CLINICAL STUDY

Myocardial contractility and total arterial stiffness in patients with overt hyperthyroidism: acute effects of β_1 -adrenergic blockade

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Abstract

Objectives: To ascertain whether myocardial contractility and total arterial stiffness are significantly altered in human thyrotoxicosis, and to what extent they are affected by acute β_1 -adrenergic blockade.

Methods: Doppler-echocardiography was used to assess left ventricular (LV) structure and function, hemodynamics and total arterial stiffness in untreated overt hyperthyroid patients before and 2 h after 5 mg bisoprolol given orally compared with age- and sex-matched healthy euthyroid controls.

Results: Compared with controls, untreated patients ($n = 20$) had a higher heart rate (HR) and LV stroke index (SI), which were associated with higher pulse pressure (PP), larger LV end-diastolic volume index (EDVI, an index of preload, + 11%, $P < 0.05$), marginally increased stress-corrected LV midwall fractional shortening (MWS, an index of myocardial contractility, + 5%; $P = 0.066$), and shorter isovolumic relaxation time (IVRT). These changes resulted in a higher cardiac index (CI) and a lower systemic vascular resistance (SVR), which were associated with fairly normal mean blood pressure (BP) but higher PP/stroke volume (an index of total arterial stiffness, + 29%; $P < 0.01$). After bisoprolol, compared with controls, the randomly treated patients ($n = 10$) had comparable HR but additionally increased SI; PP remained enhanced, EDVI was further enlarged (+ 26%, $P < 0.001$), stress-corrected MWS was substantially unchanged, and IVRT remained shorter. Overall, these effects attenuated the high-output state, which was associated with normalization of PP/stroke volume without changes of mean BP.

Conclusions: In human overt hyperthyroidism, myocardial contractility does not play a major role in increasing LV performance, which is instead predominantly sustained by increased preload with enhanced LV diastolic function. In addition, human thyrotoxicosis is associated with increased total arterial stiffness despite fairly normal mean BP. In this scenario, acute β_1 -adrenergic blockade blunts the cardiovascular hyperkinesia predominantly by slowing HR – a process that is associated with normalization of total arterial stiffness.

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Introduction

Overt hyperthyroidism exerts remarkable effects on the heart and vasculature leading to a well recognized hyperkinetic cardiocirculatory state (1). However, it is unclear whether, in humans, thyrotoxic cardiovascular hyperkinesia is predominantly sustained by changes in myocardial contractility, or by changes in peripheral hemodynamics (2). This uncertainty is at least partially fuelled by the fact that the increased β_1 -adrenergic activity that characteristically accompanies overt hyperthyroidism may confound the analysis of the genuine effects of thyroid hormone on the heart and vasculature (2). In addition, it is not known whether total arterial stiffness is changed in human overt hyperthyroidism (2).

Accordingly, we evaluated left ventricular (LV) structure and function, hemodynamics and total arterial stiffness by Doppler-echocardiography in newly diagnosed and untreated overt hyperthyroid patients before and soon after β_1 -adrenergic blockade, as compared with age- and sex-matched healthy euthyroid controls.

Subjects and methods

Patients' characteristics and study protocol

Twenty patients with overt hyperthyroidism (thyrotropin (TSH): < 0.03 mU/l (reference range, 0.3–3.8); free-thyroxine (F-T₄), 44.4 ± 9.5 pmol/l (reference range, 7.7–20.6); free-triiodothyronine (F-T₃),

21.4±6.5 pmol/l (reference range, 4.0–9.2)), and 20 healthy euthyroid controls matched by sex and age (TSH: 1.63±0.42 mU/l, $P < 0.001$; F-T₄, 12.1±2.0 pmol/l, $P < 0.001$; F-T₃, 6.9±0.9 pmol/l, $P < 0.001$) entered the study after giving informed consent. Hyperthyroid patients, recruited from a pool of outpatients with newly diagnosed and untreated Graves' disease, were enrolled in the study if they had a sedentary life style, were not taking medication, and had no clinical or anamnestic evidence of non-thyroidal illnesses. The mean duration of hyperthyroidism was 6.6±1.6 months (range: 4–9 months), as assessed from a detailed medical history. Healthy control subjects were recruited from a large group of outpatients evaluated for atypical chest pain and/or palpitations. All had a sedentary life style and none had clinical or biochemical evidence of thyroid or non-thyroidal disease.

