CLINICAL RESEARCH STUDY

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Pulmonary and Systemic Hemodynamics in Patients with Hyperthyroidism

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ABSTRACT

BACKGROUND: There is an association between hyperthyroidism and pulmonary hypertension. However, the prevalence of pulmonary hypertension in hyperthyroidism and the underlying mechanisms are incompletely defined.

METHODS: Consecutive patients with severe hyperthyroidism, mostly due to Graves disease, were included in this single-center study. Echocardiographic assessment of pulmonary hemodynamics was performed at the time of hyperthyroidism diagnosis (baseline) and after normalization of thyroid hormones (follow-up; median 11 months). In a subset of patients, right heart catheterization and noninvasive assessment of central hemodynamics was performed.

RESULTS: Among all 99 patients, 31% had pulmonary hypertension at baseline. The estimated systolic pulmonary artery pressure correlated significantly with the estimated left ventricular filling pressure (E/e′). The invasively measured systolic pulmonary artery pressure correlated well with the estimated systolic pulmonary artery pressure. Cardiac output, E/e′, left and right ventricular dimensions were significantly reduced from baseline to follow-up, whereas the estimated pulmonary vascular resistance did not differ. Diastolic blood pressure was significantly higher at follow-up, with no change in systolic blood pressure. The central systolic blood pressure, however, exhibited a trend for a reduction at follow-up, while the pulse wave velocity was significantly lower at follow-up.

CONCLUSIONS: Approximately one-third of patients with hyperthyroidism have evidence of pulmonary hypertension. Our data suggest that an increased cardiac output and left ventricular filling pressure are the main mechanisms underlying the elevated systolic pulmonary artery pressure in hyperthyroidism, whereas there is no evidence of significant pulmonary vascular disease.

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INTRODUCTION

Studies have shown a variable prevalence of pulmonary hypertension in patients with hyperthyroidism,[1,2] and there is little information on the echocardiographic follow-up after normalization of thyroid hormone levels.[3] The pathophysiology of increased pulmonary artery pressure, that is, pulmonary hypertension, in hyperthyroidism is controversial, with some studies reporting an increased pulmonary vascular resistance induced by thyroid hormones or other associated autoimmune phenomena[4-6] and other studies revealing similar pulmonary vascular resistance in hyperthyroidism compared with euthyroidism.[7] There are even fewer data about systemic hemodynamics in patients with hyperthyroidism.

CLINICAL SIGNIFICANCE

- Thirty-one percent of hyperthyroid patients showed echocardiographic evidence of pulmonary hypertension at baseline.
- Both cardiac output and left ventricular filling pressure were lower after reaching euthyroidism, while pulmonary vascular resistance was similar.
- Hyperthyroidism is associated with a brachial blood pressure amplification with lower central systolic blood pressure, similar peripheral systolic blood pressure, and a lower diastolic blood pressure compared with euthyroidism.

The aim of the present study was to assess the prevalence of pulmonary hypertension and to examine pulmonary and systemic hemodynamic variables using echocardiography in hyperthyroidism compared with euthyroidism, that is, after treatment. In addition, we aimed for invasive characterization of pulmonary hemodynamics and noninvasive measurement of central hemodynamics in a subset of patients. We hypothesized that in hyperthyroidism an elevated pulmonary artery pressure occurs due to increased cardiac output, plasma volume, and left ventricular filling pressures rather than an increased pulmonary vascular resistance. Furthermore, we hypothesized that hyperthyroid patients show a lower central blood pressure with systolic blood pressure amplification in the brachial artery.

METHODS

This study was a prospective, observational, single-center study performed at the Kantonsspital St.Gallen from January 2015 to December 2022. The local institutional review board approved the study protocol. All patients provided a written informed consent.

Consecutive patients aged >18 years with a new diagnosis of severe hyperthyroidism (thyroid-stimulating hormone [TSH] <0.01 μIU/mL and free triiodothyronine [fT3] or free thyroxine [fT4] >50% of upper limit of normal) due to Graves disease or focal autonomy were included. Patients with known pulmonary hypertension, patients taking substances predisposing to pulmonary hypertension (eg, anorectic drugs, amphetamines, methamphetamines, cocaine) and patients with any established condition possibly leading to pulmonary hypertension were excluded.

After referral to our hospital for evaluation of hyperthyroidism and after obtaining informed consent, patients were scheduled for a baseline echocardiographic assessment within 3 days. If they agreed to participate in the invasive substudy, a right heart catheterization was scheduled at the same day. In the first visit, laboratory tests were performed.

Follow-up examination was performed after euthyroidism was confirmed by an endocrinologist. Follow-up biochemical and central hemodynamic variables were assessed at the same visit as the follow-up echocardiography.

