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International Journal of Cardiology 103 (2005) 1–6

International Journal of Cardiology

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Arterial stiffness is increased in subjects with hypothyroidism

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Received 29 February 2004; received in revised form 29 April 2004; accepted 5 May 2004
Available online 1 September 2004

Abstract

Background: The association between hypothyroidism and increased vascular resistance, arterial wall thickening and endothelial dysfunction is well recognized. The aim of the present study was to examine if hypothyroid subjects have increased arterial stiffness, a risk factor for cardiovascular morbidity and mortality.
Methods: Sixty-five subjects (59 females and 6 males) with normal thyroid function or hypothyroidism of varying degree were investigated by radial artery applanation tonometry and pulse wave analysis, for evaluation of arterial stiffness.
Results: Serum TSH values were positively correlated with central systolic blood pressure (r=0.258, p=0.037), central pulse pressure (r=0.316, p=0.010), augmentation pressure (r=0.299, p=0.015) and negatively with reflection time index (RTI), which indicates the pressure wave velocity (r=−0.311, p=0.012). Hypothyroid patients presented higher central systolic pressure and pulse pressure, higher augmentation pressure and lower RTI, indicating increased arterial stiffness in these subjects. RTI was independently related to age, central systolic pressure and TSH. Mild changes of arterial stiffness were observed even in subjects with TSH range 2.01–4.0 μU/ml suggesting that this group may have an early stage of mild thyroid failure.
Conclusions: Hypothyroidism, even in the subclinical stage, is associated with changes in arterial stiffness. The observed abnormalities in arterial stiffness may have detrimental effects on left ventricular function and coronary perfusion in hypothyroid subjects.

Keywords: Arterial stiffness; Hypothyroidism; Cardiovascular disease

1. Introduction

For many years, an association has been recognized between thyroid disease and the cardiovascular system. Especially hypothyroidism leads to abnormalities of the size and the function of the heart [1], increased vascular resistance [2] and greater arterial wall thickness [3]. We recently reported that patients with hypothyroidism present abnormalities in flow-mediated, endothelium-dependent vasodilatation of the brachial artery [4], whereas the capacity of the artery to dilate in response to nitrates is preserved; these abnormalities are compatible with endothelial dysfunction and impaired release of nitric oxide, an early step in the atherosclerotic process. Finally, recent epidemiological data [5] suggest that subclinical hypothyroidism is a strong indicator of risk for aortic atherosclerosis and myocardial infarction in elderly women.

Arterial stiffness appears to be an important risk factor for cardiovascular disease; changes in arterial wall elasticity may occur before and during the early stages of atherosclerosis, while increased arterial stiffness is an independent risk factor for cardiovascular morbidity and mortality [6–8]. Various techniques have been developed to assess arterial stiffness; radial artery applanation tonometry and pulse wave analysis is a non-invasive, reliable and reproducible technique providing information

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0167-5273/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2004.05.068

about systemic arterial stiffness [9–11], while other ultrasound techniques provide measurements of stiffness within a small arterial segment, which does not necessarily reflect the compliance of the arterial system as a whole [12,13].

Recently, Obuobie et al. [14] observed that patients with overt hypothyroidism (TSH>10 μU/ml) presented increased arterial stiffness, which was reversed following adequate thyroxine replacement. No data are available on milder subclinical forms of hypothyroidism, which are also associated with endothelial dysfunction [4] and increased risk for atherosclerosis [5]. Therefore, in the present study, we used pulse wave analysis in waveforms obtained from radial artery by applanation tonometry, to examine arterial stiffness in patients with recently diagnosed and untreated hypothyroidism of varying severity and compare the results with those obtained from subjects with normal thyroid function.

2. Subjects and methods

2.1. Population

Sixty-five subjects (59 women and 6 men, aged 44.4±13.5 years), who were referred for evaluation of suspected hypothyroidism, comprised the study population. No subject had evidence of atherosclerotic disease (based on clinical history, clinical examination and electrocardiogram), diabetes mellitus or renal failure. Subjects with clinical history of treated or untreated arterial hypertension were excluded from the study; none of the participants was receiving any medications. There were eight smokers who were equally divided in each group of our study. Each subject gave informed consent before entering the study and the local Scientific Committee approved the protocol.

