

# The Impact of Subclinical Hypothyroidism or Thyroid Autoimmunity on Coronary Vasospasm in Patients without Associated Cardiovascular Risk Factors

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**Background and Objectives:** Subclinical hypothyroidism is associated with endothelial dysfunction and impaired coronary flow reserve. However, the effect of subclinical hypothyroidism or thyroid autoimmunity on variant angina has yet to be determined.

**Subjects and Methods:** Among 385 consecutive patients without associated cardiovascular risk factors who underwent coronary angiography with the ergonovine provocation test (EPT), 165 had a positive EPT {EPT(+)} and 220 had a negative EPT {EPT(-)}. The relationship between coronary artery spasm and the presence of subclinical thyroid dysfunction as well as serum thyroid peroxidase autoantibody (TPO Ab) was evaluated.

**Results:** The proportion of patients with subclinical hypothyroidism among those who were EPT(+) was significantly higher than that in those who were EPT(-) (18% vs. 11%,  $p=0.001$ ). However, there was no significant difference in the proportion of patients with subclinical hyperthyroidism between the groups. Moreover, EPT(+) patients showed significantly more positive TPO Ab (33% vs. 14%,  $p<0.001$ ) than those with EPT(-). There was a positive correlation between EPT(+) and TPO positivity ( $r=0.226$ ,  $p<0.001$ ), subclinical hypothyroidism ( $r=0.112$ ,  $p=0.033$ ), and body mass index ( $r=0.123$ ,  $p=0.018$ ). Binary logistic regression analysis revealed that the significant predictors of EPT(+) were body mass index {adjusted odds ratio (OR)=1.042, 95% confidence interval (CI)=1.005–1.080}, presence of subclinical hypothyroidism (OR=3.047, 95% CI=1.083–8.572), TPO Ab titer (OR=1.028, 95% CI=1.015–1.041), and the presence of TPO Ab (OR=4.904, 95% CI=1.544–15.567).

**Conclusion:** Subclinical hypothyroidism and the presence of TPO Ab are significantly associated with coronary vasospasm in patients without cardiovascular risk factors. (*Korean Circ J* 2015;45(2):125–130)

**KEY WORDS:** Hypothyroidism; Autoimmunity; Coronary vasospasm.

## Introduction

Coronary artery spasm, defined as transient occlusive or suboc-

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clusive vasoconstriction in large epicardial arteries, plays an important role in variant angina (VA). Pharmacologic provocative testing with vasomotor agents such as acetylcholine<sup>1)</sup> or ergonovine<sup>2)</sup> has generally been used in the diagnosis of VA. Although the precise mechanism of VA is unclear, it has been reported that one of the major causes of VA is endothelial dysfunction of the coronary artery.<sup>3)</sup>

Endothelial dysfunction is an important, early, and reversible feature of atherogenesis.<sup>4)</sup> Thyroid hormones have a direct effect on cardiac myocytes, endothelial cells, and vascular smooth muscle cells, resulting in hypertrophy and stiffness of the vessels.<sup>5,6)</sup> Previous reports have shown that overt or subclinical hypothyroidism is associated with endothelial dysfunction,<sup>6–8)</sup> which might be due to reduced nitric oxide (NO) availability.<sup>8)</sup> When the bioavailability of NO is reduced, the vasoconstrictor effect prevails and coronary blood flow does not increase, and may even decrease, despite the

increase in cardiac work expressed as the rate-pressure product. In addition, coronary flow reserve was shown to be lower in overt or subclinical hypothyroidism<sup>9)10)</sup> which is an important factor in VA.<sup>3)</sup> However, there is no consensus on the association between subclinical hypothyroidism and VA. There have also been reports that thyroid autoimmunity is associated with arterial stiffness.<sup>11)12)</sup> Furthermore, we previously showed that the presence of thyroid antibody is correlated with arterial stiffness in patients with fibromyalgia.<sup>13)</sup> However, the effect of subclinical hypothyroidism or thyroid autoimmunity on VA has not yet been determined. Therefore, the purpose of the present study was to investigate whether subclinical hypothyroidism or thyroid autoimmunity is related to VA, as established by the ergonovine test.

