

Myocardial perfusion and intima-media thickness in patients with subclinical hypothyroidism

Knapp M*, Lisowska A, Sobkowicz B, Tycińska A, Sawicki R, Musiał WJ

Department of Cardiology, Medical University of Białystok, Białystok, Poland

* CORRESPONDING AUTHOR:

Department of Cardiology
Medical University of Białystok,
M. Skłodowskiej-Curie 24A,
15-276 Białystok, Poland
Tel: +48 85 746 8656
Fax: +48 85 746 8604
E-mail: malgo33@interia.pl (Małgorzata Knapp)

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ABSTRACT

Purpose: The data concerning the relation between subclinical hypothyroidism (SH) and the risk of cardiovascular disease are divergent. We aimed to assess myocardial perfusion in contrast-enhanced echocardiography and intima-media thickness (IMT) in patients with SH.

Material/Methods: Forty females with SH without symptoms of coronary artery disease and 15 healthy female volunteers were examined. Echocardiographic evaluation of the left ventricle function as well as carotid and femoral IMT complex measurements were performed at baseline. Thereafter, dobutamine stress echocardiography with myocardial perfusion assessment at rest and on the peak of stress test was performed. SonoVue® intravenous bolus as a contrast medium was used. The myocardial perfusion was assessed by quantitative method using Q-LAB Philips software (ROI modality). The perfusion index was calculated (a number of left ventricle segments with improved perfusion/a number of all segments).

Results: A mean IMT value in the SH group was significantly higher than in the controls (0.7 mm vs. 0.38 mm, $p=0.001$). Myocardial perfusion at rest and at the peak of stress test was significantly lower in the SH patients as compared to the controls (at rest 120 Db in SH vs. 181 Db in controls, $p=0.039$ and at the peak of stress 115 Db and 188 Db, $p=0.01$, respectively). The perfusion index was not significantly worse in the SH group ($p=0.6$). IMT values negatively correlated with the myocardial perfusion index at the peak of stress ($r=-0.54$, $p=0.014$).

Conclusions: In patients with SH contrast-enhanced echocardiographic examination revealed myocardial hypoperfusion and increased IMT. Our results may suggest that the patients with SH are at risk of the development of cardiovascular disease.

Key words: subclinical hypothyreosis, myocardial perfusion, intima-media thickness

INTRODUCTION

Subclinical hypothyreosis (SH) is featured by elevated concentration in plasma TSH concomitant with normal concentration in plasma free thyroxine (fT4). The literature data indicate clearly that patients with SH have increased incidence of coronary heart disease (CHD) and increased risk of death as a consequence of cardiovascular complications [1]. It was shown that SH is also accompanied by increased plasma concentration of LDL-cholesterol and increased

incidence of arteriosclerotic plaques in the coronary and peripheral arteries [2]. The results of the Rotterdam Study revealed that in SH patients the arteriosclerotic changes in the abdominal aorta are more advanced than in subjects with unchanged thyroid function [3]. However, there are also contradictory reports in that matter [4]. There are also reports showing that SH is not accompanied by an increased number of cardio-vascular events [1,2]. SH is diagnosed more often in women than in men. In general population, its incidence is 4%, but in elderly it increases up to 15% [1]. It indicates that

there is a necessity to develop new, noninvasive indices of arteriosclerosis development in the elderly. In case of thyroid dysfunction, examination with the use of radiologic contrast in asymptomatic patients is very limited. In this work, we employed two ultrasonographic methods, namely with the dobutamine stress test and evaluation of myocardial perfusion by means of contrast echocardiography. The latter is a new technique allowing noninvasive estimation of myocardial perfusion. The technique combined with the stress test allows observation of dynamic changes in myocardial perfusion between resting and peak values. Echocardiographic evaluation of the intima-media (IMT) is an acknowledged method of estimation of cardiovascular events risk.

The aim of the present study was to measure myocardial perfusion during stress echocardiography and perform ultrasonographic evaluation of the intima-media complex of peripheral vessels as the indices of development of arteriosclerosis in patients with SH as well to estimate a relationship between them.

MATERIAL AND METHODS

The experimental protocol was approved by the Ethical Committee for Human Studies of the Medical University of Bialystok. The subjects gave written consents for the study. 40 women, aged 34.8 ± 4.1 years with diagnosed SH in the course of Hashimoto disease were included. The diagnosis of SH was confirmed by elevation in TSH concentration coexisting with normal concentration of fT4, the presence of antibodies against thyroid peroxidase (aTPO) and hypogenic (typical) picture of ultrasonographic examination of the thyroid. Hypercholesterolemia was diagnosed by total cholesterol and LDL-cholesterol concentrations exceeding 200 mg/dL and 130 mg/dL respectively. In the study group thyroid disorders as well as hypercholesterolemia were diagnosed in the same time. Besides hypothyreosis and pathological lipids profile related to SH, the patients did not have any classical risk factors of the coronary heart disease. The control group consisted of 15 healthy female volunteers aged 31.6 ± 9.3 years.