2.2. Thyroid hormone measurements

Serum TSH, T3 and T4 levels were measured in all study participants within 1 week of the vascular studies. In subclinical hypothyroidism group, TSH values were confirmed on two chronically different occasions, separated by 2–3 months, and were accompanied by positive titers of thyroid autoantibodies and/or hypoechogenic pattern in thyroid ultrasound in all cases. Serum TSH was assayed by IRMA, Amerlex hs TSH coated Tube Assay (Ortho-Clinical Diagnostics, Amersham, UK, Johnson and Johnson Clinical Diagnostics) (intra- and interassay coefficients of variation 3.2% and 5.7%, respectively). Serum T3 and T4 levels were assayed by Amerlex-M T3 RIA kit and Amerlex-M T4 RIA kit, respectively (Johnson and Johnson Clinical Diagnostics). Normal range for T4 is 5.0–12.8 μg/dl for T3 0.5–1.75 ng/ml and for TSH 0.3–3.7 mU/ml.

2.3. Applanation tonometry and pulse wave analysis

In all studies, the Sphygmocor apparatus (ATCOR Medical, Sydney, Australia) was used; this system uses the principle of the pressure wave reflection from the periphery and their summation with the forward-going wave. Normally, the reflected wave arrives in the central arteries after closure of the aortic valve and does not influence central systolic pressure. However, in the presence of increased arterial stiffness, the increased pulse wave velocity of the stiffened arteries causes earlier wave reflection that reaches the heart in early systole. This increase in central systolic pressure due to wave reflection is referred to as augmentation and is an index of arterial stiffness.

Each subject was studied in the morning after a 10-min rest period. After blood pressure measurement, an arterial pressure waveform was recorded by applanating the radial artery with a hand-held tonometer as previously described [9–11]. The tip of the tonometer contains a micromanometer that accurately records the pressure within the artery; pressure waveforms obtained by this method have been validated by comparing them with waveforms obtained by high fidelity transducer within the artery [15]. Data were collected directly into a portable microcomputer; after 20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform. Central aortic pressure waveforms were derived from the radial artery waveforms by using a transfer function; this method has been recently validated and shown to produce accurate transformation of the pressure wave, even under hemodynamic manipulation [16].

The following parameters were measured from the central aortic waveform: (1) augmentation pressure (AP: mm Hg), which is the difference between the second (reflected) and the first (primary) wave in mm Hg, (2) augmentation index (AI: %), which is the difference between the second and the first peaks of the central aortic waveform expressed as a percentage of the aortic pulse pressure, (3) central systolic, diastolic and mean pressures, (4) central pulse pressure, (5) time to the beginning of the reflected wave (t_1: ms) and (6) reflection time index (RTI: %) which is the time to the beginning of the reflected wave expressed as a percentage of cardiac period (Fig. 1); this index is an estimate of the pulse wave velocity. The higher the augmentation pressure, augmentation index and pulse pressure, the higher is the arterial stiffness; the lower the time to the beginning of the reflected wave, the higher is the arterial stiffness.

2.4. Statistical analysis

Numeric values are expressed as mean±S.D. Linear regression and multiple regression (stepwise method) analysis were used to assess the relationship between

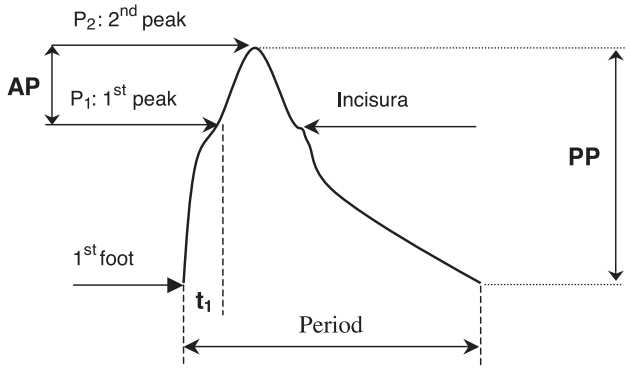

Fig. 1. Illustration of a central aortic pressure waveform. AP: augmentation pressure, the difference between the reflected and the primary wave, PP: pulse pressure, t_1: time to the beginning of the reflected wave.

selected variables. Analysis of variance was performed to compare variables in the various groups according to TSH values. Multiple comparisons between groups of different TSH levels were made by Bonferroni corrected Student's *t*-test. A p-value <0.05 was taken as the level of statistical significance. Continuous variables that were not normally distributed were log transformed.