## Subjects and Methods

### Study population

A total of 770 consecutive patients who underwent coronary angiograms with an ergonovine provocation test (EPT) at our hospital from January 2007 to August 2013 were enrolled. Exclusion criteria were: a previous history of thyroid disease and treatment, medications that could change thyroid hormone levels including amiodarone and corticosteroids, diabetes mellitus, hypertension, stroke, high serum creatinine, known atherosclerotic disease, any rhythm other than sinus, psychiatric conditions, and pregnancy within the last two years. We also excluded patients who had significant coronary stenosis ( $\geq 50\%$ ) as determined from the coronary angiogram and current smokers. Written informed consent was obtained from all patients, and the study protocol was approved by the ethics committee at our institution.

### Blood sampling

Thyroid function was assessed by measuring levels of free thyroxine (FT4) and thyroid stimulating hormone (TSH). FT4 (reference range 0.89–1.76 ng/dL) and TSH (reference range 0.38–4.7  $\mu$ IU/mL) were measured by a chemiluminescent microparticle immunoassay (Architect-I 2000, Abbot, Ireland, UK). Subclinical hypothyroidism was defined as a TSH level  $>4.0$   $\mu$ IU/mL and a normal free thyroxine level; and subclinical hyperthyroidism was defined as a TSH level  $<0.45$   $\mu$ IU/mL and a normal free thyroxine level. Thyroid peroxidase autoantibody (TPO Ab) was measured by a chemiluminescent immunoassay (ADVIA centaur, Siemens, Muenchen, Germany) with a cut-off value of 60 IU/mL. A fasting laboratory analysis of blood collected early in the morning prior to catheterization included measures of serum low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol, uric acid, hemoglobin A1c, high-sensitivity C-reactive protein, and creatinine.

### Echocardiography

Measurements of the thickness of the interventricular septum and posterior wall and the diameter of the left ventricular (LV) cavity were performed according to the American Society of Echocardiography (ASE) criteria. The LV mass was calculated using the corrected ASE cube formula, and the value was indexed for body surface area to obtain the LV mass index (LVMI). The relative wall thickness was measured as the ratio between the double posterior wall thickness and the LV diastolic cavity diameter at end diastole. A pulsed wave Doppler of transmitral LV inflow was performed in the apical four-chamber view, with the sample volume placed at the level of the mitral valve tips; Doppler variables were analyzed during three consecutive beats. The following measurements of global LV diastolic function were determined: peak early (E) and late (A) diastolic mitral flow velocity and their ratio E/A, early (Ea) diastolic mitral annular velocity, deceleration time of the E wave, and LV isovolumic relaxation time (IVRT).

### Ergonovine test for provocation of coronary spasm

Patients with normal angiography or minimal luminal narrowing ( $<50\%$  stenosis) underwent the EPT. The EPT was performed with an intravenous injection of methyergometrine maleate. After a diagnostic coronary angiography, incremental doses of ergonovine were injected intravenously (50, 100, 200  $\mu$ g) over ten seconds.<sup>2)</sup> Two minutes after each injection, the coronary angiogram, electrocardiogram (ECG), blood pressure and patient symptoms were assessed. Coronary spasm was defined as near total or localized spasm ( $\geq 90\%$  diameter) of the focal epicardial coronary artery with signs of chest pain or ischemic ST changes according to the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina.<sup>14)15)</sup> An intracoronary injection of isosorbide dinitrate was performed at the completion of the ergonovine test, regardless of whether or not coronary spasm was confirmed. We continuously assessed the coronary angiogram and ECG for changes in vessel dilatation and electrophysiology. No patients had a previous history of myocardial infarction, congestive heart failure, previous coronary stenting, or other serious disease. We divided the study patients into a VA group who showed definite coronary spasms induced by the ergonovine test and an atypical chest pain group who did not show typical vasoconstriction. The relationship between coronary artery spasms and the presence of subclinical thyroid dysfunction as well as serum thyroid peroxidase autoantibody (TPO Ab) were evaluated.

### Statistical analysis

All data are expressed as the mean  $\pm$  standard deviation. Data were analyzed using standard statistical software (Statistical Package for the Social Sciences package version 12.0, SPSS Inc., Chicago, IL, USA).

