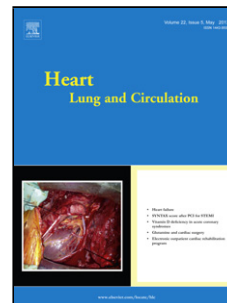Accepted Manuscript

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Hyperdynamic Right Heart Function in Graves' Hyperthyroidism Measured by Echocardiography Normalises on Restoration of Euthyroidism.

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Abstract

Background: Graves' hyperthyroidism commonly causes tachycardia and may result in pulmonary hypertension and high output cardiac failure. There is limited information regarding the effect of treatment on cardiac function measured using modern echocardiographic techniques.

Methods: Eight individuals with Graves' hyperthyroidism, aged 22–64 years, underwent comprehensive transthoracic echocardiography at three time points: before treatment, two weeks after commencement of carbimazole, and at six months or more when euthyroid. Exercise capacity was assessed using the 6-minute-walk-distance (6MWT), and quality of life was assessed by Medical Outcome Study 36-item Short-Form Health Status Survey.

Results: All individuals were rendered euthyroid by final assessment. At presentation, there was evidence of hyperdynamic right ventricular function as measured by peak systolic velocity of the free wall of the tricuspid annulus, tricuspid annular plane systolic excursion and right ventricular ejection fraction, which normalised after resolution of thyrotoxicosis. Baseline heart rate correlated significantly with severity of the thyrotoxicosis for either free T4 ($r = 0.91$, $p = 0.01$) or free T3 ($r = 0.94$, $p = 0.001$). No individual had measurable pulmonary hypertension. Cardiac output was significantly lower in the euthyroid compared to the thyrotoxic state ($p = 0.03$). A higher baseline TSH-receptor antibody corresponded to a greater improvement in exercise capacity ($r = 0.76$, $p < 0.05$) and physical quality of life ($r = 0.73$, $p < 0.05$) on resolution of the hyperthyroidism.

Conclusion: Graves' hyperthyroidism causes increased cardiac output and a hyperdynamic right ventricle which normalise on restoration of the euthyroid state.

Introduction.

Graves' disease is the most common cause of hyperthyroidism, with a prevalence of 0.6% of the population, a female to male ratio of 5–10:1, and peaking in incidence at 40–60 years of age [1]. It is an autoimmune disorder resulting from thyroid-stimulating hormone (TSH)-receptor antibodies (TRAb), which stimulate thyroid growth and thyroid hormone synthesis and release. All-cause mortality is increased by 20% in subjects with hyperthyroidism [2]. Cardiovascular symptoms including palpitations and dyspnoea are common, irrespective of background cardiovascular disease, and do not resolve in all individuals even after return to the euthyroid state [3]. A schematic of the cardiac pathology of Graves' hyperthyroidism is provided in Figure 1.

Hyperthyroidism is associated with reduced peripheral resistance [4,5], elevation in left ventricular diastolic function [6,7], and activation of the renin-angiotensin-aldosterone system [8] resulting in increased preload. By application of the Frank Starling law, increased preload results in a higher stroke volume, and coupled with the chronotropic effects of thyroid hormone, cardiac output is increased. Increased heart rate via atrial pacing is known to increase intrinsic contractility by upregulating calcium entry to myocytes, but it is not clear whether hyperthyroidism *per se* increases contractility over and above the effects on heart rate alone [9]. Animal studies have suggested that there may be increased myocyte contractility, but the effects of this on left ventricular systole are tempered by increasing left heart fibrosis with chronic exposure to hyperthyroidism [10].

The performance of the left heart in hyperthyroidism may impact on the performance of the right heart as a result of ventricular interdependence whereby increased left heart preload may increase lateral wall pressure via the pericardium. Right ventricular systole is also dependent on the more muscular left ventricle for the final phase of systole via its tethering points. A study on Graves' patients with left heart failure in hyperthyroidism, however, failed to identify any features of left heart performance or any individual characteristics that might predict right heart performance, and it was concluded that separate mechanisms were at play [11]. TRAb titre and thyroid hormones were (non-significantly) higher in the group with normal or elevated right heart function compared with the group with low right heart function, implying that there are factors other than hyperthyroidism that underlie right heart dysfunction. Hyperthyroidism may thus unmask a predisposition to right heart dysfunction.