3. Results

Of the 65 subjects examined, 16 had low-normal TSH values (0.3–2.0 μU/ml, mean 1.08±0.4 μU/ml, group 1), 18 had high-normal TSH levels (2.01–4.0 μU/ml, mean 2.9±0.7 μU/ml, group 2), 16 had elevated TSH values 4.01–10.0 μU/ml (mean 5.9±1.3 μU/ml, group 3) and 15 subjects had overt hypothyroidism TSH>10.0 μU/ml (mean 33.8±22.3 μU/ml, group 4). There were no significant differences among the four groups regarding body mass index, peripheral diastolic and mean blood pressure, HDL and LDL cholesterol, blood urea nitrogen, uric acid and blood glucose. Patients in group 4 were older had higher peripheral systolic blood pressure, lower heart rate, higher triglycerides and tended to have higher total cholesterol. Characteristics of the four groups are shown in Table 1.

Serum TSH levels (log transformed) were significantly correlated to central systolic blood pressure (r=0.258, p=0.037), central pulse pressure (r=0.316, p=0.010), age (r=0.405, p=0.001), cholesterol (r=0.339, p=0.020), triglycerides (r=0.336, p=0.027), heart rate (r=−0.272, p=0.028), the reflection time index (r=−0.311, p=0.016) and augmentation pressure (r=0.299, p=0.015). No correlation was found between TSH and height, weight, body mass index, peripheral systolic, diastolic and mean pressure, central diastolic and mean blood pressure, augmentation index, HDL and LDL cholesterol, glucose, urea and uric acid.

Hemodynamic parameters for the four groups are given in Table 2. By analysis of variance, statistically significant differences were observed in peripheral systolic blood pressure (F=3.27, p=0.027), central systolic blood pressure (F=4.0, p=0.011), heart rate (F=3.67, p=0.017), central pulse pressure (F=3.17, p=0.03) and the following indices of arterial stiffness: augmentation pressure (F=3.63, p=0.018), augmentation index (F=2.8, p=0.047) and the reflection time index (F=6.71, p=0.001).

RTI (log transformed) was significantly related to central systolic blood pressure (r=−0.268, p=0.031), central pulse pressure (r=−0.306, p=0.013), augmentation index (r=−0.588, p<0.001), augmentation pressure (r=−0.515, p<0.001), age (r=−0.260, p=0.036) and TSH (r=−0.311, p=0.012). To control for any effect of age, which is an important factor affecting arterial stiffness, multiple regression analysis was performed with RTI as dependent variable. Augmentation index, TSH and age were entered to the model as independent variables. It was showed that RTI was independently correlated to TSH (p=0.012).

Table 1
Study groups characteristics

Variable	Group 1	Group 2	Group 3	Group 4
N	16	18	16	15
Gender (females/males)	16/0	17/1	13/3	13/2
TSH range (μU/ml)	0.4–1.7	2.1–3.9	4.4–8.5	10.1–75.0
Age (years), ANOVA, F=6.17, p=0.001	37.6±9.9	42±13.9	43.4±13.9	55.5±11.2
TSH (μU/ml), ANOVA, F=31.6, p<0.001	1.08±0.42	2.95±0.67	5.9±1.28	33.7±22.3
T4 (μg/dl), ANOVA, F=19.6, p<0.001	8.6±1.6	9.2±1.7	7.2±1.2	4.7±2.3
T3 (ng/ml), ANOVA, F=4.3, p=0.009	1.1±0.18	1.35±0.33	1.16±0.38	0.87±0.54
Cholesterol (mg/dl), ANOVA, ns	205±51	226±51	213±46	268±90
Triglycerides (mg/dl), ANOVA, F=3.35, p=0.031	79±38	100±37	63±23	134±68
HDL-cholesterol (mg/dl), ANOVA, ns	57±11.1	54.7±12	60.2±13	59±10.9
LDL-cholesterol (mg/dl), ANOVA, ns	138.7±44.3	158.3±69	144.3±43.6	192±79
Systolic blood pressure (mm Hg), ANOVA, F=3.27, p=0.027	116.1±14.8	120.8±17.4	118.2±18.4	134±21.8
Diastolic blood pressure (mm Hg), ANOVA, ns	75.6±12.6	79.6±10.6	72.6±11.5	83.6±15
Glucose (mg/dl), ANOVA, ns	88.9±5.6	91.3±11	84.7±12.9	92.6±10.3
Blood urea nitrogen (mg/dl), ANOVA, ns	26.4±5.3	31.9±8.3	33.3±4.3	29.8±6.8
Uric acid (mg/dl), ANOVA, ns	3.3±0.9	4.0±0.69	4.1±1.1	3.5±1.6

ANOVA, degrees of freedom=3.