Body weight, height, and heart rate were assessed at the time of echocardiography. Left ventricular dimensions, systolic and diastolic function, and left atrial volume were measured according to current guidelines.[8,9] Left atrial enlargement was defined as indexed left atrial volume index >34 mL/m^2.[8] Cardiac output was estimated by multiplying stroke volume by heart rate, with stroke volume calculated by multiplying the velocity-time integral of the left ventricular (LV) outflow tract by its cross-sectional area.

Right ventricular (RV) and right atrial dimensions were assessed according to current guidelines.[10] A fractional area change <35% was considered RV dysfunction.[8] Peak tricuspid regurgitant velocity was obtained by continuous wave Doppler of the tricuspid regurgitant jet and was used for estimating the RV systolic pressure. Peak tricuspid regurgitant velocity >2.8 m/s was defined as abnormal.[10,11] Systolic pulmonary artery pressure was estimated by adding the estimated right atrial pressure to the RV systolic pressure, whereby the right atrial pressure was estimated according to the vena cava inferior dimensions.[10] For the purpose of this study, pulmonary hypertension was defined as systolic pulmonary artery pressure >35 mm Hg.[10] The mean pulmonary artery pressure was estimated as systolic pulmonary artery pressure * 0.6 + 2.[12] The ratio of the peak velocity of early mitral inflow (E) to the average of septal and lateral tissue Doppler early diastolic flow velocities e′ (E/e′) was used as surrogate of LV filling pressure. An E/e′ ratio <8 is associated with normal LV filling pressure, while an E/e′ >14 is associated with elevated LV filling pressures.[13] The pulmonary artery wedge pressure was estimated as 1.9 + 1.24 * E/e′.[14] Pulmonary vascular resistance was calculated according to the Abbas formula.[15]

Immediately prior to right heart catheterization, an echocardiographic assessment of tricuspid regurgitant velocity was performed in the catheterization laboratory. Right heart catheterization was performed via a brachial vein using 6 French Swan Ganz catheters. Systolic, diastolic, mean pulmonary artery pressure, and mean pulmonary artery wedge pressure were measured by direct pressure sensors. Cardiac

output was assessed by the indirect Fick method. The pulmonary vascular resistance was calculated as transpulmonary gradient divided by cardiac output.

Patients included after December 2018 were scheduled for noninvasive peripheral and central hemodynamic measurements at baseline and follow-up. The simultaneous measurements of brachial and central blood pressure, aortic augmentation index, and aortic pulse wave velocity were performed in the supine position after 10 minutes of rest by an invasively validated oscillometric, cuff-based, noninvasive technique (Arteriograph, TensioMed Ltd, Budapest, Hungary).[16]

All laboratory tests were performed with a chemiluminescence immunoassay. Reference values for B-type natriuretic peptide (BNP, <37 ng/L), cardiac troponin I (cTnI, <30 ng/L), TSH (0.25-4.0 μIU/mL), fT3 (3.5-6.4 pmol/L), and fT4 (6.8-18.0 pmol/L) were chosen according to the test assay.

Statistics

Continuous data are reported as mean ± standard deviation or median (interquartile range), as appropriate. Categorical data are reported as numbers and percentages. For comparisons of paired continuous data with normal distribution, a paired *t* test was used; for independent samples, Student's *t* test was used. The Wilcoxon test was used for paired data with skewed deviation and Mann-Whitney test was used for independent samples without normal distribution of data. For comparisons of more than 2 groups of independent continuous data with skewed distribution, the Kruskal-Wallis test was used. The McNemar test was used to compare dichotomous paired variables, and chi-square test was used to calculate proportions in independent samples. For correlations of continuous data with skewed distribution, Spearman's rho was calculated. Bland-Altman statistics were used to assess the agreement between invasively assessed pressures and noninvasively estimated pressures. A P value < .05 was considered statistically significant.

RESULTS

We included 84 (84%) women and 16 (16%) men in the study. One patient was excluded due to coronary artery disease. Baseline characteristics of the remaining 99 patients are presented in Table 1. The mean age was 40.6 ± 13.4 years. All patients had sinus rhythm; 54 patients (55%) took a beta-blocker.

Baseline Examinations

Echocardiographic baseline characteristics are presented in Table 2. LV ejection fraction was normal in all patients, and none had definite diastolic dysfunction. A tricuspid regurgitant jet was present in 88 (88%) patients. Twenty-seven patients (31%) had pulmonary hypertension, and the systolic pulmonary artery pressure correlated significantly with the LV filling pressure (E/e′; r = 0.3, P = .02). Five patients (6%) had RV enlargement and right atrial pressure elevation/enlargement in addition to a peak tricuspid regurgitant velocity >2.8 m/s and thus, fulfilled criteria for high probability of pulmonary hypertension according to current guidelines.[11]

Eight patients underwent right heart catheterization. Three patients (38%) had a mean pulmonary artery pressure >20 mm Hg, which is diagnostic for pulmonary hypertension.[11] Systolic pulmonary artery pressure >35 mm Hg was observed in 3 patients (38%). The median pulmonary vascular resistance was 1.4 (range 0.9-1.6) Wood units. Among the 3 patients with pulmonary hypertension, pulmonary vascular resistance was not obtainable in one patient, and 2 had

