CLINICAL STUDY

The effects of thyrotoxicosis and its treatment on central arterial stiffness

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Abstract

Objective: To assess central arterial stiffness in thyrotoxicosis using the technique of pulse wave analysis.

Design: Case control study designed to determine the effect of thyrotoxicosis on central arterial stiffness and at 6 months after radioiodine treatment.

Patients: Twenty (18 women and 2 men) thyrotoxic patients and 20 age- and sex-matched controls were studied at baseline. Thyrotoxic patients were re-studied at 6 months following treatment of thyrotoxicosis with 555 MBq ¹³¹I with no additional therapy for the six-month period.

Measurements: Using the sphygmocor apparatus, peripheral pressure waveforms were recorded non-invasively from the radial artery and central pressure waveforms were generated from these. Indices of arterial stiffness, central augmentation index (AI), augmentation of central arterial pressure (AG) and central blood pressures were derived. AI corrected for heart rate (AIC) was calculated.

Results: Thyrotoxic patients recorded a significantly lower AI (means±S.E.M.) compared with controls (15.0±2.1 vs 28.0±2.1%; $P < 0.0005$) even when corrected for differences in heart rate AIC (20.0±2.1 vs 28.0±2.1%; $P < 0.005$) as well as AG (6.0±0.8 vs 10.0±1.1 mmHg; $P < 0.002$) but higher pulse pressure (58.0±3.5 vs 47.0±2.0 mmHg; $P < 0.02$). At 6 months following treatment, a significant rise in AIC (27.0±1.8 vs 20.0±2.1%; $P < 0.005$) and AG (11.0±1.0 vs 6.0±0.8 mmHg; $P < 0.005$) was noted. Lipid profiles were comparable between the groups.

Conclusions: These data suggested that subjects with untreated thyrotoxicosis have a decreased augmentation of central arterial pressure or lowered central arterial stiffness that would not appear to contribute to any excess cardiovascular risk in that condition.

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Introduction

The cardiovascular features of thyrotoxicosis, such as increased cardiac contractility, heart rate, cardiac output, red cell mass, blood volume and a decreased total peripheral resistance are well recognised (1). The influence of pulse pressure on some of these parameters is appreciated but the role of central arterial stiffness or large artery compliance, which increases cardiac afterload, has gained increasing recognition (2). This has become even more evident with the development of non-invasive techniques of studying peripheral and central pressure waveforms (3, 4). Although thyroid hormones may directly affect smooth muscle relaxation (5), which may partly explain the decrease in total peripheral resistance seen in thyrotoxicosis, little is known about their effect on aortic or central arterial stiffness in humans. The aim of the present study was to determine central arterial stiffness in thyrotoxicosis before and 6 months after radioiodine treatment, by use of a

method of pulse wave analysis, which is based on the principle of applanation tonometry.

Subjects and methods

Twenty patients with thyrotoxicosis, 19 with Graves' disease (mean age 48.0 years, range 28 to 66) were recruited from the adult thyroid clinic at the University Hospital of Wales, Cardiff. Selected patients had not been taking any β -adrenoceptor antagonist, anti-thyroid medications as monotherapy or in combination with thyroid hormone replacement, for at least 3 months prior to commencement of the study. Patients with a previous history of established cardiac disease, hypertension, diabetes mellitus, renal disease and hyperlipidaemia were excluded but cigarette smokers were not excluded from the study and did not change the smoking habit over the study period. Concurrently, 20 age-, body mass index (BMI)- and sex-matched healthy hospital workers were recruited as controls.

All the patients received 555 MBq ^{131}I with no additional therapy for the 6-month period. Five patients required thyroxine replacement and were all euthyroid at 6 months. This study was approved by the institutional ethics committee and all patients gave informed consent before participating in the study.

Pulse wave analysis

Measurements were taken after 15 min rest in a quiet room. Peripheral blood pressure was measured in duplicate in the dominant arm as the mean of three recorded readings using brachial sphygmomanometry. Central aortic pressure waveforms were derived from the non-invasive recordings of peripheral pressure waveforms using the method of pulse wave analysis using a pencil-shaped pressure tonometer (SPC-301; Millar Instruments, Houston, Texas, USA) and the sphygmocor signal processing device (Scor; PWV Medical, Sydney, Australia) as detailed elsewhere (3). Briefly, the pressure tonometer was placed on the radial artery of the dominant arm, supported on a firm surface. With the application of gentle pressure the artery was flattened but not occluded and the peripheral pressure waveforms were accurately recorded with the aid of a computer. Data were excluded if the systolic or diastolic variability exceeded 5% or the pulse height was less than 100 mV. The central pressure waveform may be derived by mathematical transformation of the peripheral pressure

waveforms using a generalised transfer function and closely approximates invasive recordings of central pressure and waveforms (6). The pressure waveform at each site is a composite of the forward going wave and the reflected wave travelling backwards towards the heart. The latter has a tendency to increase central systolic pressure especially in the setting of increased aortic stiffness. Figure 1 represents a typical central pressure waveform. The central pressure waveform enables estimation of certain reliable indices of arterial stiffness as well as indices of systolic and diastolic function. The central augmentation index (AI) represents the difference between the first and second peaks of the central pressure waveform, and the augmentation of central pressure (AG) is expressed as a percentage of the pulse pressure and is an important index of arterial stiffness (7, 8). Radial pulse pressure waveforms were recorded in duplicate. A single observer carried out all the recordings and the reproducibility data for AI showed a mean difference $\pm$ S.D. of within-observer variability between repeated measurements of $0.64 \pm 4.0\%$ (95% confidence interval (-0.72 to 1.89)), which compares favourably with published data (9).

