many patients complained

of poor oral intake during RAI therapy, reduced body weight or fluid status might influence their blood pressure changes; however, we did not evaluate body mass or fluid status quantitatively. Additionally, we cannot exclude the delayed hemodynamic effect of hormonal changes, because the AI@75 and SBP were elevated again 1 month after RAI. Thyroid function changes affect lipid profiles within a short period, but short-term changes in thyroid function did not promptly alter arterial stiffness.

The present study had several limitations. First, the sample size was small, and more samples are needed for greater statistical power. Second, the postoperative LT4 replacement period varied and lasted approximately 80 days before the hypothyroidic state and may have affected the results. However, we believe the protocol reflected actual practice, and our study showed factual results based on the change in thyroid hormones and lipid profiles. Third, other hemodynamic changes, changes of weight and fluid status were not considered. Direct effects on the heart, such as cardiac contractility, cardiac output and diastolic function using echocardiography, were not evaluated. Also, we did not consider the changes of weight or fluid status of the patients due to the low-iodine diet.

In conclusion, the results of this study suggest that the short-term alterations in thyroid functions after total thyroidectomy or before RAI therapy may have affect AI@75. The SBP change was an independent factor for short-term AI@75 change. However, the patterns of AI@75 and SBP changes differed during thyrotoxic and hypothyroidic states. Recognizing the influence on the cardiovascular system during LT4 replacement and withdrawal is important, but whether the AI@75 change is related to adverse cardiovascular events is inconclusive. Therefore, further studies employing a longer observation period and a greater number of cases for cardiovascular outcomes are necessary, as well as a comparison of the LT4 withdrawal protocol in a control group using recombinant human TSH injection.

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