Table 2
Hemodynamic parameters in the study groups (TSH levels groups 1 to 4: 0.3–2.0, 2.01–4.0, 4.01–10.0, >10 μU/ml)

Variable	Group 1, n=16	Group 2, n=18	Group 3, n=16	Group 4, n=15
Heart rate (bpm), ANOVA, F=3.67, p=0.017	82±14.4	71.9±6.2	77.2±8.8	70.9±12.3
Central systolic pressure (mm Hg), ANOVA, F=4.01, p=0.011	105.7±16.1	112.3±17.3	107.2±15.3	125.3±20.9
Central diastolic pressure (mm Hg), ANOVA, ns	77±12.6	80.6±10.6	73.8±11.4	84.7±15.3
Central pulse pressure (mm Hg), ANOVA, F=3.17, p=0.03	28.8±8.9	31.9±11.5	33.4±12.5	40.8±12.1
Augmentation pressure (mm Hg), ANOVA, F=3.63, p=0.018	5.9±5.3	9.7±6.7	7.7±5.12	12.7±6.5
Augmentation index(%), ANOVA, F=2.8, p=0.047	18.6±14.6	27.5±13.6	22.8±9.5	29.5±9.7
t_1(ms), ANOVA, F=2.29, p=0.08	121±27	108±24	107±9	103±11
Reflection time index(%),ANOVA,F=6.71,p=0.001	16.62±5.49	12.37±1.74	13.77±1.48	12.24±2.24

ANOVA, degrees of freedom=3.

Subgroup analysis showed that arterial stiffness was statistically increased in group 2 (TSH=2–4 μU/ml) compared to group 1 (controls, TSH 0–2 μU/ml) as indicated by decreased RTI (p=0.001). Age, blood pressure and blood lipids were comparable between the two subgroups. On the other hand, mean RTI at group 2 was not significantly different from the respective RTI values of groups 3 (p=0.665) and 4 (p=0.99).

4. Discussion

The findings of the present study indicate that subjects with even mild forms of hypothyroidism present augmentation of the central arterial pressure by wave reflection, resulting from systemic arterial stiffening. These results suggest that hypothyroidism has detrimental effects on systemic arterial stiffness analogous to that of aging.

Applanation tonometry of the radial artery and pulse wave analysis used in the present study is a quick, noninvasive examination, with excellent reproducibility when used by trained observers and has been validated previously [11,17,18]. This method has been used before to describe changes of arterial stiffness in diabetes mellitus, hypertension and aging [19–21].

In the present study, subjects with hypothyroidism appear to present a lower RTI value reflecting the higher pulse wave velocity and arterial stiffness; it should be noticed that this change is independent of age and gender, which are well-known factors that affect arterial stiffness. Also other indices of arterial stiffness, like augmentation pressure and index, central pulse pressure and central systolic pressure, appear to be increased as well, suggesting a lower arterial compliance (increased stiffness) in these patients. Increased arterial stiffness in hypothyroid patients with TSH>10 μU/ml has been recently presented by Obuobie et al. [14]. The observed changes in arterial wall properties could be explained by various mechanisms: (1) endothelial function appears to be abnormal in patients with hypothyroidism [4] and it is known that elastic behavior of the arteries may be influenced by endothelium-derived relaxing factors [22]; therefore, the impaired endothelial function observed in hypothyroidism may lead to increased arterial stiffness and augmentation of the central aortic pressure. (2) Hypercholesterolemia, a frequent feature of hypothyrodism, is associated with increased arterial stiffness [23]; in our study, subjects with TSH>10 μU/ml tended to have higher cholesterol levels. (3) Hyperhomocysteinemia, which is frequently present in hypothyroid patients [24], may lead to endothelial dysfunction [25] and, subsequently, to decreased arterial distensibility [22]. (4) Finally, a direct effect of TSH on arterial wall cannot be excluded [26].

Abnormalities of the arterial wall have been previously described in hypothyroid patients. Using ultrasound measurements, Giannattasio et al. [3] reported that radial artery wall thickness was significantly and markedly greater in patients with a recent diagnosis of hypothyroidism; despite this increase in radial wall thickness, compliance at the same site was increased, a phenomenon not seen in the carotid artery. We should mention that the method used in our study examines the systemic arterial stiffness and not a local phenomenon as seen in the above mentioned report and that alterations in arterial function are not uniform throughout the arterial tree.