Basally, all participants underwent noninvasive cardiovascular assessment (see below). In addition, a subgroup of 10 randomly selected hyperthyroid patients were re-evaluated 2 h after oral administration of 5 mg bisoprolol (a β_1 -adrenergic blocker), and compared with a subgroup of 10 age- and sex-matched controls. We used this dose of bisoprolol because of preliminary experience showing a heart rate reduction of about 20% in overt hyperthyroid patients compared with the pretreatment value 2 h after oral administration of the drug (S Fazio, personal observation).

Echocardiographic methods

Using a standard echocardiographic protocol according to the American Society of Echocardiography recommendations (3), we conducted a two-dimensionally guided M-mode analysis of LV morphology and LV filling with an ultrasound machine equipped with a 2.5–3.5 MHz transducer (Apogee CX, Interspec, Inc., Ambler, PA, USA). All subjects were examined while in a supine lateral position after resting for 30 min. M-mode and Doppler echocardiographic tracings were acquired during quiet respiration and were recorded on a strip-chart recorder at a paper speed of 100 mm/s. ECG tracing was displayed simultaneously on the echo-tracings. Three cardiac cycles were averaged for measurements. Brachial artery pressure (blood pressure (BP)) was measured by cuff-sphygmomanometer after the echocardiographic study with subjects in supine decubitus.

Echocardiographic measurements

LV end-diastolic and end-systolic diameters (EDD and ESD), interventricular septal (EDIVS and ESIVS) and posterior wall thicknesses (EDPWT and ESPWT) were measured from M-mode tracings according to the Penn convention (4). LV end-diastolic and end-systolic volumes (EDV and ESV) were obtained by two-dimensional echocardiography with the single plane

area-length method (5), and were indexed for body surface area (EDVI and ESVI). The intra-observer variability for LV structure and volume, calculated as the percentage difference between reading sessions (6), was <8% and <13% respectively. Early (E wave) and late (A wave) peak transmitral flow velocities of LV fillings were sampled at the tip of the mitral valve by pulsed-wave Doppler in apical four-chamber view (7). LV isovolumic relaxation time (IVRT), i.e. the time from the end of transaortic flow to the onset of early diastolic flow, was assessed by placing the continuous-wave cursor Doppler beam across the LV outflow tract in the proximity of the mitral valve anterior leaflet (7). The intra-observer variability of measures of diastolic filling parameters, calculated as the percentage difference between reading sessions (6) was <8%.

Derived variables

Heart rate (HR) was calculated as the 60/the time, in seconds, between two consecutive QRS complexes from ECG on echo-tracings. Pulse pressure (PP) was systolic – diastolic BP, and mean BP was diastolic BP + PP/3. LV mass was calculated by the following anatomically validated Penn-cube formula (8):

$$1.04 \times [(EDD + EDIVS + EDPWT)^3 - (EDD)^3] - 13.6$$

and was indexed for body surface area. LV stroke volume was EDV-ESV, and was indexed by body surface area to calculate stroke index (SI). Cardiac index (CI) was calculated as SI × HR. Systemic vascular resistance (SVR) was calculated as (mean BP/cardiac output) × 80. LV myocardial contractility was estimated based on the afterload-shortening relationship (9, 10). Because most of the LV myocardial fibers are orientated circumferentially and located at midwall, LV afterload and fractional shortening were calculated at this site. Specifically, afterload was estimated by LV midwall circumferential end-systolic stress (CESS) using the following validated formula (11):