The chi-square test or Fisher's exact test was used to compare frequencies. Quantitative data were analyzed with the Mann-Whitney U test. Comparisons of all measurements were made with two-sample unpaired t-test for continuous variables, and correlations were assessed with Pearson's correlation analysis. To identify independent contributors for VA, binary logistic regression analysis was performed. A  $p < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

Among 385 consecutive patients, who underwent coronary angiography with EPT without associated cardiovascular risk factors, 165 patients showed positive EPTs {EPT(+)} and 220 patients showed negative EPTs {EPT(-)}. Baseline clinical characteristics are

**Table 1.** Baseline characteristics of groups

	Positive EPT (n=165)	Negative EPT (n=220)	p
Age (years)	53.3±11.3	52.1±11.0	0.278
Male, n (%)	70 (42.4)	92 (41.8)	0.494
History of smoking, n (%)	49 (29.7)	56 (25.5)	0.178
Systolic blood pressure (mm Hg)	128.5±19.6	125.3±15.8	0.082
Diastolic blood pressure (mm Hg)	79.3±13.4	77.6±12.0	0.210
Body mass index (kg/m <sup>2</sup> )	23.6±4.8	21.6±8.0	0.004
White blood cell (10 <sup>3</sup> /mm <sup>3</sup> )	7184±2107	7367±5531	0.654
Hemoglobin (g/dL)	13.1±1.34	13.6±8.05	0.395
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	219.8±63.9	214.1±53.5	0.363
eGFR, MDRD (mL/min)	106.7±30.0	108.0±28.2	0.655
Total cholesterol (mg/dL)	177.2±36.1	173.6±39.6	0.373
HDL-C (mg/dL)	49.2±13.1	49.3±15.4	0.955
Triglycerides (mg/dL)	122.3±77.5	121.6±105.1	0.938
LDL-C (mg/dL)	106.5±36.5	101.3±33.9	0.172
hsCRP (mg/dL)	2.59±7.35	2.67±9.06	0.925
Uric acid (mg/dL)	5.3±1.56	5.1±1.38	0.142
Fasting glucose (mg/dL)	102.9±30.0	98.6±21.9	0.177

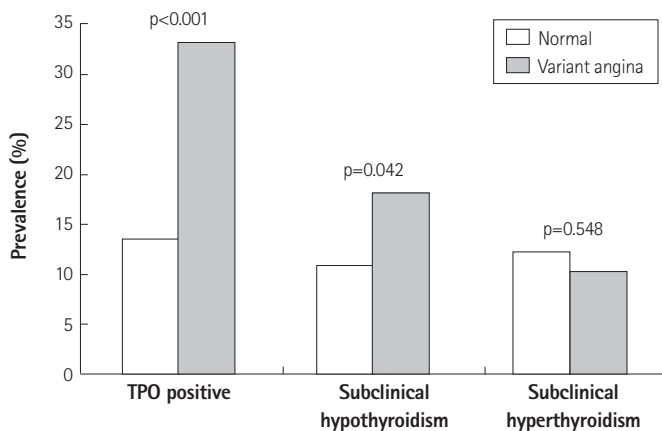
Data are n (%) or mean±SD. EPT: ergonovine provocation test, eGFR: estimated glomerular filtration rate, MDRD: modification of diet in renal disease, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, hsCRP: high-sensitivity C-reactive protein

**Table 2.** Echocardiographic parameters between groups

	Positive EPT (n=165)	Negative EPT (n=220)	p
LVEDD (mm)	45.7±4.43	45.3±5.00	0.425
LVESD (mm)	28.5±4.33	28.2±4.18	0.453
Ejection fraction (%)	67.8±8.34	67.8±7.54	0.969
IVSd (mm)	11.0±1.83	11.3±2.16	0.223
PWDd (mm)	10.1±1.80	9.9±1.62	0.439
Relative wall thickness	0.44±0.11	0.43±0.12	0.716
LV mass index (gram/m <sup>2</sup> )	114.8±33.6	105.3±45.8	0.019
Left atrial diameter (mm)	34.0±5.6	34.3±5.3	0.625
Aortic diameter (mm)	32.0±4.1	31.8±4.0	0.292
E velocity (cm/sec)	67.8±19.5	64.8±17.4	0.841
A velocity (cm/sec)	65.9±19.5	64.8±17.4	0.590
Deceleration time (cm/sec)	235.0±52.2	236.6±55.5	0.791
E/Ea	9.2±4.0	9.3±3.1	0.856