Pulmonary hypertension has been reported to occur in 50% of cases of Graves' hyperthyroidism, with an incidence that appears to increase with higher TRAb titre and higher cardiac output [12]. It also occurs in non-Graves' related

hyperthyroidism [13]. This impacts the right heart by increasing afterload. It is not, however, the only mechanism mediating right heart function in hyperthyroidism, as demonstrated by a number of case reports of isolated right heart failure [14-16]. Right heart function is challenging to quantify using echocardiography, partly because of its shape making echo measurements more difficult. There is conjecture as to which measurements are best at discriminating contractility from loading conditions [17].

There is a paucity of longitudinal data regarding right ventricular function in cases with Graves' disease. The aim of this study was to evaluate the change in right heart function in individuals with Graves' disease using transthoracic echocardiography at baseline in the hyperthyroid state, during the early phase of treatment and on restoration of euthyroidism. The hypothesis to be tested was that hyperthyroidism has a pronounced effect on right heart function that normalises on attaining euthyroidism.

Methods

This was a longitudinal observational case series study investigating the effect of standard medical treatment of Graves' thyrotoxicosis using carbimazole, with or without beta blockers, on cardiac function as measured by transthoracic echocardiography, exercise capacity and quality of life at three time points.

The study was approved by the local Human Research Ethics Committee and written informed consent was obtained from each participant.

Study Population

Individuals aged between 18 and 70 years referred to the hospital Thyroid Clinic were eligible for enrolment if they met the criteria for untreated thyrotoxic Graves' disease, diagnosed by elevated free thyroxine (free T4) and/or free tri-iodothyronine (free T3) concentrations, a suppressed TSH, and positive TRAb. Exclusion criteria included presenting on beta blockers or anti-thyroid medications, known pre-existing cardiac or respiratory disorders, leg pain on walking which would limit their ability to perform a 6-minute-walk-test (6MWT) and pregnancy.

Eight consecutive individuals meeting the above criteria were recruited to the study, and all were studied at baseline prior to commencement of any treatment, after two weeks of carbimazole ± a beta blocker and at 6–15 months once euthyroidism had been achieved. The decision regarding starting dose of carbimazole, serial dose adjustments and whether to commence beta blockade were made by the treating clinician according to severity of hyperthyroidism.

All individuals underwent serial biochemical testing as clinically indicated for thyroid function tests (free T4, free T3, TSH) and TRAb. In addition, 24-hour blood pressure and heart rate monitoring (30 minutely by day, 60 minutely by night), functional exercise capacity measured via the 6MWT, echocardiography before and directly after 6MWT, and quality of life estimates (measured by Medical Outcome Study 36-item Short-Form Health Status Survey Version 2 (SF36v2) questionnaire) were undertaken at time points 0, 2 weeks, and 26+ months.

Echocardiography

Echocardiographic loops were recorded using grey-scale harmonic imaging and saved in raw data format (Vivid 7, General Electric Medical Systems, Horten, Norway). Images were obtained at a frame rate of 50 to 70 per second, and digital loops were saved onto optical disc for off-line analysis (EchoPac, General Electric Medical Systems). All individuals were in sinus rhythm. End-diastolic and end-systolic volumes were used to calculate EF by Simpson biplane method from the apical four- and two-chamber views [18]. Measures of right heart function — peak systolic velocity of the free wall of the tricuspid annulus (RVs'), tricuspid annular plane systolic excursion (TAPSE) and right ventricular ejection fraction (RVEF) were made from the four-chamber view. Right and left ventricular stroke volume and cardiac output were also measured according to current guidelines [19].

Left ventricular global longitudinal strain was measured using 2D speckle strain. The endocardial borders were traced in the end-systolic frame of the 2D images from the three apical views. Speckles were tracked frame-by-frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created. Segments that failed to track were manually adjusted by the operator. Glutaminase (GLS) was calculated as the mean strain of 18 segments. Right ventricular free wall strain, a novel measure of right heart function, was calculated according to guidelines [19].

Statistical Analysis

Data sets were analysed by within-subjects ANOVA. Pairwise comparisons were made between 0 and 2 weeks on treatment, 0 and 26+ weeks on treatment, and 2 and 26+ weeks on treatment. Z-score of the skew was determined to ensure normal distribution for significant results. Significance across all three time points was also determined with F-statistic corrected with the Huynh-Feldt correction. Pearson correlations were performed on baseline thyroid function, baseline heart rate, age, and change in echo parameters between baseline and 26+ weeks. Unless otherwise specified, data are presented as mean ± standard error of the mean.