$$\frac{\text{Systolic BP} \times (ESD/2)^2 \times \left\{ 1 + \frac{[(ESD/2) + ESPWT]^2}{[(ESD/2) + (ESPWT/2)]^2} \right\}}{[(ESD/2) + ESPWT]^2 - (ESD/2)^2}$$

and LV midwall fractional shortening (MWS) was calculated using the following validated formula (10):

$$100 \times \frac{(EDD + EDIVS/2 + EDPWT/2) - (ESD + H_s)}{(EDD + EDIVS/2 + EDPWT/2)}$$

where H_s is the LV inner shell in systole calculated as follows:

$$[(EDD + EDIVS/2 + EDPWT/2)^3 - (EDD)^3 + (ESD)^3]^{0.333} - ESD$$

The computation of the inner shell in systole is based on the assumption that the total LV mass does not change during the cardiac cycle (10). Thus, individual

LV MWS was compared with LV MWS predicted for measured CESS using the following equation developed in a reference population (10):

$$\text{predicted MWS} = (-0.022 \times \text{CESS}) + 20.01$$

and the percentage ratio of observed and predicted MWS, termed 'stress-corrected MWS', was used as an index of myocardial contractility (10). This approach allows assessment of myocardial contractility because myocardial shortening and stress are on the same axis. Total arterial stiffness was estimated as PP/stroke volume (12).

Statistical analysis

The statistical analysis was performed using SPSS v. 9.0.1 for Windows (SPSS, Chicago, IL, USA). Data in the text and tables are expressed as mean values and s.d. The two-tailed unpaired Student's *t*-test was used to compare continuous variables in hyperthyroid patients and control subjects. The two-tailed paired Student's *t*-test was used to analyze the effects of bisoprolol in the subgroup of treated hyperthyroid patients. A *P* value less than 0.05 was considered statistically significant.

Results

Hyperthyroid patients vs healthy euthyroid controls (Table 1)

Compared with controls, hyperthyroid patients had a higher HR (+37%), systolic BP (+8%) and PP

(+53%), a lower diastolic BP (−17%), and similar mean BP. The LV mass index was similar in hyperthyroid patients and in controls (105 ± 23 vs 98 ± 16 , $P = 0.265$). Compared with controls, hyperthyroid patients had a higher LV SI (+22%), with a larger EDVI (+11%), and similar ESVI. LV CESS (an index of afterload) was similar and stress-corrected LV MWS (an index of myocardial contractility) was marginally increased in hyperthyroid patients versus controls (+5%; $P = 0.066$). Compared with controls, hyperthyroid patients had a higher E wave (+14%) and A wave (+19%) of LV filling, but a similar E/A, and a shorter IVRT (−30%). CI was increased (+64%) and SVR was lower (−43%) in hyperthyroid patients than in controls. As shown in Fig. 1, the PP/stroke volume (an index of total arterial stiffness) was about 29% higher in hyperthyroid patients versus controls (0.99 ± 0.27 vs 0.77 ± 0.18 mmHg/ml; $P < 0.01$).

Acute effects of bisoprolol treatment in hyperthyroid patients (Table 2)

In 10 treated hyperthyroid patients, bisoprolol reduced HR (−17%), systolic BP (−11%) and pp (−25%), and slightly increased diastolic BP (+7%), without affecting mean BP. After bisoprolol, LV SI was slightly increased (+6%) due to a larger EDVI (+9%), whereas ESVI was essentially unchanged. The treatment had no significant effect on LV CESS, nor did it affect stress-corrected LV MWS. Bisoprolol increased the E/A ratio (+23%) mostly by decreasing the A wave (−16%), and it marginally prolonged the IVRT. After bisoprolol, CI was

Table 1 Clinical characteristics, left ventricular structure and function, and hemodynamics in overt hyperthyroid patients and in matched healthy euthyroid controls. Results are means $\pm$ s.d.