Data are n (%) or mean±SD. EPT: ergonovine provocation test, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end diastolic diameter, IVSd: diastolic interventricular septal thickness, PWDd: posterior wall thickness, LV: left ventricular, E: peak early diastolic mitral flow, A: peak late diastolic mitral flow, Ea: peak early diastolic annular velocity

summarized in Table 1. As shown in Table 1, there was no statistically significant difference between the patients with VA and controls with respect to demographic characteristics except for body mass index. Table 2 outlines the echocardiographic data of the study groups. All echocardiographic parameters, except LVMI, were similar between the groups; these parameters included IVRT, DT, E/A ratio and E/E' ratio, which are indicators of diastolic dysfunction. The proportion of patients with subclinical hypothyroidism among those with EPT(+) was significantly higher than among those patients with EPT(-) (18% vs. 11%,  $p=0.042$ ) (Fig. 1). However, there was no significant difference in the proportion of subclinical hyperthyroidism between the groups (Table 3). Moreover, TPO Ab positivity was significantly more common in patients with EPT(+) than those with EPT(-) (33% vs. 14%,  $p<0.001$ ). There was a significant positive correlation between EPT(+) and TPO positivity ( $r=0.235$ ,  $p<0.001$ ), TPO Ab titer ( $r=0.293$ ,  $p<0.001$ ), subclinical hypothyroidism ( $r=0.104$ ,  $p=0.042$ ), and body mass index ( $r=0.143$ ,  $p=0.005$ ). Binary logistic regression analysis revealed that the significant predictors of EPT(+) were body mass index {adjusted odds ratio (OR)=1.042, 95% confidence interval (CI)=1.005–1.080,  $p=0.026$ },



**Fig. 1.** The proportion of patients with subclinical hypothyroidism among those with positive ergonovine provocation tests was significantly higher than among those patients with negative ergonovine provocation tests. TPO: thyroid peroxidase.

**Table 3.** Thyroid function of groups

	Positive EPT (n=165)	Negative EPT (n=220)	p
Normal TFT, n (%)	118 (71.5)	169 (76.8)	0.237
Subclinical hypothyroidism, n (%)	30 (18.2)	24 (10.9)	0.042
Subclinical hyperthyroidism, n (%)	17 (10.3)	27 (12.3)	0.548
Free T4 (pmol/L)	1.15±0.20	1.16±0.21	0.463
TSH (mIU/L)	4.31±14.1	2.15±2.04	0.026
TPO Ab titer	90.0±154.9	25.4±33.3	<0.001
Positive TPO Ab, n (%)	55 (33.3)	30 (13.6)	<0.001

Data are n (%) or mean±SD. EPT: ergonovine provocation test, TFT: thyroid function test, TSH: thyroid stimulating hormone, TPO Ab: thyroid peroxidase antibody

presence of subclinical hypothyroidism (OR=3.047, 95% CI=1.083–8.572,  $p=0.035$ ), TPO Ab titer (OR=1.028, 95% CI=1.015–1.041,  $p<0.001$ ) and the presence of TPO Ab (OR=4.904, 95% CI=1.544–15.567,  $p=0.007$ ) (Table 4).

## Discussion

Variant angina is an important cause of critical situations such as acute myocardial infarction, fatal arrhythmia, and sudden cardiac death.<sup>16</sup> Therefore, it is important to predict the risk of coronary artery spasms in the general population in order to reduce its associated complications. One of the important mechanisms underlying VA is thought to be endothelial dysfunction of coronary arteries.<sup>3,17</sup> In this study, we showed that subclinical hypothyroidism, not subclinical hyperthyroidism, is associated with coronary spasms as established by the ergonovine test. The presence of TPO Ab was also found to be significantly associated with increased coronary vasospasm in patients without cardiovascular risk factors.

Since the cardiovascular system is one of the major sites of action for thyroid hormones, it is relatively sensitive to changes in hormonal levels.<sup>18</sup> The first case of hyperthyroidism-associated angina pectoris (secondary to coronary spasm) was reported clinically in 1950 and by angiography in 1979; since then, several reports additional reports have appeared.<sup>19</sup> However, there is no consensus on the association between subclinical thyroid disease and VA. Subclinical hypothyroidism is characterized by normal serum free T4 and free T3 levels and increased serum TSH levels, which is relatively common in the general population.<sup>20</sup> Although the relationship between subclinical hypothyroidism and cardiovascular diseases has become a popular topic recently, there is still some controversy concerning the cardiovascular effect of subclinical hypothyroidism and management protocols.<sup>20,21</sup> Due to its metabolic and hemodynamic effects, such as hyperlipidemia and hypertension, overt hypothyroidism is associated with atherosclerosis.<sup>19</sup> Subclinical hypothyroidism may be related to endothelial dysfunction and atherogenesis in several ways. First, subclinical hypothyroidism is associated with

