Left ventricular function in acute hypothyroidism: a Doppler echocardiography study

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Acute hypothyroidism; Doppler echocardiography; Left ventricular function.

Background. **Acute changes in cardiac parameters may occur after L-thyroxine withdrawal in patients totally thyroidectomized for thyroid cancer. The literature data regarding cardiac function in acute hypothyroidism are limited and discordant.**

Methods. **In order to evaluate the effects of acute hypothyroidism on cardiac function, 20 athyreotic patients (3 males, 17 females, mean age 46.4 ± 8.6 years, range 18-58 years) underwent Doppler echocardiography during L-thyroxine therapy (euthyroid phase) and 5 weeks after hormone therapy withdrawal (hypothyroid phase).**

Results. **Significant changes in the left ventricular mass (83 ± 12 vs 93 ± 17 g/m^2, p = 0.004) and end-diastolic volume (56 ± 9 vs 50 ± 9 ml/m^2, p = 0.01) were found. Among systolic function parameters, the pre-ejection period/left ventricular ejection time (PEP/LVET) ratio (0.33 ± 0.07 vs 0.40 ± 0.08, p = 0.0002), aortic peak flow velocity corrected for heart rate (3.9 ± 0.7 vs 3.5 ± 0.5 cm/s, p = 0.02) and mean aortic acceleration corrected for heart rate (45 ± 15 vs 38 ± 9 cm/s^2, p = 0.007) showed significant variations, whereas the left ventricular fractional shortening (39 ± 5 vs 40 ± 6%, p = NS) and ejection fraction (69 ± 6 vs 68 ± 7%, p = NS) did not change. Among diastolic function parameters, only the E-wave velocity decreased (73 ± 17 vs 65 ± 12 cm/s, p = 0.01); no significant modification was found in the A-wave velocity (62 ± 19 vs 58 ± 14 cm/s, p = NS), E/A ratio (1.2 ± 0.5 vs 1.1 ± 0.3, p = NS), isovolumic relaxation time (93 ± 16 vs 95 ± 37 ms, p = NS) and E-wave deceleration time (233 ± 48 vs 235 ± 45 ms, p = NS). The pattern of left ventricular filling remained unchanged, except in 2 patients. The Suga-Sagawa's index, a known parameter of myocardial contractility, was unchanged (5.6 ± 2 vs 6.1 ± 2 mmHg/ml, p = NS). The systemic vascular resistance increased (1511 ± 599 vs 2216 ± 408 dynes-s-cm^{-5}, p = 0.002), while the stroke index (39 ± 8 vs 33 ± 7 ml/m^2, p = 0.001) and cardiac index (2.74 ± 0.6 vs 2.07 ± 0.5 l/min/m^2, p = 0.0001) significantly decreased.**

Conclusions. **Acute hypothyroidism was associated with left ventricular systolic dysfunction, probably due to pre- and afterload alterations rather than to an impaired myocardial contractility. The diastolic function was not significantly modified. An increase in cardiac mass was also found, possibly a consequence of early interstitial myxedema. Unlike the PEP/LVET ratio, both the fractional shortening and ejection fraction may be unreliable indicators of left ventricular systolic dysfunction in patients with acute hypothyroidism.**

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Introduction

In patients totally thyroidectomized for thyroid cancer, transient hypothyroidism often occurs after replacement therapy withdrawal, a procedure that is required for the detection of metastases[1]. Severe acute thyroid hormone deficiency may modify the function of many organs and apparatuses.

The consequences of chronic (overt or clinically latent) hypothyroidism on the cardiovascular system are known[2-7], whereas only a few studies investigated the effects of acute hypothyroidism on cardiac function[8-16]. Unfortunately, the surveys of these studies are very limited and the results often discordant.

Furthermore, knowledge regarding the influences of acute hypothyroidism on cardiac inotropism is even scantier and the literature data on this issue are controversial. Indeed, some authors[14,15] report a decrease in myocardial contractility, but others[9] describe no variation in heart contractile function. Finally, the effects of acute hypothyroidism on myocardial contractility, previously investigated either in experimental models[14] or by means of non-echocardiographic methods[9,15], have never been evaluated in humans at echocardiography.

The aim of the present study was to assess, using conventional echocardiography, the influences of severe acute hypothyroidism on left ventricular function and contractility in humans.

Methods

We studied 20 subjects (3 males, 17 females, mean age 46. 4 ± 8.6 years, range 18-58 years), all previously submitted to total thyroidectomy because of differentiated thyroid cancer and then placed on long-term treatment with L-thyroxine (T4) (median 3.7 years, range 1-19 years). No patient had signs of cardiovascular disease, rhythm disorders, diabetes mellitus or arterial hypertension. In no case were valvular abnormalities present. In no case was any patient on any drug known to alter cardiac function.