	Controls (<i>n</i> = 20)	Hyperthyroid patients (<i>n</i> = 20)	<i>P</i>
Age (years)	34 $\pm$ 6	33 $\pm$ 8	0.598
Sex (m/f)	6/14	6/14	—
BSA (m ²)	1.72 $\pm$ 0.16	1.68 $\pm$ 0.21	0.494
BMI (kg/m ²)	24 $\pm$ 3	22 $\pm$ 4	0.115
HR (beats/min)	75 $\pm$ 9	103 $\pm$ 16	<0.001
Systolic BP (mmHg)	117 $\pm$ 10	126 $\pm$ 15	0.025
Diastolic BP (mmHg)	74 $\pm$ 8	62 $\pm$ 11	<0.001
PP (mmHg)	42 $\pm$ 7	65 $\pm$ 14	<0.001
Mean BP (mmHg)	88 $\pm$ 8	83 $\pm$ 11	0.091
EDVI (ml/m ²)	52 $\pm$ 7	58 $\pm$ 9	0.027
ESVI (ml/m ²)	19 $\pm$ 4	18 $\pm$ 5	0.302
SI (ml/m ²)	33 $\pm$ 6	40 $\pm$ 5	<0.001
MWS (%)	18 $\pm$ 2	20 $\pm$ 1	0.011
CESS (kdyne/cm ²)	111 $\pm$ 20	101 $\pm$ 24	0.153
Stress-corrected MWS (%)	104 $\pm$ 11	110 $\pm$ 7	0.066
E wave (cm/s)	77 $\pm$ 11	88 $\pm$ 14	0.009
A wave (cm/s)	47 $\pm$ 7	56 $\pm$ 13	0.009
E/A	1.7 $\pm$ 0.3	1.6 $\pm$ 0.4	0.850
IVRT (ms)	83 $\pm$ 10	58 $\pm$ 12	<0.001
CI (l/min/m ²)	2.5 $\pm$ 0.6	4.1 $\pm$ 0.5	<0.001
SVR (dyne $\times$ s/cm ⁵)	1736 $\pm$ 433	989 $\pm$ 213	<0.001

BSA, body surface area; BMI, body mass index; HR, heart rate; BP, blood pressure; PP, pulse pressure; EDVI, left ventricular end-diastolic volume index; ESVI, left ventricular end-systolic volume index; SI, stroke index; MSW, left ventricular midwall fractional shortening; CESS, left ventricular midwall circumferential end-systolic stress; IVRT, isovolumic relaxation time; CI, cardiac index; SVR, systemic vascular resistance. kdyne/cm² and dyne $\times$ s/cm⁵, standard units for CESS and SVR, respectively.

Figure 1 Pulse pressure to stroke volume ratio in overt hyperthyroid patients ($n = 20$) and in matched healthy euthyroid controls ($n = 20$).

reduced (-12%) and SVR was increased ($+12\%$). As shown in Fig. 2, after bisoprolol treatment, the PP/stroke volume was reduced by about 30% in hyperthyroid patients (0.99 ± 0.22 vs 0.70 ± 0.19 mmHg/ml; $P < 0.001$).

Treated hyperthyroid patients vs healthy euthyroid controls (Table 2)

Compared with controls, treated hyperthyroid patients had only a marginally faster HR and similar systolic, diastolic and mean BP, whereas PP remained higher ($+24\%$). LV SI was further increased ($+42\%$) in treated hyperthyroid patients versus controls, through a further enlargement in EDVI ($+26\%$), without changes in ESVI. Compared with controls, treated patients had a

similar LV CESS and near equal stress-corrected LV MWS. After bisoprolol treatment, hyperthyroid patients had a higher E wave ($+20\%$) than controls, but similar A wave and E/A, whereas IVRT remained shorter (-19%). Table 2 shows that compared with controls, treated hyperthyroid patients had a higher CI ($+58\%$) and a reduced SVR (-34%). As shown in Fig. 2, PP/stroke volume was similar between treated patients and controls (0.70 ± 0.19 vs 0.77 ± 0.12 mmHg/ml, $P = 0.339$).