Table 1 Baseline Characteristics of the Study Population

	Total Population (n = 99)	Patients Without PH (n = 61)	Patients with PH (n = 27)	*P* Value
Female sex, n (%)	84 (84.8)	52 (85.2)	25 (92.6)	.33
Age (years), mean ± SD	40.6 ± 13.4	39.8 ± 13.6	42.2 ± 13.0	.43
Graves disease, n (%)	96 (97)	59 (96.7)	26 (96.3)	.67
Height (cm), mean ± SD	166.5 ± 7.9	166.1 ± 8.0	166.2 ± 6.9	.96
Weight (kg), median (IQR)	62.0 (55.0, 71.8)	60 (53.8, 67.8)	63 (55.5, 71.5)	.48
Body mass index (kg/m^2), median (IQR)	22.2 (20.2, 25.2)	21.7 (20.2, 24.5)	23.1 (20.4, 25.5)	.30
Heart rate (beats per minute), mean ± SD	82.6 ± 13.2)	81.9 ± 14.0	84.9 ± 12.9	.35
Sinus rhythm, n (%)	99 (100)	61 (100)	27 (100)	—
Beta-blocker, n (%)	54 (57.4)	32 (56.1)	15 (57.7)	.89
TSH (μIU/mL), median (IQR)	0 (0, 0.2)	0 (0, 0.1)	0 (0, 0.2)	.86
fT3 (pmol/L), median (IQR)	13.9 (11.2, 18.8)	13.2 (11.2, 18.0)	15.5 (11.8, 23.5)	.15
fT4 (pmol/L), median (IQR)	37.3 (30.2, 47.6)	37.3 (30.1, 45.9)	43.9 (32.8, 58.7)	.06
BNP (ng/L), median (IQR)	66 (46.0, 103.5)	63.0 (41.3, 41.3, 98.8)	98.0 (64.8, 135.5)	< .01
cTnI (ng/L), median (IQR)	0 (0, 3.3)	0 (0, 3.1)	0 (0, 6.5)	.15
cTnI >30 ng/L, n (%)	2 (2)	1 (1.7)	1 (3.7)	.57

BNP = brain natriuretic peptide; cTnI = cardiac troponin I; fT3 = free triiodothyronine; fT4 = free thyroxine; IQR = interquartile range; PH = pulmonary hypertension; SD = standard deviation; TSH = thyroid-stimulating hormone.

Table 2 Baseline Echocardiographic Data

	Total Population (n = 99)	Patients Without PH (n = 61)	Patients with PH (n = 27)	*P* Value
LVEF (%), mean (SD)	64.3 (5.1)	64.1 (5.9)	64.1 (4.0)	.98
LV end-diastolic diameter (mm), mean ± SD	44.9 ± 5.0	44.7 ± 4.8	44.8 ± 5.6	.95
Stroke volume (mL), mean ± SD	81.6 ± 19.2	79.8 ± 16.7	84.0 ± 23.2	.36
Cardiac output (L/min), median (IQR)	6.4 (5.3, 7.9)	6.4 (5.3, 7.8)	6.4 (5.3, 8.5)	.51
Average E/e′, median (IQR)	7.5 (6.4, 9.3)	7.4 (6.2, 8.5)	8.0 (7.3, 10.0)	.08
LA volume index (mL/m^2), median (IQR)	28.7 (23.4, 33.6)	26.9 (23.3, 33.0)	31.1 (25.6, 34.5)	.22
Estimated PAWP, median (IQR)	11.2 (9.9, 13.5)	11.1 (9.5, 12.8)	11.8 (11.0, 14.3)	.10
RV basal diameter (mm), mean ± SD	28.4 ± 5.6	27.5 ± 5.8	30.4 ± 5.2	.03
RV end-diastolic area index (cm^2), mean ± SD	10.0 ± 2.2	9.9 ± 2.1	10.3 ± 2.2	.33
Peak TRV (m/s), mean ± SD	2.6 ± 0.3	2.5 ± 0.2	2.9 ± 0.3	< .01
Peak TRV >2.8 m/s, n (%)	22 (25)	2 (3.3)	20 (74.1)	< .01
FAC (%), mean ± SD	49.2 ± 7.7	48.8 ± 7.9	49.2 ± 7.9	.85
Estimated RAP (mm Hg), median (IQR)	3.0 (3.0, 8.0)	3.0 (3.0, 3.0)	8.0 (3.0, 15.0)	< .01
Estimated sPAP (mm Hg), median (IQR)	32.0 (27.0, 37.0)	29.0 (26.0, 33.0)	41.0 (38.0, 46.8)	< .01
Estimated mPAP (mm Hg), median (IQR)	21.5 (18.5, 24.6)	19.7 (17.9, 22.1)	27.0 (25.2, 30.5)	< .01
Estimated PVR (WU), median (IQR)	1.5 (1.4, 1.7)	1.5 (1.4, 1.6)	1.6 (1.4, 1.7)	.06