**Table 4.** Binary logistic regression analysis

	Ergonovine provocation test(+)			
	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.010 (0.992–1.029)	0.439		
Female gender	1.025 (0.681–1.543)	0.615		
Smoking	1.213 (0.762–1.499)	0.300		
SBP	1.010 (0.999–1.022)	0.152		
Total cholesterol	1.002 (0.997–1.008)	0.342		
Subclinical hypothyroidism	1.347 (1.008–1.800)	0.044	3.047 (1.083–8.572)	0.035
Body mass index	1.049 (1.013–1.085)	0.007	1.042 (1.005–1.080)	0.026
TSH	1.081 (1.002–1.167)	0.045	1.114 (0.991–1.251)	0.070
TPO Ab titer	1.013 (1.008–1.019)	<0.001	1.028 (1.015–1.041)	<0.001
Positive TPO Ab	3.167 (1.915–5.237)	<0.001	4.903 (1.544–15.567)	0.007

OR: odds ratio, CI: confidence interval, SBP: systolic blood pressure, TSH: thyroid stimulating hormone, TPO Ab: thyroid peroxidase antibody

increased levels of LDL-C,<sup>22)</sup> diastolic blood pressure,<sup>23)</sup> and altered coagulation parameters.<sup>24)</sup> Second, because thyroid hormone receptors have been identified in human vascular smooth muscle cells,<sup>25)</sup> thyroid hormone deficiency with low grade inflammation may cause endothelial dysfunction and impaired NO availability,<sup>26)</sup> and slow blood flow may contribute to the process.<sup>27)</sup> Previous studies have identified impaired endothelial function in patients with subclinical hypothyroidism,<sup>6–8)</sup> which resulted from a reduction in NO availability and was reversed by levothyroxine supplementation.<sup>8)</sup> In the present study, we found a higher frequency of coronary artery spasm induced by ergonovine in patients with subclinical hypothyroidism defined by TPO autoantibody positivity. There have also been reports regarding the impact of thyroid autoimmunity on the cardiovascular system. For example, among euthyroid women, the presence of Hashimoto's thyroiditis has been found to be positively associated with arterial stiffness.<sup>11)</sup> Furthermore, thyroid autoimmunity has been associated with an increase in carotid atherosclerosis in obese women, independent of thyroid function, obesity, and cardiovascular risk factors.<sup>12)</sup> We previously showed that the presence of TPO Ab was significantly associated with increased arterial stiffness in postmenopausal female fibromyalgia patients.<sup>13)</sup> Considering that increased arterial stiffness is also caused by mildly impaired thyroid function,<sup>28)</sup> the increased arterial stiffness associated with endothelial dysfunction might explain our result.

Another interesting finding in our study is that there is a significant association between body mass index and VA. Although there was no clear evidence that obesity might initiate coronary artery spasms, excess body fat may indirectly affect insulin resistance, an enhanced inflammatory state, and the plasma free insulin-like growth factor-I, which are reported to be related to coronary artery spasms.<sup>29)</sup> Obesity itself also has been shown to be indepen-

dently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries.<sup>30)</sup>

There are several limitations to this study. Because we used strict criteria to define a positive ergonovine angiographic study (near total, localized spasm, reproducing the patient's typical symptoms or associated with ST-segment shifts), our results are not applicable to patients with mild generalized vasoconstriction (<20% narrowing) of apparently normal coronary arteries with clinically suspected VA. The cross-sectional study design is also a limitation in that it precludes our ability to infer causal associations. Moreover, our patients were on a variety of medications, which may have had some effect on endothelial function. In addition, the weak correlation we found between the presence of subclinical hypothyroidism (r=0.104) or TPO antibody (r=0.235) will require a larger prospective study.

However, we believe the results of this study have shown a valuable trend in VA, especially regarding the use of TPO Ab to evaluate this condition. In conclusion, we demonstrated that combined thyroid autoimmunity is significantly associated with increased coronary vasospasm in patients without cardiovascular risk factors. These results support the need to re-evaluate the effects of thyroid autoimmunity on the vasculature of VA patients without cardiovascular risk factors. However, longitudinal studies that employ a large population will be needed to determine the pathophysiologic and prognostic implications of coronary vasospasm.