The characteristics of the subjects is presented in *Tab. 1*. Both groups of patients underwent transthoracic echocardiography examination at rest with evaluation of contractility of the left ventricle and ultrasound examination of the IMT complex of the common carotid artery (CCA), carotid bulb, and common femoral artery (CFA). The examination was performed with an ultrasound device (Philips iE33) equipped with a 1-5 Mhz sector transducer and a 3-11 MHz linear-array high resolution transducer, using dedicated software for B-mode analysis. Next, the patients were subjected to the dobutamine stress test. Both at rest and on the peak of the stress test the contrast was administered. After echocardiographic examination at rest slow bolus injection of the contrast agent (SonoVue 1 ml) was administered into the left ulnar vein and it was followed by saline flush. 20 patients with SH and 10 control subjects were included in this part of the study. The instrument setting for myocardial contrast echocardiography was optimized in order to have maximum sensitivity and ideal conditions for visual myocardial contrast detection. MCE was performed using a modality of real-time perfusion imaging with the low mechanical index (MI: 0.1).

Contrast bolus was administered prior to acquisition of the peak stress loops and then the dobutamine infusion was stopped. When there was sufficient myocardial contrast enhancement in the apical views, high energy ultrasound pulse was delivered to destroy microbubbles. The assessments were performed using harmonic imaging in either four or two chamber apical views. Echocardiographic images were digitally stored in a sine loop format for the off-line analysis. Next, dobutamine stress echocardiography was performed according to the protocol of European Echocardiography Association. After acquisition of 4 standard views at rest (parasternal long and short axis view, apical 4-chamber and 2-chamber view), dobutamine hydrochloride (Dobutamin Hexal AG, Germany) was infused intravenously. During the test (every 3 minutes) and 10min after the dobutamine infusion was stopped, the heart rate and blood pressure were measured. The contractility of the left ventricle was evaluated by the analysis of contractile increase of thickness of its walls and the ejection fraction. At the peak of the stress

Table 1. The characteristics of the subjects.

	SH group	Control group	p
Age (years)	34.8 ± 4.1	31.6 ± 9.3	0.8
BMI (kg/m ² body surface)	24.43 ± 4.3	21.8 ± 1.48	0.027
SBP (mmHg)	127.5 ± 8.3	120.8 ± 7.4	0.85
DBP (mmHg)	81.0 ± 8.4	74.2 ± 8.0	1.0
TCh (mg/dl)	213.17 ± 58.5	168.5 ± 6.74	0.03
LDL (mg/dl)	133.67 ± 45.3	88.0 ± 9.0	0.0057
HDL (mg/dl)	55.41 ± 14.8	62.5 ± 8.8	0.28
TG (mg/dl)	120.75 ± 25.6	77.5 ± 21.3	0.6
TSH (uIU/mL)	20.499 ± 6.4	2.165 ± 0.8	0.00073
EF (%)	61.0 ± 7.4	65.8 ± 2.0	0.12

test the contrast was administered again in order to evaluate the myocardial perfusion. The perfusion assessment at rest and at the peak of the stress test was quantified using Philips Q-LAB software (ROI modality) (Fig.1). The perfusion index: the ratio of the number of walls of the left ventricle with improvement of perfusion to the number of all walls was also calculated.

Ultrasonographic evaluations of the thickness of the intima-media peripheral artery complex (IMT) were carried out within the common carotid artery (CCA), the bulb of the artery, and the common femoral artery (CFA). CCA was scanned along a 10 mm-long segment from the carotid bulb. The CFA was examined along a 10 mm-long segment proximal to the origin of the deep femoral artery. IMT measurements were made for the distal wall because the IMT assessment for the proximal wall was complicated by the higher echo density of the adventitia than of the media and intima. The distance between the first clearly delineated bright line (the lumen/intima interface) and the second bright line (the media/adventitia interface) of the distal wall was measured as the IMT. For each analyzed segment of the vessel, two IMT measurements were taken and an average was calculated.

Statistical analysis

The results are presented as a mean \pm standard deviation for quantitative variables and as a percentage for qualitative variables. The improvement of myocardial perfusion was defined as a difference between the value after maximal load and at rest. The values below zero indicated lack of improvement in the perfusion. The perfusion index was defined as the ratio of the left ventricular wall with improved perfusion to the number of all walls. According to the type of variables, Mann-Whitney U-test and χ^2 -test were used to compare the experimental and control group. For evaluation of the global change in the perfusion Cochran Q-test was employed. The correlation between IMT and the perfusion and IMT and the cholesterol level was evaluated with Spearman correlation coefficient. Values of $p < 0.05$ were

regarded as significant. The statistical analysis was performed with Statistica 9.0PL.