Biochemical measurements

Venous blood was drawn for the measurement of plasma glucose, total cholesterol, high density lipoprotein

Figure 1 Schematic representation of central arterial pressure waveform which is a composite wave form representing the forward travelling and the reflected wave from the extremities. With stiffening of central arteries the reflected wave travels faster and arrives at the aortic root in systole (rather than diastole in the normal situation), thus resulting in an augmentation of central pressure (AG) difference between the peaks. Augmentation index (AI) is AG, expressed as a percentage of the pulse pressure (PP). TR, time of travel of the reflected wave.

(HDL) and low density lipoprotein (LDL) cholesterol and serum triglycerides by standard enzymatic techniques.

Serum concentrations of thyrotrophin (TSH), free thyroxine (FT4) and tri-iodothyronine (FT3) were measured using an automated immunoassay analyser, the Bayer Advia Centaur (Bayer Diagnostics Division, Newbury, Berkshire, UK). FT4 and FT3 were competitive labelled antibody assays utilising an acridinium ester as a label and paramagnetic particles as a solid phase and TSH was a two-site immunochemiluminometric assay. The batch imprecision values of the assays were as follows: FT4 (9.8–23.1 pmol/l) coefficient of variation (CV) 4%, FT3 (3.5–6.5 pmol/l) CV 3.1% and TSH (0.35–5.50 mU/l) CV 5.3%.

Height and weight were recorded and BMI calculated (weight/height²).

Statistics

Normally distributed data were analysed using independent and paired *t*-tests, Mann–Whitney U test and Wilcoxon sign test were used for non-parametric data (SPSS version 7.5 for Windows). All results are

expressed as means±S.E.M. A *P* value of less than 0.05 was considered as significant.

Results

All subjects in the patient group were thyrotoxic at baseline but were all euthyroid with one exception who had mild subclinical hypothyroidism when re-studied at 6 months (Table 1). Before treatment, there were no significant differences in peripheral systolic and diastolic blood pressures between thyrotoxic patients and controls. However, they had a higher pulse pressure than controls (58.0 vs 51.0 mmHg; *P* < 0.05; Table 1). Fasting blood glucose levels and lipid profiles were comparable between the two groups. Haemodynamic data are shown in Table 2. Despite similar aortic blood pressures, AI was lower in untreated thyrotoxics than controls at the observed heart rate and persisted following correction for differences in heart rate (10). There was also a decreased AG in this group compared with controls. Following treatment at 6 months, when nearly all patients were biochemically euthyroid, AI was significantly higher

Table 1 Demographic and biochemical characteristics of subjects at baseline and 6 months after ³¹I therapy. *n* = 20 in both the thyrotoxic and control groups. Values are means±S.E.M. except for TSH (median) with ranges in parentheses.

Variable	Thyrotoxics (before therapy)	Thyrotoxics (after 6 months therapy)	Controls
Age	48.0±2.7		48.0±2.6
Sex (M/F)	2/18		2/18
Smokers	4	4	4
BMI (Kg/m ²)	26.0±1.0	26.7±1.1	27.0±0.8
TSH (mU/l)	<0.02 ^a	1.40 (0.03–6.10) ^b	1.23 (0.50–2.00)
FT3 (pmol/l)	15.1±0.8 ^a	3.82±0.2 ^b	3.9±0.3
FT4 (pmol/l)	42.4±2.2 ^a	13.8±1.0 ^b	13.5±0.5
Plasma Glucose (mmol/l)	5.1±0.6	5.0±0.6	4.8±0.7
Total Cholesterol (mmol/l)	4.5±0.1	5.0±0.3	4.8±0.2
LDL Cholesterol (mmol/l)	2.8±0.2	2.6±0.4	2.3±0.3
HDL Cholesterol (mmol/l)	1.0±0.1	1.1±0.2	1.2±0.1
Trigs (mmol/l)	1.8±0.2	2.0±0.1	2.0±0.2
BSBP (mmHg)	134.0±4.4	134.0±2.3	129.0±3.8
BDBP (mmHg)	76.0±1.4	78.0±1.3	78.0±1.6
PP (mmHg)	58.0±3.5 ^c	48.4±2.1	51.0±2.0

^a*P* < 0.0005 vs controls; ^b*P* < 0.005 vs untreated thyrotoxics; ^c*P* < 0.05 vs controls or treated group. BSBP, brachial systolic blood pressure; PP, pulse pressure; BDBP, brachial diastolic blood pressure.

Table 2 Haemodynamic characteristics in thyrotoxic and control subjects. Data are shown as means±S.E.M., *n* = 20 in each group.