During the 6 months before the beginning of the study, thyroid stimulating hormone (TSH) levels had been maintained between 0.1 and 0.3 µIU/ml, with free triiodothyronine (FT3) and free thyroxine (FT4) levels in the normal range. T4 administration was discontinued for 5 weeks (during the first 3 weeks T4 was replaced by L-triiodothyronine at the increasing dosage of 20, 40 and 60 µg/day during the first, second and third week respectively) and it produced a state of transient profound hypothyroidism in all subjects. This procedure, according to international protocols, is necessary when screening for possible metastases by means of iodine-131 total body scan[1].

Each patient underwent cardiological evaluation twice: 1) in a state of euthyroidism, before T4 withdrawal; 2) 5 weeks after T4 discontinuation, during the phase of severe acute hypothyroidism (TSH values > 25 µIU/ml).

On these same occasions, thyroid hormone (FT3 and FT4) and TSH levels were measured in all subjects using an immunoenzyme technique (AxSym System, Abbott Diagnostic, Wiesbaden, Germany).

Cardiological evaluation consisted of clinical examination including measurement of the arterial blood pressure (BP) and heart rate, ECG and color Doppler echocardiography.

BP, heart rate and ECG were recorded in the supine position after 5 min of rest. Systolic and diastolic BP were measured using a mercury sphygmomanometer. The mean arterial BP was calculated as diastolic BP plus one third of differential BP[7,15,17-19].

Doppler echocardiography study, always performed at midday to avoid the known influence of the circadian rhythm on left ventricular diastolic function[20], was carried out, using a Sonos 5500 echocardiograph (Hewlett-Packard, Agilent Technologies, Andover, MA, USA) equipped with a 3.5 MHz transducer, in the left lateral decubitus and during simultaneous ECG monitoring. M-mode measurements were obtained from the left parasternal view in accordance with the recommendations of the American Society of Echocardiography[21,22]. The left ventricular mass (LVM) was calculated using Devereux's equation[23]. The left ventricular volumes and ejection fraction (LVEF) were measured from the apical view using Simpson's method[22,24]. The stroke volume was calculated as the difference between the left ventricular end-diastolic volume and end-systolic volume; this method is well known to be reliable in the absence of significant valvular regurgitations[25] and has been shown to correlate well with the angiographic method[26]. The cardiac output was calculated as the product of stroke volume and heart rate. The systemic vascular resistance (SVR) was measured in the supine position using the following formula[18]: SVR = 80 × [(mean arterial BP - mean right atrial pressure)/cardiac output], assuming a mean right atrial pressure equal to 4 mmHg. This non-invasive calculation of the SVR, previously used by several authors[7,10,15,19,27], showed an acceptable correlation with the hemodynamic measurement[18]. LVM, left ventricular diameters and volumes, stroke volume and cardiac output were calculated as the mean of the values recorded during five consecutive cardiac cycles and normalized for the body surface. The pulsed-wave flow velocity profiles across the mitral and aortic valves were obtained from the apical 4- and 5-chamber views respectively, at end expiration and in accordance with standard techniques[28-30]. As previously described[31,32], the patterns of left ventricular filling were defined as follows: normal, impaired relaxation, pseudonormal, restrictive. In order to distinguish a normal from a pseudonormal pattern, the transmitral flow recording was repeated during the Valsalva maneuver[33], whose results are in accordance with those of the pulmonary venous flow recording[31,34]. The mean aortic acceleration (Acc) was derived as previously described[30]. The systolic time intervals (pre-ejection period [PEP], left ventricular ejection time [LVET], isovolumic relaxation time [IVRT]) were obtained by simultaneous Doppler registration of the mitral and aortic transvalvular flows[35]. Each of the systolic time intervals and the Doppler indexes was calculated as the mean of the values recorded during five consecutive cardiac cycles and corrected ($_c$) for heart rate in accordance with Bazett's formula (divided by the square root of the R-R interval), in order to avoid the well-known impact of heart rate on the assessment of Doppler parameters[36]. Suga-Sagawa's index (left ventricular end-systolic pressure/end-systolic volume), a parameter which is related to myocardial contractility[37,38], was calculated as the ratio between the instantaneous systolic BP (measured using a sphygmomanometer) and the left ventricular end-systolic volume (measured at echocardiography)[39].

Statistical analysis. Data are expressed as mean ± SD. The paired Student's t-test was used to compare the variables assessed in the two phases of the study. A p value < 0.05 was considered as statistically significant.

Results

No patient developed symptoms or signs of cardiovascular disease. ECG was normal during the euthyroid stage and showed no significant modification in the hypothyroid phase. In no case was pericardial effusion detected.

The thyroid hormone levels, heart rate and BP values before and after T4 withdrawal are summarized in tables I and II respectively. In particular, BP values did not change substantially whereas heart rate decreased significantly.

The variations in echocardiographic parameters between the first and the second cardiological evaluation are reported in tables II and III. We noted that some indexes (LVET, Vmax, Acc) showed statistically significant changes only when corrected for heart rate.