FAC = fractional area change; IQR = interquartile range; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricular; sPAP = systolic pulmonary artery pressure; SD = standard deviation; TRV = peak tricuspid regurgitation velocity; WU = Wood units.

a resistance <2 Wood units, whereas all 3 patients had a pulmonary artery wedge pressure >15 mm Hg, indicating isolated postcapillary pulmonary hypertension.[11] Echocardiographically estimated systolic and mean pulmonary artery pressures correlated significantly with the invasively assessed equivalents (r = 0.85, P < .01, Figure 1, and r = 0.8, P = .02). The Bland-Altman plot indicated a significant systematic overestimation of the mean pulmonary artery pressure by 5.1 (95% confidence interval, 0.8-9.5) mm Hg, P = .03, by echocardiography.

BNP was elevated in 78% of the patients and was higher in patients with, compared with patients without, pulmonary hypertension (Table 1), and correlated with fT3 (r = 0.3, P = .001) and fT4 (r = 0.3, P = .002). There were significant correlations of fT3 and fT4 with cardiac output (r = 0.3, P = .005 and r = 0.3, P = .01), and furthermore, fT3 and fT4 were higher in patients with peak tricuspid regurgitant velocities >2.8 m/s compared with patients with normal velocities (14.3 [IQR 12.1-23.6] vs 13.1 [IQR 11.2-19.0] pmol/L, P = .07; 46.4 [IQR 36.0-58.8] vs 36.7 [IQR 30.2-46.1] pmol/L, P = .02).

Systemic hemodynamic variables at baseline were available in 27 (27%) patients. One patient (4%) had isolated systolic hypertension. Diastolic blood pressure, central

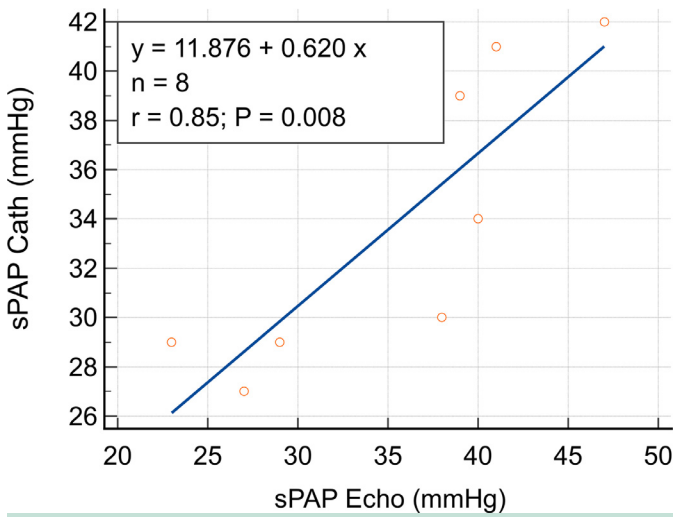

Figure 1 Scatter plot and regression line of invasively measured systolic pulmonary artery pressure (y-axis) and echocardiographically estimated systolic pulmonary artery pressure (x-axis). sPAP = systolic pulmonary artery pressure.

Table 3 Hemodynamic and Echocardiographic Parameters at Baseline and Follow-Up (n = 68)

	Baseline	Follow-Up	*P* Value
Heart rate (bpm), mean ± SD	82.1 ± 13.6	68.7 ± 11.2	< .01
Stroke volume (mL), mean ± SD	84.9 ± 19.7	76.0 ± 17.1	< .01
Cardiac output (L/min), median (IQR)	6.7 (5.5, 8.0)	5.1 (4.1, 5.9)	< .01
LV end-diastolic diameter, mean ± SD	45.4 ± 4.7	43.7 ± 4.3	< .01
LA volume index (mL/m^2), median (IQR)	30.2 (23.9, 33.9)	26.6 (21.5, 23.3)	.01
Average E/e', median (IQR)	7.6 (6.5, 8.8)	6.7 (5.5, 7.6)	< .01
Estimated PAWP, median (IQR)	11.3 (9.9, 12.7)	10.2 (8.5, 11.3)	< .01
RV basal diameter (mm), mean ± SD	29.5 ± 5.5	25.3 ± 4.8	< .01
RV end-diastolic area index (cm^2), mean ± SD	10.1 ± 2.2	7.8 ± 1.5	< .01
Peak TRV (m/s), mean ± SD	2.6 ± 0.3	2.2 ± 0.3	< .01
Peak TRV >2.8 m/s, n (%)	15 (27.3)	2 (3.6)	< .01
FAC (%), mean ± SD	49.0 ± 8.0	45.0 ± 6.1	< .01
Estimated RAP (mm Hg), median (IQR)	3 (3, 8)	3 (3, 3)	.05
Estimated sPAP (mm Hg), median (IQR)	32.0 (27.3, 36.8)	24.0 (21.0, 27.9)	< .01
sPAP >35 mm Hg, n (%)	16 (29.1)	2 (3.6)	< .01
Estimated mPAP (mm Hg), median (IQR)	21.5 (18.6, 24.4)	16.6 (14.8, 19.0)	< .01
Estimated PVR (WU), median (IQR)	1.5 (1.4, 1.7)	1.4 (1.3, 1.7)	.23