Parameter	Thyrotoxics	Controls	Thyrotoxics (after 6 months therapy)
Aortic systolic BP (mmHg)	116.0±2.9	116.0±3.0	121.0±2.0 ^d
Aortic diastolic BP (mmHg)	79.0±1.5	79.0±1.7	79.0±1.2
AI (%)	15.0±2.1 ^b	28.0±2.1	27.0±1.8 ^d
Heart rate (beats/min)	95.0±2.3 ^b	80.0±0.7	79.0±1.8
AI corrected for heart rate (%)	20.0±2.1 ^b	28.0±2.1	27.0±2.0 ^d
Augmentation of AG (mmHg)	6.0±0.8 ^b	10.0±1.1	11.0±1.0 ^d

^a*P* < 0.02 vs controls; ^b*P* < 0.005 vs controls; ^c*P* < 0.03 vs untreated hyperthyroids; ^d*P* < 0.005 vs untreated group.

than before treatment, even when corrected for the differences in heart rate, as was AG, and were similar to control values (Table 2). Figure 2 depicts the increase in augmentation index (an augmented aortic systolic peak) in a 50-year-old thyrotoxic patient studied at baseline and when euthyroid at 6 months. Figure 3 shows AI in thyrotoxic patients, before and after treatment, and controls.

A multiple regression analysis model carried out on hyperthyroid and euthyroid individuals, separately

and together, with AI as the dependent variable, revealed age as the strongest predictor of AI when compared with FT3, heart rate, BMI and pulse pressure.

Discussion

Although thyrotoxicosis is well known to be associated with an increased pulse pressure, the physiology of this state in relation to the arterial vasculature has not been

Figure 2 The peripheral and central arterial pressure waveforms in a 50-year-old subject. The aortic waveform in (b) shows an augmented systolic peak. Sp, systolic pressure; Dp, diastolic pressure; MP, mean pressure; PP, pulse pressure.

Figure 3 AI in thyrotoxic patients vs controls. Box (and whisker) plots showing AI index in patients and controls. The rectangular boxes are drawn between the interquartile ranges. Thick lines represent median (= mean for this normal distribution). Whiskers extend to extremes of the data. * $P < 0.005$ compared with control group/thyrotoxic patients (6 months after ^{131}I).

characterised. The main finding of our study following analysis of the derived central pressure waveform was evidence of a decreased central arterial stiffness (lower AI and AG) in the untreated thyrotoxic patients compared with controls closely matched for age, sex, height, BMI, blood pressures, lipid profiles and plasma glucose levels. All these variables are known to influence AI (10–12). The assessment of central arterial stiffness by the technique of pulse wave analysis involves the study of peripheral arterial pressure waveforms and is based on the principle of applanation tonometry. Using a validated generalised transfer function, the corresponding aortic pressure waves may be synthesised and are almost identical to those recorded invasively and even following haemodynamic manipulation (13).

The compliance or stiffness of large vessels, which is a feature of the ageing process, has long been recognised as an important determinant of the pulse pressure (14). Indeed a high pulse pressure has been shown to be a powerful determinant of cardiovascular risk, especially in the elderly (15–17). However, in our study, the lowered central arterial stiffness (greater central arterial compliance) observed in the untreated thyrotoxic patients may be cardio-protective, counteracting the effect of the increased in pulse pressure. This may have more significance in elderly subjects with thyrotoxicosis, whose central arteries are already stiffened by the ageing process, resulting in a further increase in cardiac afterload.

Central arterial stiffness is not synonymous with total peripheral resistance. The aortic walls are structurally different from those smaller arteries, being richer in elastic tissue. Therefore decreased total peripheral resistance cannot be extrapolated to mean

decreased central arterial stiffness. For example, in systolic hypertension there is increased central arterial stiffness with no change in peripheral resistance (13); the converse has been shown in postmenopausal women receiving oestrogen replacement therapy (18). It is possible that similar mechanisms apply in hyperthyroidism and are responsible for the lowering of both total peripheral resistance and central arterial stiffness. The identification of four thyroid hormone receptor mRNA isoforms in human aortic vascular smooth muscle and the presence of iodothyronine deiodinase activity within these cells (19) may explain the ability of thyroid hormones to alter central arterial stiffness by upregulating genes involved in vascular smooth muscle relaxation. Thyroid hormones have been shown to cause acute relaxation of smooth muscle (5) by their non-genomic effects, including the selective inhibition of the binding of the Ca^{2+} –calmodulin complex to smooth muscle myosin light chain (MLC) kinase (20). Thyrotoxicosis is associated with a rise of markers of impaired endothelial function (21, 22); however, the absence of a rise in nitric oxide levels in the thyrotoxic state (5) would suggest that the reduction in central arterial stiffness seen in the untreated state is the result of the direct effect of excess thyroid hormones on the aortic smooth muscle.

In conclusion, we believe that this study is the first to show a decreased augmentation of central pressure and reduced aortic or central arterial stiffness (increased compliance) in hyperthyroidism, based on analysis of the central arterial pressure waveforms. This does not appear to contribute to the increased pulse pressure or the cardiovascular risk seen in the condition.

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