Discussion

Two main findings emerge from our study on the impact of human overt hyperthyroidism on the cardiovascular system. The first is that myocardial contractility does not play a major role in increasing LV performance in overt hyperthyroid patients, which is instead predominantly sustained by increased preload, with enhanced LV diastolic function. In fact, compared with controls, our hyperthyroid patients showed only a marginal increase in stress-corrected MWS, which is an index of myocardial contractility. By contrast, in our hyperthyroid patients, the supra-normal EDVI despite the remarkably faster HR is evidence of a net increase in preload given the inverse relationship between these variables (13). Augmented preload in hyperthyroid patients is also supported by our observation of an increase in the E wave of LV diastolic filling in patients versus controls, which, given the faster HR in the former, is indicative of a greater left atrium-LV pressure

Table 2 Clinical characteristics, left ventricular structure and function, and hemodynamics in a randomly selected subgroup of overt hyperthyroid patients (H) before and 2 hours after 5 mg bisoprolol given orally, as compared with matched healthy euthyroid controls (C). Data are means $\pm$ s.d.

	H before bisoprolol ($n = 10$)	P H before vs after	H after bisoprolol ($n = 10$)	Controls ($n = 10$)	P C vs H after
Age (years)	30 $\pm$ 5	—	—	30 $\pm$ 3	—
Sex (m/f)	5/5	—	—	5/5	—
BSA (m^2)	1.70 $\pm$ 0.15	—	—	1.80 $\pm$ 0.17	—
BMI (kg/m^2)	22 $\pm$ 2	—	—	24 $\pm$ 3	—
HR (beats/min)	103 $\pm$ 11	<0.001	86 $\pm$ 9	78 $\pm$ 8	0.061
Systolic BP (mmHg)	128 $\pm$ 5	<0.001	114 $\pm$ 6	112 $\pm$ 9	0.423
Diastolic BP (mmHg)	59 $\pm$ 9	0.108	63 $\pm$ 12	70 $\pm$ 9	0.152
PP (mmHg)	69 $\pm$ 8	<0.001	52 $\pm$ 9	42 $\pm$ 5	0.005
Mean BP (mmHg)	82 $\pm$ 7	0.368	80 $\pm$ 10	84 $\pm$ 9	0.353
EDVI (ml/m^2)	58 $\pm$ 9	0.001	64 $\pm$ 9	49 $\pm$ 6	<0.001
ESVI (ml/m^2)	16 $\pm$ 5	0.148	19 $\pm$ 6	19 $\pm$ 3	0.999
SI (ml/m^2)	42 $\pm$ 5	0.017	45 $\pm$ 6	30 $\pm$ 4	<0.001
MWS (%)	19 $\pm$ 1	0.310	19 $\pm$ 1	18 $\pm$ 1	0.229
CESS ($kdyne/cm^2$)	107 $\pm$ 14	0.486	110 $\pm$ 11	114 $\pm$ 24	0.659
Stress-corrected MWS (%)	109 $\pm$ 7	0.356	106 $\pm$ 8	103 $\pm$ 9	0.350
E (cm/s)	92 $\pm$ 10	0.674	93 $\pm$ 6	77 $\pm$ 13	0.003
A (cm/s)	61 $\pm$ 16	0.009	50 $\pm$ 7	46 $\pm$ 6	0.157
E/A	1.5 $\pm$ 0.2	0.002	1.9 $\pm$ 0.2	1.7 $\pm$ 0.3	0.187
IVRT (ms)	60 $\pm$ 8	0.168	63 $\pm$ 10	76 $\pm$ 7	0.004
CI ($l/min/m^2$)	4.4 $\pm$ 0.8	<0.001	3.9 $\pm$ 0.8	2.4 $\pm$ 0.4	<0.001
SVR ($dyne \times s/cm^5$)	904 $\pm$ 182	0.027	1019 $\pm$ 277	1608 $\pm$ 194	<0.001

See Table 1 for abbreviations.