Both overt and subclinical hypothyroidism have been associated with cardiovascular disease. Silent myocardial ischemia is common in severe hypothyroidism [27], while low free-thyroxine levels are associated with carotid atherosclerosis [28]. Subclinical hypothyroidism has recently been shown to be a strong indicator of risk for aortic atherosclerosis and myocardial infarction in elderly women [5]. Lipid abnormalities, increased homocysteine, as well as a hypercoagulable state may account for this association between hypothyroidism and atherosclerotic disease [23,24,29,30]. The observed signs of increased arterial stiffness in the present study may be an early evidence of the atherosclerotic process in these patients, as they appear to occur before clinically apparent vascular disease. Recent data suggest that pulse pressure, a surrogate marker of arterial stiffness, is an independent predictor of cardiovascular risk in middle-aged and older subjects [6–8] and therefore our finding of increased pulse pressure in hypothyroid patients appears to be of interest, since it could be pathophysiologically linked to the increased risk of coronary heart disease in these subjects.

Subtle abnormalities in left ventricular systolic and diastolic function have been demonstrated in overt and subclinical hypothyroidism [31–34]. Arterial stiffening and

the resulting augmentation of the systolic aortic pressure adversely affects left ventricular performance and could contribute to the pathogenesis of left ventricular abnormalities observed in hypothyroid patients. In patients with arterial hypertension early return of the enhanced wave reflection may profoundly impair left ventricular relaxation function assessed by radionuclide angiography [35].

In our analysis of data, the group with high-normal TSH values (2.01–4.0 μU/ml) was considered separately. In these subjects, indices like augmentation pressure, augmentation index, pulse pressure and central aortic pressure did not differ compared to subjects with low-normal TSH values; however, RTI was markedly decreased in this group, suggesting that arterial stiffness was increased in these subjects. This is in accord with previous findings that these subjects with high-normal TSH values frequently develop hypothyroidism later in life [36], usually present hypercholesterolemia, which improves with thyroxine administration [37] and may have decreased endothelium-dependent vasodilatation, a sign of endothelial dysfunction [4]. More recently, it has also been suggested that an association between increasing TSH and LDL cholesterol becomes apparent in insulin resistant subjects with TSH values still in the normal range [38]. Together with the results presented here, it may be proposed that TSH values between 2.01 and 4.0 μU/ml are rather mildly abnormal and not high-normal and that the definition of the "normal" range for TSH values should probably be reconsidered.

In conclusion, patients with hypothyroidism present increased arterial stiffening leading to augmentation of the central aortic pressure with possible detrimental effects on left ventricular function and coronary perfusion. Until a specific treatment that can modify arterial stiffness is available, early treatment of hypothyroidism may be important in reducing the effects of this hemodynamic abnormality. The availability of a simple and accurate technique like applanation tonometry and pulse wave analysis will be of value in the early identification of the hemodynamic abnormalities and the evaluation of any interventions.

References

[1] Klein I, Levey GS. Unusual manifestations of hypothyroidism. Ann Intern Med 1984;144:123–8.

[2] Anthonisen P, Holst E, Thomsen AA. Determination of cardiac output and other hemodynamic data in patients with hyper- and hypothyroidism, using dye dilution technique. Scand J Clin Lab Invest 1960;12:472–80.

[3] Giannattasio C, Rivolta MR, Failla M, Magnoni AA, Stella ML, Mancia G. Large and medium sized artery abnormalities in untreated and treated hypothyroidism. Eur Heart J 1997;18: 1492–1498.

[4] Lekakis J, Papamichael C, Alevizaki M, Piperigos G, Marafelia P, Mantzos J, 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.

[5] Hak AE, Pols HAP, Visser TJ, Drexhage HA, Hofman A, Witteman JCM. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. Ann Intern Med 2000; 132:270–8.

[6] Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, et al. Pulse pressure: a predictor of long-term mortality in a French male population. Hypertension 1997;30:1410–5.

[7] Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560–4.

[8] Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–60.

[9] O'Rourke MF, Yaginuma T. Wave reflections and the arterial pulse. Arch Intern Med 1984;144:366–71.

[10] Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. Eur Heart J 1993;14:160–7.