## References

1. Yasue H, Horio Y, Nakamura N, et al. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. *Circulation* 1986;74:955–63.
2. Akasaka T, Yoshida K, Hozumi T, et al. Comparison of coronary flow re-

- serve between focal and diffuse vasoconstriction induced by ergonovine in patients with vasospastic angina. *Am J Cardiol* 1997;80:705-10.
3. Kugiyama K, Ohgushi M, Motoyama T, et al. Nitric oxide-mediated flow-dependent dilation is impaired in coronary arteries in patients with coronary spastic angina. *J Am Coll Cardiol* 1997;30:920-6.
  4. Selwyn AP, Kinlay S, Creager M, Libby P, Ganz P. Cell dysfunction in atherosclerosis and the ischemic manifestations of coronary artery disease. *Am J Cardiol* 1997;79(5A):17-23.
  5. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. *Thyroid* 2007;17:519-24.
  6. Lekakis J, Papamichael C, Alevizaki M, et al. Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. *Thyroid* 1997;7:411-4.
  7. Cikim AS, Oflaz H, Ozbey N, et al. Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. *Thyroid* 2004;14:605-9.
  8. Taddei S, Caraccio N, Virdis A, et al. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab* 2003;88:3731-7.
  9. Schultz M, Kistorp C, Raymond I, et al. Cardiovascular events in thyroid disease: a population based, prospective study. *Horm Metab Res* 2011;43:653-9.
  10. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. *Clin Lab* 2011;57:719-24.
  11. Stamatielopoulou KS, Kyrkou K, Chrysochoou E, et al. Arterial stiffness but not intima-media thickness is increased in euthyroid patients with Hashimoto's thyroiditis: the effect of menopausal status. *Thyroid* 2009;19:857-62.
  12. Ciccone MM, De Pergola G, Porcelli MT, et al. Increased carotid IMT in overweight and obese women affected by Hashimoto's thyroiditis: an adiposity and autoimmune linkage? *BMC Cardiovasc Disord* 2010;10:22.
  13. Cho KI, Lee JH. The impact of thyroid autoimmunity on arterial stiffness in postmenopausal patients with fibromyalgia. *Int J Rheum Dis* 2014 Jan 11 [Epub]. <http://dx.doi.org/10.1111/1756-185X.12257>.
  14. Zaya M, Mehta PK, Merz CN. Provocative testing for coronary reactivity and spasm. *J Am Coll Cardiol* 2014;63:103-9.
  15. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008): digest version. *Circ J* 2010;74:1745-62.
  16. Bory M, Panagides D, Desfossez L. Coronary artery spasm in myocardial infarction. *Lancet* 1993;342:436.
  17. Yasue H, Kugiyama K. Coronary spasm: clinical features and pathogenesis. *Intern Med* 1997;36:760-5.
  18. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000;10:665-79.
  19. Wei JY, Genecin A, Greene HL, Achuff SC. Coronary spasm with ventricular fibrillation during thyrotoxicosis: response to attaining euthyroid state. *Am J Cardiol* 1979;43:335-9.
  20. Cooper DS. Clinical practice. Subclinical hypothyroidism. *N Engl J Med* 2001;345:260-5.
  21. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med* 2002;137:904-14.
  22. Pirich C, Müllner M, Sinzinger H. Prevalence and relevance of thyroid dysfunction in 1922 cholesterol screening participants. *J Clin Epidemiol* 2000;53:623-9.
  23. Cai Y, Ren Y, Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertens Res* 2011;34:1098-105.
  24. Cantürk Z, Cetinarslan B, Tarkun I, Cantürk NZ, Ozden M, Duman C. Hemostatic system as a risk factor for cardiovascular disease in women with subclinical hypothyroidism. *Thyroid* 2003;13:971-7.
  25. Mizuma H, Murakami M, Mori M. Thyroid hormone activation in human vascular smooth muscle cells: expression of type II iodothyronine deiodinase. *Circ Res* 2001;88:313-8.
  26. Taddei S, Caraccio N, Virdis A, et al. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 2006;91:5076-82.
  27. Obuobie K, Smith J, Evans LM, John R, Davies JS, Lazarus JH. Increased central arterial stiffness in hypothyroidism. *J Clin Endocrinol Metab* 2002;87:4662-6.
  28. Nagasaki T, Inaba M, Kumeda Y, et al. Increased pulse wave velocity in subclinical hypothyroidism. *J Clin Endocrinol Metab* 2006;91:154-8.
  29. Kashiwagi Y, Harada E, Mizuno Y, et al. Coronary spastic angina is associated with insulin resistance-possible involvement of endothelial dysfunction. *Coron Artery Dis* 2013;24:559-65.
  30. Al Suwaidi J, Higano ST, Holmes DR Jr, Lennon R, Lerman A. Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. *J Am Coll Cardiol* 2001;37:1523-8.