Figure 2 Pulse pressure to stroke volume ratio in a subgroup of randomly selected overt hyperthyroid patients ($n = 10$) before and 2 h after 5 mg bisoprolol given orally, as compared with matched healthy euthyroid controls ($n = 10$).

gradient due to augmented venous return. In fact, in the absence of a simultaneous increase in preload, the faster HR would be associated with a decrease in the E wave (14). In addition, in line with previous reports (15–18), hyperthyroid patients also had a shorter IVRT suggesting optimal diastolic function. This probably helped to accommodate the increased preload without relevant changes in LV filling pressure potentially through enhancement of LV suction (19).

Using echocardiography, Feldman *et al.* (20) found that LV circumferential fiber shortening velocity at the endocardial level, corrected for HR and LV meridional end-systolic stress, was higher in 11 hyperthyroid patients than in age-matched controls. They concluded that increased myocardial contractility plays a mandatory role in increasing LV systolic performance. However, it should be emphasized that the estimation of myocardial contractility by endocardial fiber shortening velocity may overestimate the true myocardial inotropic state, especially when preload and HR are increased (21). By contrast, assessment of myocardial contractility by relating MWS to CESS provides a more physiological measure of the myocardial inotropic state (10). In fact, most of the LV myocardial fibers are oriented circumferentially and are located at midwall, which is where shortening and stress are *de facto* measured (10, 11). Indeed, our findings that myocardial contractility does not play a major role in increasing LV performance in human overt hyperthyroidism is in agreement with a report by Merillon *et al.* (22), who assessed LV systolic function by cardiac catheterization in 7 thyrotoxic patients and 11 normal controls atrially paced at a near identical heart rate, and found no differences between the two groups in several parameters of LV contractile performance. They concluded that in human hyperthyroidism there is no increase in the level of myocardial contractility independent of changes in heart rate.

The second major finding of our study is that total arterial stiffness is increased in overt hyperthyroid

patients. In fact, compared with controls, our hyperthyroid patients had a higher PP/stroke volume because of disproportionately increased PP with respect to stroke volume. It is noteworthy that the higher PP/stroke volume in our hyperthyroid patients was associated with a fairly normal mean BP, indicating that the increase in total arterial stiffness was not due to a higher arterial load at the onset of LV ejection. Accordingly, one mechanism that would explain our finding is that the faster HR in overt hyperthyroidism results in an earlier return of the forward pressure wave in systole, thereby resulting in a greater overlapping in the forward and reflected pressure waves. The clinical outcome of this physiological process would be an increase in systolic BP and a decrease in diastolic BP, with a net increase in PP and an essentially unchanged mean BP (23). This hypothesis is supported by the fact that, in bisoprolol-treated patients, the decrease in HR was accompanied by a reduction in systolic BP and by a slight elevation in diastolic BP, with a net decrease in PP and quite unchanged mean BP, whereas stroke volume was further increased, thereby resulting in normalization of the PP/stroke volume. Because the hemodynamic setting of overt hyperthyroid patients is strikingly like that of athletes performing physical exercise (24), it is a tempting to speculate that, in overt human hyperthyroidism, the increase in total arterial stiffness represents an important dynamic adaptation to allow a faster transfer of blood from the LV towards the peripheral vascular tree, which, in turn, sustains the hyperkinetic circulatory state.

In conclusion, in human overt hyperthyroidism, myocardial contractility does not play a major role in increasing LV performance, which is instead predominantly sustained by increased preload with enhanced LV diastolic function. In addition, human thyrotoxicosis is associated with increased total arterial stiffness despite a fairly normal mean BP. In this scenario, acute β_1 -adrenergic blockade blunts the thyrotoxic cardiovascular hyperkinesia predominantly by slowing HR – a process that is associated with normalization of total arterial stiffness.

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