[11] Siebenhofer A, Kemp CRW, Sutton AJ, Williams B. The reproducibility of central aortic blood pressure measurements in healthy subjects using applanation tonometry and sphygmocardiography. J Hum Hypertens 1999;13:625–9.

[12] van Merode T, Lodder J, Smeets FAM, Hoeks APG, Reneman RS. Accurate noninvasive method to diagnose minor atherosclerotic lesions in carotid artery bulb. Stroke 1989;20:1336–40.

[13] Riley WA, Barnes RW, Evans GW, Burke GL. Ultrasonic measurement of the elastic modulus of the common carotid artery. The Atherosclerosis Risk in Communities [ARIC] Study. Stroke 1992;23: 952–6.

[14] 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.

[15] Kelly R, Hayward C, Ganis J, Daley J, Avolio A, O'Rourke M. Noninvasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. J Vasc Med Biol 1989; 1:142–9.

[16] Chen CH, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan L, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Circulation 1997;7: 1827–36.

[17] Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079–84.

[18] Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932–7.

[19] Brooks B, Molyneaux L, Yue DK. Augmentation of central arterial pressure in type 1 diabetes. Diabetes Care 1999;22:1722–7.

[20] Cameron JD, McGrath BP, Dart AM. Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension. J Am Coll Cardiol 1998;32:1214–20.

[21] Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. Circulation 1989;80:1652–9.

[22] Ramsey MW, Goodfellow J, Jones CJH, Luddington LA, Lewis MJ, Henderson AH. Endothelial control of arterial distensibility is impaired in chronic heart failure. Circulation 1995;92:3212–9.

[23] Giannattasio C, Mangoni AA, Failla M, Carugo S, Stella ML, Stefanoni P, et al. Impaired radial artery compliance in normotensive subjects with familial hypercholesterolemia. Atherosclerosis 1996; 124:249–60.

[24] Hussein WI, Green R, Jacobsen DW, Faiman C. Normalization of hyperhomocysteinemia with L-thyroxine in hyperthyroidism. Ann Intern Med 1999;131:348–51.

[25] Takawol A, Omland T, Gerhard M, Wu JT, Creager MA. Hyperhomocysteinemia is associated with impaired endothelium-dependent vasodilation in humans. Circulation 1997;95:1119–21.
[26] Sellitti DF, Dennison D, Akamizu T, Doi SQ, Kohn LD, Koshiyama H. Thyrotropin regulation of cyclic adenosine monophosphate production in human coronary artery smooth muscle cells. Thyroid 2000;10:219–25.
[27] Bernstein R, Muller C, Midtbo K, Smith G, Haug E, Hertzenberg L. Silent myocardial ischemia in hypothyroidism. Thyroid 1995;5: 443–7.
[28] Bruckert E, Giral P, Chadarevian R, Turpin G. Low free-thyroxine levels are a risk factor for subclinical atherosclerosis in euthyroid hyperlipidemic patients. J Cardiovasc Risk 1999;6:327–31.
[29] Diekman T, Demacker PNM, Kastelein JJP, Stalenhoef AFH, Wiersinga W. Increased oxidizability of low-density lipoproteins in hypothyroidism. J Clin Endocrinol Metab 1998;83:1752–5.
[30] Muller B, Tsakiris DA, Roth CB, Guglielmetti M, Staub JJ, Marbett GA. Haemostatic profile in hypothyroidism as potential risk factor for vascular thrombotic disease. Eur J Clin Investig 2001;31:131–7.
[31] Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 2000;10:665–79.
[32] Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 1999;84:2064–7.
[33] Arem R, Rokey R, Kiefe C, Escalante DA, Rodriguez A. Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. Thyroid 1996;6: 397–402.
[34] Lee RT, Plappert M, Sutton JMG. Depressed left ventricular systolic ejection force in hypothyroidism. Am J Cardiol 1990;54:526–7.
[35] Chang KC, Tseng YZ, Kuo TS, Chen HI. Impaired left ventricular relaxation and arterial stiffness in patients with essential hypertension. Clin Sci (Colch) 1994;87:641–7.
[36] Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates F, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55–68.
[37] Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, et al. High serum cholesterol levels in persons with high-normal TSH levels: should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol 1998; 138:141–5.
[38] Bakker SJL, TerMaaten JC, Popp-Snigders C, Staets JP, Heine RJ, Gans ROB. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab 2001;86:1206–11.