bpm = beats per minute; FAC = fractional area change; IQR = interquartile range; LA = left atrial; LV = left ventricular; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricular; SD = standard deviation; sPAP = systolic pulmonary artery pressure; TRV = peak tricuspid regurgitation velocity; WU = Wood units.

augmentation index, and central systolic blood pressure were inversely correlated with fT3 ($r = -0.4$, $P = .04$; $r = -0.4$, $P = .04$; $r = -0.4$, $P = .07$) and fT4 ($r = -0.4$, $P = .03$; $r = -0.2$, $P = .27$; $r = -0.4$, $P = .05$).

Follow-Up

The median time from baseline to the follow-up examination was 11.0 (IQR 8.3-13.1) months. The median body weight at baseline was 4.5 (3.0, 5.5) kg lower than at follow-up (63.0 [55.0, 72.0] vs 65.6 [60.0, 80.0] kg, $P < .01$). Only 2 patients (2%) took beta-blockers.

Follow-up echocardiography was available in 69 patients, with tricuspid regurgitant jet available in 55/69 (80%) patients. A comparison between baseline and follow-up data is given in Table 3. Peak tricuspid regurgitant velocity was significantly higher at baseline compared with follow-up (Figure 2), and the proportion of patients with pulmonary hypertension was higher at baseline compared with follow-up (Figure 3). Cardiac output, heart rate, and E/e' were significantly higher at baseline compared with follow-up. In contrast, pulmonary vascular resistance did not differ (Table 3).

The difference between the baseline and follow-up values was significantly higher in patients with pulmonary hypertension at baseline compared with patients without baseline pulmonary hypertension only for cardiac output and stroke volume (Table 4).

BNP was significantly higher at baseline compared with follow-up (66 [40.8, 106.8] vs 19 [13.8, 34.5], $P < .01$). The reduction of BNP correlated significantly with baseline fT3 and fT4 ($r = 0.4$, $P = .004$; $r = 0.4$, $P = .003$).

Paired data for systemic hemodynamic variables were available in 20 patients. Diastolic blood pressure was significantly lower at baseline compared with follow-up with a similar brachial systolic blood pressure, whereas there was a trend toward a lower central systolic blood pressure and a significantly lower augmentation index and higher pulse wave velocity in hyperthyroidism vs euthyroidism (Table 5). Similarly, in the subset of patients without beta-blocker at baseline (n = 10), diastolic (62.8 [61.7, 70.0] vs 70.5 [67.0, 77.7], $P = .007$), central systolic blood pressure (107.2 [100.3, 114.7] vs 112.5 [104.0, 126.0], $P = .05$), and augmentation index (21.0 [8.9, 33.3] vs 26.5 [18.2, 47.9], $P = .002$) were significantly lower at baseline compared with follow-up.

DISCUSSION

In the present prospective study evaluating the prevalence and mechanism of pulmonary hypertension in hyperthyroidism, almost one-third of the patients with hyperthyroidism and a measurable tricuspid regurgitation signal had pulmonary hypertension based on echocardiography. In the vast majority of these patients, pulmonary hypertension resolved after successful treatment of hyperthyroidism. In the hyperthyroid state, right-sided cardiac chambers were larger, filling pressures were higher, and systolic pulmonary artery pressure and cardiac output were higher compared with the euthyroid state. In contrast, there was no evidence of a difference in pulmonary vascular resistance. Our data collectively suggest that an increased cardiac output is the main mechanism underlying the elevated systolic pulmonary artery pressure in hyperthyroidism, whereas the data provide no evidence for the presence of significant pulmonary vascular disease.

The literature includes different reports on the prevalence of pulmonary hypertension in hyperthyroidism, ranging from 14%[2] to 44%,[7] depending on patient population

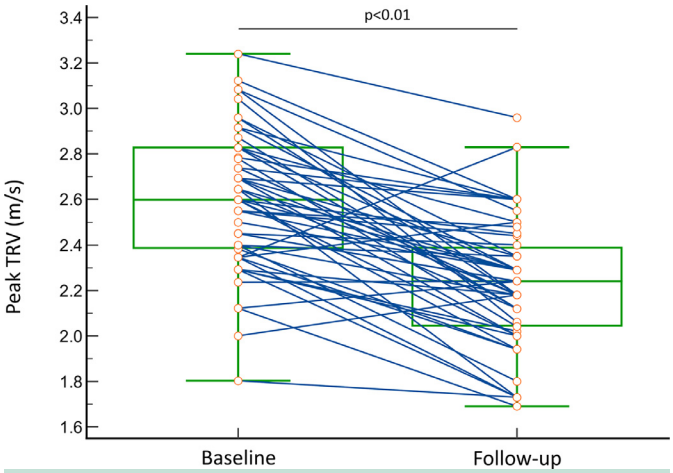

Figure 2 Tricuspid regurgitation velocity (TRV) at baseline compared with follow-up in individual patients.