Results

There were five males and three females, mean age 47 ± 5 years, range 20–64 years. Each had their first study visit within two weeks of diagnosis with Graves' disease. They had experienced symptoms suggestive of hyperthyroidism for mean 6 ± 3 months, range 0–24 months. All were seen prior to the initiation of carbimazole, and were followed up two weeks later, although for one individual the echocardiogram data at two weeks could not be analysed for technical reasons. The final visit was carried out at a median of 26 weeks, range 26–65 weeks, after commencement of therapy, once a euthyroid state had been achieved. The initial carbimazole dose in all individuals was 10 mg twice daily, and this was titrated on the basis of subsequent thyroid function tests. One individual required thyroidectomy at 12 months because of the presence of suspicious nodules. Histology on the surgical specimen was benign. The remaining seven individuals were still on carbimazole at the final assessment, but at a reduced dose of 5 mg daily. For those individuals who received a beta blocker, propranolol was prescribed at a dose of 40 mg three times daily, and this was continued for at least two weeks and then as required.

Thyroid Function and Antibodies

All individuals had elevation in TRAb titre (6.2 ± 1.1 U/L) that reduced or normalised (2.6 ± 1.0 U/L) at 26 weeks+ (Table 1). All individuals had biochemical hyperthyroidism (fT4 30.4 ± 6.8 pmol/L, fT3 12.9 ± 2.7 pmol/L) that had normalised (fT4 11.7 ± 1.2 pmol/L $p = 0.02$, fT3 5.4 ± 0.4 pmol/L $p = 0.04$) at 26 weeks+ (Table 1), indicating effective treatment of the primary disorder.

Heart Rate and Blood Pressure

At baseline, there was an inverse relationship between weight and fT4 concentration, ($r = -0.71$, $p < 0.05$), but the change in weight over time did not reach statistical significance (Table 1). Mean heart rate over 24 hours either remained unchanged or reduced at two weeks, independent of whether beta blockers had been commenced (Table 1). There was a non-significant reduction in mean 24-hour heart rate at 26 weeks+ (Table 1). There was no significant change in mean 24-hour systolic or diastolic blood pressure by 26 weeks+ (Table 1).

Heart rate was highly correlated with fT4 and fT3 at baseline ($r = 0.91$ $p = 0.01$, $r = 0.94$, $p = 0.001$ respectively) and at two weeks, but there was no correlation once thyroid function had normalised.

Exercise Capacity and Quality of Life

Whilst an increase in distance walked after resolution of hyperthyroidism corresponded to higher baseline TRAb titre (r = 0.76, p < 0.05), there was no significant improvement in 6MWT distance overall (Table 2). Greater increase in SF36v2 physical after resolution of hyperthyroidism correlated with an increase in 6MWT distance (r = 0.73, p < 0.05) but there was no significant improvement in physical and mental SF36v2 (Table 2).

Echocardiography

No individual had a sufficient tricuspid regurgitant jet to enable the measurement of pulmonary systolic pressure. There were statistically significant changes over time in RVs' (pre-walk and post-walk), TAPSE (post-walk) and RVEF (pre-walk) (Table 3). These changes all demonstrated normal to elevated measures of right heart function when hyperthyroid, which reduced with time as hyperthyroidism and TRAb titre normalised. These data are consistent with a hyperdynamic right ventricular functional state whilst hyperthyroid, which normalised with treatment and restoration of euthyroidism. This change began to appear after two weeks of carbimazole treatment with a reduction towards normal of RVs', TAPSE and RVEF after two weeks, which reached significance at 26 weeks+.

There was no statistically significant change over time in RV strain or global strain. However, a substantial change in strain measurements occurred in the oldest member of the cohort (ID 3), who also had the highest baseline TRAb titre. Global and RV strain worsened markedly in the two weeks after diagnosis and initiation of carbimazole treatment. Global strain, reflecting function of the left ventricle, recovered on resolution of hyperthyroidism, but right ventricular strain only partially recovered. The change in strain measurements mirrored the physical SF36v2 and 6MWT distance for this individual. When considering the remainder of the cohort, three individuals had an abnormal RV strain at 26 weeks+, and these three individuals were all greater than 45 years of age. Cardiac output was significantly lower in the euthyroid (5.0 ± 0.5 L/min) compared to the thyrotoxic state (6.2 ± 0.5 L/min, p = 0.03) (Table 3).