RESULTS

The characteristics of the investigated subjects is presented in the *Tab. 1*. The patients with SH had elevated concentration in the plasma total cholesterol and LDL-cholesterol as compared to the control group ($p < 0.03$ and 0.006 , respectively). The subjects with SH were not obese but their BMI was higher than in the control group ($p < 0.03$).

Myocardial Contrast Echocardiography

The average perfusion of the particular left ventricle walls is presented in *Tab. 2*. The average perfusion of the myocardium in the study group at rest and after the stress was lower than in the control group. It was 120Db at rest in patients with SH and 181 Db in the control group ($p < 0.05$) and 115 and 188 Db after the stress, respectively ($p < 0.01$). In SH group the infusion of dobutamine improved the perfusion of the anterior and lateral wall and reduced the perfusion of the inferior wall and the apex. In the control group the perfusion was improved in each wall with the exception of the inferior one. The index of the left ventricle perfusion in the study group was not significantly different to the control one (0.38 vs. 0.63; $p = 0.06$).

In both groups, the stress test was evaluated classically, by judging clinical symptoms, ECG and echo was negative.

Intima – media Thickness

The mean values are presented in *Tab. 3*. The thickness of the intima-media complex (IMT) was below 1.3 mm in each of the examined vessels. It indicates lack of the atherosclerotic plaques. None of the means meets the ESC criteria of increased thickness of IMT. However, they are significantly thicker than the respective values in the control group. The myocardial perfusion of the anterior wall after dobutamine test was reduced in the group of patients with thicker IMT in the bulb of both carotid arteries (right- $p = 0.014$ and left- $p = 0.006$).

Spearman correlations revealed significant relations between total cholesterol and LDL cholesterol as well as IMT (*Tab. 4*). The parameters of myocardial perfusion did not correlate significantly with the lipids profile.

DISCUSSION

A relationship between thyroid disorders and the condition of the vascular bed is not thoroughly recognized. SH occurs quite often. According to the Third National Health and Nutrition Examination Survey, it occurs in 4.3% of adults in the United States of America and the incidence of its prevalence increases with ageing. It concerns ~10% of women above the age of sixty [5]. There are a few theories

Figure 1. Myocardial perfusion during the dobutamine stress test.

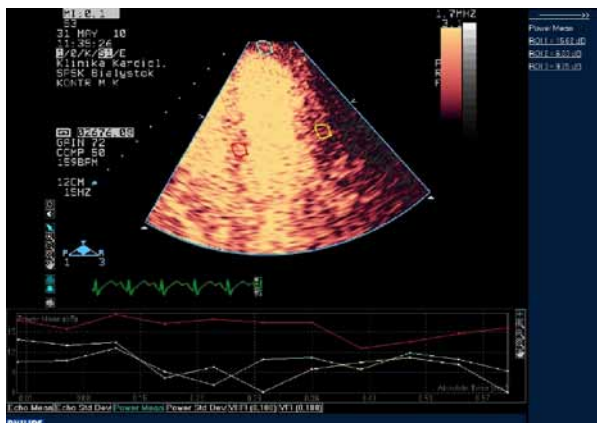


Table 2. Average perfusion of the left ventricle walls at the rest and on the peak of the dobutamine stress test (values in Db).

Walls of the LV	SH group before stress test	SH group after stress test	Control group before stress test	Control group after stress test
anterior	42.9	57.1	16.7	83.3
septum	50.0	50.0	33.3	66.7
lateral	42.9	57.1	33.3	66.7
inferior	92.9	27.1	83.3	16.7
apex	78.6	21.4	16.7	83.3
LV average	120	181	115	188

Table 3. IMT complex in the study and the control group (values in mm).

	SH group	Control group	p>0.05
CCA right	0.58±0.17	0.33±0.07	0.003
CCA left	0.64±0.19	0.32±0.04	0.001
CA bulb right	0.77±0.25	0.40±0.04	0.002
CA bulb left	0.75±0.34	0.40±0.08	0.014
CFA right	0.77±0.31	0.43±0.05	0.004
CFA left	0.75±0.28	0.40±0.04	0.003

trying to explain the mechanism of the influence of SH on the cardiovascular system. According to one of them, autoimmunization developing in its course leads to local vasculitis with subsequent development of atherosclerotic plaque [6]. Thyroid hormones were shown to inhibit platelet aggregation induced by collagen. The reversed effect was observed in the deficiency of the hormones [7]. Hypothyreosis is also accompanied by endothelial dysfunction and impaired nitric oxide production. These disturbances occur also in the early stage of development of atherosclerosis [8].