and definition of pulmonary hypertension. The present population represents the largest cohort of hyperthyroid patients undergoing a systematic assessment for pulmonary hypertension. We applied an accepted echocardiographic definition of pulmonary hypertension, which has been used in other important studies.[17] The availability of right heart catheterization data in all patients would have been ideal, but given the lack of a clear clinical indication for invasive procedure, it could not be performed in the entire cohort. Still, we were able to recruit a subgroup of patients with invasive data on pulmonary hypertension in hyperthyroidism, which is unique. We found a similar proportion of hyperthyroid patients with pulmonary hypertension both in the total and the invasively examined cohort. Furthermore, we found a significant correlation of the invasively and the echocardiographically assessed systolic pulmonary artery pressure.

We observed a hyperdynamic RV function and enlarged chamber diameters in hyperthyroidism compared with euthyroidism, which is in line with other studies.[3,18] Interestingly, a substantial proportion of patients had an elevated right atrial pressure contributing to the pulmonary hypertension. Only one-quarter of the patients had a peak tricuspid regurgitant velocity >2.8 m/s, whereas almost one-third had an estimated systolic pulmonary artery pressure >35 mm Hg due to a high right atrial pressure. In our study, the systolic pulmonary artery pressure reduction after reaching euthyroidism was associated with a significant reduction of cardiac output and pulmonary artery wedge pressure, whereas pulmonary vascular resistance remained similar. The extent of cardiac output reduction by thyreostatic therapy was significantly larger in patients with pulmonary hypertension than in patients without. It is interesting to note that although no patient had echocardiographic signs of elevated left ventricular filling pressure, we found in our small invasive substudy that all patients with pulmonary hypertension had a pulmonary artery wedge pressure >15 mm Hg. This is, however, in line with

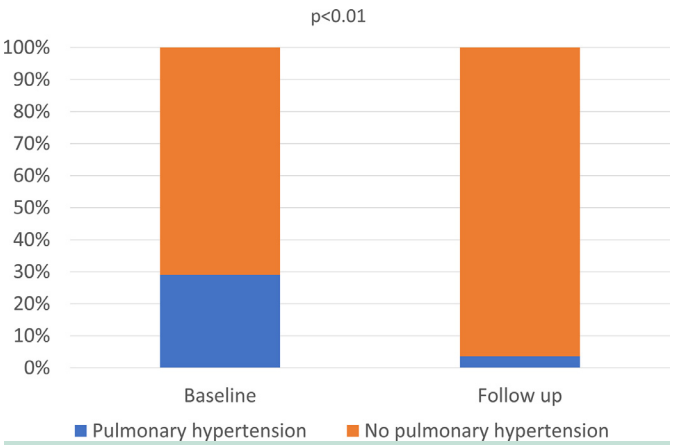

Figure 3 Proportion of patients with pulmonary hypertension at baseline compared with follow-up.

Table 4 Baseline to Follow-Up Differences in Patients With/Without Pulmonary Hypertension

Delta Baseline − Follow-Up	All Patients	Without PH	With PH	*P* Value
Heart rate (bpm), mean ± SD	13.4 ± 12.5	13.1 ± 13.9	15.2 ± 9.5	.57
Stroke volume (mL), mean ± SD	8.9 ± 18.4	3.9 ± 17.3	17.1 ± 17.4	.01
Cardiac output (L/min), median (IQR)	1.5 (0.5, 2.5)	1.0 (0.3, 2.2)	2.3 (1.2, 3.2)	.02
Average E/e', median (IQR)	0.9 (0.1, 2.1)	0.8 (0, 2.0)	1.3 (0.4, 2.2)	.41
Estimated PAWP, median (IQR)	1.2 (0.1, 2.8)	1.1 (0.1, 2.9)	1.6 (0.6, 2.7)	.58
RV basal diameter (mm), median (IQR)	3.5 (1.7, 6.2)	3.9 (1.5, 6.5)	4.7 (2.0, 6.0)	.65
Peak TRV (m/s), mean ± SD	0.4 ± 0.3	0.3 ± 0.3	0.6 ± 0.2	< .01
FAC (%), mean ± SD	4.0 ± 9.8	3.2 ± 10.8	4.5 ± 7.1	.64
Estimated RAP (mm Hg), median (IQR)	0 (0, 3.8)	0 (0, 0)	0 (0, 5.5)	.26
Estimated sPAP (mm Hg), median (IQR)	7.0 (4.0, 12.0)	6.0 (3.0, 9.8)	12.5 (8.5, 17.0)	< .01
Estimated mPAP (mm Hg), median (IQR)	4.3 (2.4, 7.3)	3.7 (1.8, 5.9)	7.6 (5.2, 10.4)	< .01
PVR (WU), median (IQR)	0.1 (-0.3, 0.2)	0.1 (-0.1, 0.2)	0.2 (-0.2, 0.4)	.26

bpm = beats per minute; FAC = fractional area change; IQR = interquartile range; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricular; SD = standard deviation; sPAP = systolic pulmonary artery pressure; TRV = peak tricuspid regurgitation velocity; WU = Wood units.