Discussion

This longitudinal study has demonstrated alterations in right ventricular function in individuals with Graves' disease. The interpretation of these findings is that Graves' hyperthyroidism results in a hyperdynamic RV functional state which then normalises with adequate treatment and restoration of euthyroidism.

Elevation in measures of right heart function seen in our cohort may be a subclinical pathological state. In a cross-sectional study, Suk [20] reported TAPSE and RVs' values comparable with our data, and reported lower TAPSE in cases with

pulmonary hypertension. This may be a reflection of the afterload dependence of TAPSE.

In a cohort of cases with left ventricular systolic dysfunction [11], all of whom had pulmonary hypertension, approximately half had reduced right ventricular systolic dysfunction measured by TAPSE, and TAPSE increased on resolution of hyperthyroidism. They were not able to reconcile severity of left ventricular dysfunction with severity of right ventricular dysfunction, and concluded there were distinct pathological processes in each. Unfortunately the longitudinal change on resolution of hyperthyroidism was not reported in cases without reduced TAPSE, so their data could not be directly compared with the current study.

Strain measurements have been reported to be less dependent on loading conditions than TAPSE, RVs' or RVEF, although there is conjecture on this point [17]. Right ventricular and global strain did not show any significant change with treatment time. There was one outlier, however, who had a precipitous drop in right ventricular strain and global strain at two weeks. This outlier also had the highest TRAb titre, was the oldest of the cohort, and had the worst functional measures relative to the euthyroid state. The other measures of RV systolic function did not follow this pattern, suggesting that strain is measuring something different. We hypothesise that the precipitous drop in strain occurred in a right ventricle on the cusp of failure, possibly related to a more hyperthyroid state or an ageing right ventricle with reduced cardiac reserve. Right ventricular free wall longitudinal strain, excluding the interventricular septum, has prognostic value in various disease states including heart failure, acute myocardial infarction, pulmonary hypertension, and amyloidosis, and to predict RV failure after LV-assistance device implantation [21]. It could be speculated that the thin RV free wall is more susceptible to damage than the thicker septum and left ventricle.

Treatment of hyperthyroidism did not significantly affect functional outcomes across the whole cohort in either the 6MWT or the SF36, but those with a higher TRAb titre showed a greater degree of improvement in 6MWT once they reached a euthyroid state. There was a correlation between impairment in quality of life and impairment in 6MWT distance. Previous studies have not found a correlation between SF36 scores and thyroid function, but a weak correlation was seen between elevated TRAb and low physical component summary [22].

There are no previous longitudinal studies comparing echo measurements within two weeks of anti-thyroid drug commencement, and no previous studies examining right ventricular echo measurements in hyperthyroid individuals with normal LV function. The main limitation in the study was the small sample size. Recruitment of individuals with untreated

Graves' hyperthyroidism was challenging given the tendency of primary practitioners to commence carbimazole at diagnosis. The cohort was more heavily represented by males and was older than in the general Graves' disease population. None of the individuals had demonstrable pulmonary hypertension. Nevertheless, we were able to demonstrate the presence of hyperdynamic RV function (TAPSE, RVS', and RVEF).

Conclusions

Graves' hyperthyroidism is associated with tachycardia relating to the severity of the thyroid hormone excess and echocardiographic evidence of hyperdynamic function of the RV. In the extreme setting, we postulate that elevated RV preload may predispose to eventual right ventricular failure. Right ventricular function returns to normal on resolution of the hyperthyroid state.

Conflict of Interest

Legend for Figure

Figure 1:

Schematic diagram illustrating the common pathophysiological effects of elevated thyroid hormone concentrations on the major affected organs in hyperthyroidism.