Changes of the heart morphology and function in hypothyreosis may be latent and there is a number of data indicating their disappearance after the correction of the thyroid function. There is a discrepancy of the data regarding a relationship between the increased risk of coronary heart disease (CHD) and hypothyreosis. However, according to the most reports it is elevated. Rodondi et al. [4] performed a metaanalysis of 14 reports concerning this problem. The analysis confirmed the view that hypothyreosis increases the risk of development of CHD. Similar results were published by Lervasi et al. [9]. Singh et al. [10] consider hypothyreosis to be a risk factor of CHD like hypertension, obesity, hyperlipidemia, smoking or diabetes. Hypothyreosis induces hypercholesterolemia. The plasma level of total cholesterol and LDL cholesterol increases [11-13] Also in the study group the plasma total cholesterol and LDL cholesterol were elevated. Rodondi et al. [14] reported that the risk of the occurrence of CHD in SH is higher in younger population. Lervasi et al. [9] conducted a cohort study in which they showed a relationship between SH and asymptomatic CHD. Cappola et al. [15] analyzed data obtained during the Cardiovascular Health Study. In the SH group both general

Table 4. Spearman correlation revealed significant relation between TC and LDL-cholesterol as well as IMT.

	IMT	r	p
TC	CCA right	0.63	0.004
	CCA left	0.55	0.018
	CA bulb right	0.60	0.007
	CA bulb left	0.45	0.05
	CFA right	0.48	0.04
	CFA left	0.43	0.05
LDL	CCA right	0.69	0.001
	CCA left	0.68	0.001
	CA bulb right	0.57	0.01
	CA bulb left	0.53	0.02
	CFA right	0.49	0.03
	CFA left	0.42	0.05

and cardiovascular mortality increased. We studied the group of young women without typical cardiovascular risk factors and the results of myocardial perfusion in this group were worse (inferior) compared to the control group. Our study confirm positive correlations between cholesterol level and the values of IMT.

There are only a few data on the perfusion of myocardium in patients with hypothyreosis measured with using the radioisotopes. Echocardiographic examination with the use of contrast is accepted, a safe and cheap method of evaluation of the heart function including myocardial perfusion [16]. However, there are no data available on the use of contrast echocardiography in patients with hypothyreosis. Prasz et al. [17] evaluated the cardiac function with the use of thallium-201 stress/rest myocardial scintigraphy. They did not find a reduction of myocardial perfusion in patients with newly diagnosed hypothyreosis. In our group of young women with SH a reduction in the myocardial perfusion was observed.

The thickness of the intima-media complex of the carotid artery is an important marker of the stage of atherosclerosis. This parameter is included in European guidelines on prevention of cardio-vascular disorders. The thickness of IMT=0.9 mm is regarded as a border value [18]. The increase in the thickness of IMT above this value suggests the progress of atherosclerosis. It is an independent risk factor of the CHD similar to classic risk factors like diabetes, hyperlipidemia or obesity. In the present study, the patients with SH did not have any risk factors of the coronary artery

disease. A positive correlation between IMT and the degree of atherosclerotic changes in the coronary vessels was reported [19]. In the present study, the IMT in patients with SH was significantly thicker than in the control group. We also showed reduced perfusion of the anterior wall of the left ventricle in patients with thicker IMT. This is the first study comparing the data on the perfusion of myocardium and IMT as early atherosclerosis markers. Cappola et al. [15] in the Cardiovascular Health Study did not find a beneficial effect of the hormonal therapy on the cardiovascular risk. Also other data are not equivocal [20,21]. Other study showed that the treatment with the thyroid hormones for 6 month diminishes IMT [22]. It was the first study that examined the presence of early atherosclerotic vascular wall lesions by means of B-mode ultrasound measurement of IMT in SH patients. The authors observed the decrease in LDL cholesterol induced by levothyroxine replacement. They also found that early carotid artery wall lesions are present in SH patients mainly from the fourth decade of life onward. Similar findings were achieved in our study group. There are no clinical studies evaluating the effect of supplementation with the thyroid hormones on the number of cardio-vascular events. It is still an open question whether screening of SH as an independent coronary risk factor should be continued. It is also an open question how to select patients with SH threatened with a particularly high risk of early cardio-vascular complications.

Limitations of the study

It is a one center study, carried out on a relatively small group of patients and without a follow up. To confirm the present results a prospective large study with the evaluation of distant cardiovascular events should be performed.

CONCLUSIONS

In patients with SH, echocardiographic stress test with the use of ultrasonographic contrast is safe and seems to be helpful to detect the reduction of myocardial perfusion at the level of microcirculation. The results obtained clearly show that in patients with SH increased thickness of IMT which is an early and sensitive parameter indicating the degree of atherosclerosis and allowing a selection of patients much threatened with cardiovascular disorders. Both employed echocardiographic methods seem to be useful in the evaluation of the risk of development of cardiovascular events in patients with SH.

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