Table 5 Systemic Hemodynamic Variables (n = 20)

	Baseline	Follow-Up	*P* Value
SBP brachial (mm Hg), median (IQR)	115.3 (110.2, 119.1)	113.3 (109.2, 121.9)	.79
DBP brachial (mm Hg), median (IQR)	61.9 (57.7, 67.0)	67.9 (64.0, 74.0)	< .01
SBP central (mm Hg), median (IQR)	107.3 (99.9, 114.3)	109.7 (103.3, 118.0)	.05
PWV (m/s), median (IQR)	8.6 (7.7, 9.0)	7.5 (6.5, 8.2)	.03
Aix (%), median (IQR)	16.3 (6.7, 31.1)	25.9 (16.3, 33.0)	< .01

Aix = aortic augmentation index; DBP = diastolic blood pressure; IQR = interquartile range; PWV = aortic pulse wave velocity; SBP = systolic blood pressure.

the observation that E/e′ is less strongly correlated with pulmonary artery wedge pressure[19] than suggested by some initial studies.[14] In both the noninvasive and the invasive study, pulmonary vascular resistance was normal. These findings suggest that pulmonary hypertension in hyperthyroidism is the result of a certain increase in pulmonary artery wedge pressure as a consequence of an elevated cardiac output and increased pulmonary flow, while pulmonary vascular resistance is not abnormal, which is in line with the findings of Suk et al,[7] who observed similar pulmonary vascular resistance in patients with and without pulmonary hypertension.

Hyperthyroidism is associated with reduced systemic vascular resistance, which is reflected by the lower diastolic blood pressure in addition to the widened pulse pressure.[20-22] The net effect of hyperthyroidism on blood pressure is variable, depending on the increase in cardiac output vs the reduction in systemic vascular resistance, as evidenced by the observation that some patients with hyperthyroidism develop isolated systolic hypertension.[23-25] Isolated systolic hypertension of the young was shown to be due to a blood pressure amplification between the aorta and the brachial artery, with normal central blood pressure levels despite abnormal brachial systolic blood pressure.[26] We observed a decreased diastolic blood pressure, augmentation index, and central systolic blood pressure in hyperthyroidism, with similar brachial systolic blood pressure, which is indicative of a blood pressure amplification of the brachial measured systolic blood pressure. However, despite a lower augmentation index in hyperthyroidism, the pulse wave velocity was significantly higher in hyperthyroidism compared with euthyroidism, which is well in line with other studies.[27] The discrepancy between decreased augmentation index and increased pulse wave velocity in hyperthyroidism might be explained by the fact that the increased augmentation index is more likely due to the increased heart rate rather than due to the direct effects of the thyroid hormones on the vascular stiffness,[28,29] whereas the hypervolemic circulation might contribute to the higher central arterial stiffness reflected by a higher pulse wave velocity.[27]

The echocardiographic assessment of cardiac output[30] and filling pressures[31] is only moderately accurate. Although studies with large patient samples report a good correlation of echocardiographically estimated and invasively measured systolic pulmonary artery pressure,[32] the estimation of systolic pulmonary artery pressure by echocardiography might also be hampered by only moderate accuracy.[11] Especially in high output states, there might be an overestimation of echocardiographic pressure gradients.[33] We found a good correlation of invasively and echocardiographically assessed systolic pulmonary artery pressure in the high output state of hyperthyroidism, but we observed a significant overestimation of the mean pulmonary artery pressure by 5 mm Hg. Therefore, we think that the comparison of echocardiographic findings is most reliable in the intra-individual hyperthyroidism vs euthyroidism comparison because the errors are probably similar in both

settings. Another potential limitation is confounding of our data by beta-blockers, as about half of patients were taking a beta-blocker for symptom relief at baseline, whereas only 2 patients were on a beta-blocker at follow-up. Beta-blockers decrease cardiac output and cardiac inotropy (and therefore, regurgitant jet velocities) and might lead to underestimation of the effect of thyroid hormones on these variables. Thus, the true effect of hyperthyroidism on pulmonary hemodynamics may have been even stronger because it may, to some extent, have been masked by beta-blockers.