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Table 1. Demographics, thyroid function

	0 weeks	2 weeks	26+ weeks	p-value		
				0 vs 2 weeks	0 vs 26+ weeks	0 vs 26+ weeks
Age (years)	46.6 ± 4.7					
Gender (% male)	62.5					
Smoker (%)	50					
Duration symptoms (months)	6.5 ± 2.6					
Beta blocker (%)	50					
Weight (kg)	76.0 ± 8.8	75.9 ± 9.1	80.3 ± 9.0	NS	NS	NS
Heart rate (bpm)	92.5 ± 4.3	86.9 ± 3.7	83.0 ± 4.0	NS	0.05	NS
SBP (mmHg)	120.4 ± 2.7	124.4 ± 5.5	125.3 ± 5.4	NS	NS	NS
DBP (mmHg)	73.8 ± 1.6	72.8 ± 2.4	76.8 ± 2.6	NS	NS	NS
fT4 (pmol/L)	30.4 ± 6.8	25.1 ± 5.8	11.7 ± 1.2	NS	0.02	0.05
fT3 (pmol/L)	12.9 ± 2.7	8.5 ± 2.0	5.4 ± 0.4	NS	0.04	NS
TRAb (U/L)	6.2 ± 1.1	8.4 ± 0.4	4.2 ± 1.0	NS	0.06	NS

All values are expressed as mean ± SEM, SEM: standard error of the mean, SBP: systolic blood pressure, DBP: diastolic blood pressure,

fT4: free T4, fT3: free T3, TRAb: thyrotropin stimulating hormone receptor antibodies, NS: non-significant

ventricle

Table 2. Exercise and quality of life

	0 weeks	2 weeks	26+ weeks	p-value		
				0 vs 2 weeks	0 vs 26+ weeks	0 vs 26+ weeks
6MWT (m)[d1]	584.6 ± 52.6	546.7 ± 81.3	621.4 ± 17.4	NS	NS	NS
SF36v2 physical	37.9 ± 3.9	38.1 ± 3.8	42.6 ± 4.2	NS	NS	NS
SF36v2 mental	40.6 ± 3.4	41.0 ± 3.5	42.4 ± 4.3	NS	NS	NS

All values are expressed as mean ± SEM, SEM: standard error of the mean, SF36v2: Medical Outcome Study 36-item Short-Form Health

Status Survey Version 2

Table 3. Echocardiogram data

	0 weeks	2 weeks	26+ weeks	p-value		
				0 vs 2 weeks	0 vs 26+ weeks	0 vs 26+ weeks
RVs' (pre-walk) (cm^2)	0.16 ± 0.01	0.15 ± 0.01	0.13 ± 0.01	NS	0.04	0.02
RVs' (post-walk) (cm^2)	0.20 ± 0.01	0.18 ± 0.01	0.17 ± 0.14	0.07	0.03	NS
TAPSE (pre-walk) (mm)	24.35 ± 0.7	23.43 ± 1	21.57 ± 1.1	NS	0.07	NS
TAPSE (post-walk) (mm)	29.22 ± 2.3	27.77 ± 1.8	22.25 ± 1.2	NS	0.04	0.02
RVEF (pre-walk) (%)	0.62 ± 0.02	0.62 ± 0.02	0.55 ± 0.02	NS	NS	0.05
RVEF (post-walk) (%)	0.62 ± 0.02	0.65 ± 0.02	0.61 ± 0.02	NS	NS	NS
RV strain (pre-walk) (%)	-20.68 ± 1.5	-17.81 ± 2.1	-20.10 ± 1.8	NS	NS	NS
RV strain (post-walk) (%)	-20.50 ± 2.2	-19.31 ± 1.5	-20.63 ± 2.1	NS	NS	NS
Global strain (pre-walk) (%)	-18.59 ± 1.4	-16.28 ± 1.8	-19.06 ± 1	0.06	NS	NS
Global strain (post-walk) (%)	-19.39 ± 1.1	-17.57 ± 1.7	-19.82 ± 0.8	NS	NS	NS
LV stroke volume (mL)	70.26 ± 6	76.19 ± 5.8	68.20 ± 6.6	NS	NS	NS
LV cardiac output (L/min)	5.97 ± 0.5	6.24 ± 0.4	4.98 ± 0.5	NS	0.06	0.03

All values are expressed as mean ± SEM, SEM: standard error of the mean, RVs': peak systolic velocity of the free wall of the tricuspid annulus, TAPSE: tricuspid annular plane systolic excursion, RVEF: right ventricular ejection fraction, RV: right ventricle, LV: left ventricle

Figure

NERVOUS SYSTEM

Emotional lability
Insomnia
Mood disturbance

Poor concentration
Restlessness
Tremour

MUSCLE

Myopathy

BONE

Increased bone turnover
Osteoporosis

↑ T4 and T3

Pulmonary hypertension

Atrial fibrillation

Tachycardia

Increased cardiac output

Increased motility

HEART

GI TRACT