References

1. Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. *Eur J Intern Med* 2006;17(4):267–71.
2. Ata F, Khan AA, Yousaf Z, et al. The clinical characteristics and outcomes of patients with pulmonary hypertension in association with hyperthyroid state: a systematic review. *Medicine (Baltimore)* 2022;101(26):e29832.
3. Teasdale SL, Inder WJ, Stowasser M, Stanton T. Hyperdynamic right heart function in Graves' hyperthyroidism measured by echocardiography normalises on restoration of euthyroidism. *Heart Lung Circ* 2017;26(6):580–5.
4. Al Husseini A, Bagnato G, Farkas L, et al. Thyroid hormone is highly permissive in angioproliferative pulmonary hypertension in rats. *Eur Respir J* 2013;41(1):104–14.
5. Sugiura T, Yamanaka S, Takeuchi H, Morimoto N, Kamioka M, Matsumura Y. Autoimmunity and pulmonary hypertension in patients with Graves' disease. *Heart Vessels* 2015;30(5):642–6.
6. Siu CW, Zhang XH, Yung C, Kung AWC, Lau CP, Tse HF. Hemodynamic changes in hyperthyroidism-related pulmonary hypertension: a prospective echocardiographic study. *J Clin Endocrinol Metab* 2007;92(5):1736–42.
7. Suk JH, Cho KI, Lee SH, et al. Prevalence of echocardiographic criteria for the diagnosis of pulmonary hypertension in patients with Graves' disease: before and after antithyroid treatment. *J Endocrinol Invest* 2011;34(8):e229–34.
8. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28(1):1–39.e14.
9. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29(4):277–314.
10. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23(7):685–713 [quiz 786-788.
11. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022;43(38):3618–731.
12. Lindqvist P, Söderberg S, Gonzalez MC, Tossavainen E, Henein MY. Echocardiography based estimation of pulmonary vascular resistance in patients with pulmonary hypertension: a simultaneous Doppler echocardiography and cardiac catheterization study. *Eur J Echocardiogr* 2011;12(12):961–6.
13. Popescu BA, Beladan CC, Nagueh SF, Smiseth OA. How to assess left ventricular filling pressures by echocardiography in clinical practice. *Eur Heart J Cardiovasc Imaging* 2022;23(9):1127–9.
14. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30(6):1527–33.
15. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol* 2003;41(6):1021–7.
16. Rossen NB, Laugesen E, Peter CD, et al. Invasive validation of arteriograph estimates of central blood pressure in patients with type 2 diabetes. *Am J Hypertens* 2014;27(5):674–9.
17. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol* 2009;53(13):1119–26.
18. Aroditis K, Pikilidou M, Vourvouri E, et al. Changes in cardiac function and structure in newly diagnosed Graves' disease. A conventional and 2D-speckle tracking echocardiography study. *Int J Cardiovasc Imaging* 2017;33(2):187–95.
19. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009;119(1):62–70.
20. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. *Nat Rev Endocrinol* 2010;6(8):431–43.
21. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. *Curr Hypertens Rep* 2003;5(6):513–20.
22. Mercé J, Ferrás S, Oltra C, et al. Cardiovascular abnormalities in hyperthyroidism: a prospective Doppler echocardiographic study. *Am J Med* 2005;118(2):126–31.
23. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* 2017;14(1):39–55.
24. Razvi S, Jabbar A, Pingitore A, et al. Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol* 2018;71(16):1781–96.
25. Prisant LM, Gujral JS, Mulloy AL. Hyperthyroidism: a secondary cause of isolated systolic hypertension. *J Clin Hypertens (Greenwich)* 2006;8(8):596–9.
26. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39(33):3021–104.
27. Grove-Laugesen D, Malmstroem S, Ebbehoj E, et al. Arterial stiffness and blood pressure in patients newly diagnosed with Graves' disease compared with euthyroid controls. *Eur Thyroid J* 2020;9(3):148–56.
28. Sakurai M, Yamakado T, Kurachi H, et al. The relationship between aortic augmentation index and pulse wave velocity: an invasive study. *J Hypertens* 2007;25(2):391–7.
29. Rimoldi SF, Messerli FH, Cerny D, et al. Selective heart rate reduction with ivabradine increases central blood pressure in stable coronary artery disease. *Hypertension* 2016;67(6):1205–10.
30. Maeder MT, Karapanagiotidis S, Dewar EM, Kaye DM. Accuracy of echocardiographic cardiac index assessment in subjects with preserved left ventricular ejection fraction. *Echocardiography* 2015;32(11):1628–38.
31. Previtali M, Chieffo E, Ferrario M, Klersy C. Is mitral E/E' ratio a reliable predictor of left ventricular diastolic pressures in patients without heart failure? *Eur Heart J Cardiovasc Imaging* 2012;13(7):588–95.
32. Greiner S, Jud A, Aurich M, et al. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. *J Am Heart Assoc* 2014;3(4):e001103.
33. Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. *Eur Respir J* 2012;39(1):112–8.