A significant increase in LVM and interventricular septum thickness was found, while the left ventricular posterior wall was thickened, but not significantly. In no case was the LVM increase pathological, always remaining in normal range (≤ 134 g/m^2 in males, ≤ 110 g/m^2 in females)[23]. We also found a significant reduction in the left ventricular end-diastolic diameter and volume; the end-systolic diameter and volume also decreased, but not significantly.

Among the systolic time intervals, PEP was prolonged significantly, whereas LVET decreased when corrected for heart rate (Table III), thus resulting in a significant increase in the PEP/LVET ratio. In particular, this last parameter, which is related to the angiographic and echocardiographic parameters of left ventricular systolic performance[40-43] and has been used as an index of left ventricular systolic function in many thyroid[6,10,44,45] and non-thyroid[42,43,46-48] diseases, was normal (≤ 0.45)[49] in each of the investigated subjects during the euthyroid phase; after T4 withdrawal it rose in 18/20 patients, exceeding the normal limits in 5. The $Vmax_c$ and Acc_c, which are also related to invasive indexes of left ventricular systolic performance[50-52], decreased significantly; on the contrary, no significant variation was found in left ventricular fractional shortening or LVEF, that were always within normal limits.

Among the parameters of left ventricular diastolic filling, the early transmitral flow velocity (EV) showed a statistically significant decrease, whereas the late transmitral flow velocity (AV), E-wave deceleration time (EDT), E/A ratio and IVRT did not significantly change; finally, an almost statistically significant decrease (p = 0.059) was found in the heart corrected E/A

Table I. Hormonal parameters before and after L-thyroxine (T4) treatment withdrawal.

	On L-T4	Off L-T4
FT3 (pg/ml)	2.4 ± 0.5	0.6 ± 0.4*
FT4 (pg/ml)	1.3 ± 0.2	0.2 ± 0.1*
TSH (μIU/ml)	0.2 ± 0.1	49.8 ± 20.4*

FT3 = free triiodothyronine; FT4 = free thyroxine; TSH = thyroid stimulating hormone. * p < 0.001 vs on L-T4.

Table II. Clinical and echocardiographic parameters.

	On L-T4	Off L-T4	p
HR (b/min)	72 ± 9	63 ± 11	0.01
SBP (mmHg)	125 ± 17	128 ± 19	NS
DBP (mmHg)	80 ± 13	82 ± 14	NS
MBP (mmHg)	95 ± 14	97 ± 14	NS
LVEDD (mm/m^2)	25 ± 1.3	24 ± 1.1	0.025
LVESD (mm/m^2)	16 ± 1	15 ± 0.9	NS
dIVS (mm)	9.6 ± 1	11.1 ± 1.4	0.0001
dPW (mm)	9.5 ± 1.3	10.3 ± 1.4	NS
LVMI (g/m^2)	83 ± 12	93 ± 17	0.004
LVEDV (ml/m^2)	56 ± 9	50 ± 9	0.01
LVESV (ml/m^2)	16 ± 5	14 ± 5	NS
LVFS (%)	39 ± 5	40 ± 6	NS
LVEF (%)	69 ± 6	68 ± 7	NS
S-S index (mmHg/ml)	5.6 ± 2	6.1 ± 2	NS
SV (ml)	68 ± 15	58 ± 14	0.001
SI (ml/m^2)	39 ± 8	33 ± 7	0.001
CO (l/min/m^2)	4.8 ± 1.1	3.6 ± 0.9	< 0.0001
CI (l/min/m^2)	2.74 ± 0.6	2.07 ± 0.5	0.0001
SVR (dynes-s-cm^{-5})	1511 ± 599	2216 ± 408	0.002

CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; dIVS = interventricular septum diastolic thickness; dPW = posterior wall diastolic thickness; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVFS = left ventricular fractional shortening; LVMI = left ventricular mass index; MBP = mean blood pressure; SBP = systolic blood pressure; SI = stroke index; S-S = Suga-Sagawa; SV = stroke volume; SVR = systemic vascular resistance; T4 = thyroxine.

Table III. Echo-Doppler parameters.

	On L-T4	Off L-T4	p
PEP (ms)	94 ± 20	115 ± 18	< 0.0001
PEP_c (ms)	3.2 ± 0.6	3.7 ± 0.6	0.003
LVET (ms)	280 ± 18	282 ± 29	NS
$LVET_c$ (ms)	9.6 ± 0.5	9 ± 0.7	0.003
PEP/LVET ratio	0.33 ± 0.07	0.40 ± 0.08	0.0002
PEP/$LVET_c$ ratio	0.011	0.013	0.008
IVRT (ms)	93 ± 16	95 ± 37	NS
$IVRT_c$ (ms)	3.2 ± 0.5	3 ± 1.1	NS
Vmax (cm/s)	113 ± 18	111 ± 15	NS
$Vmax_c$ (cm/s)	3.9 ± 0.7	3.5 ± 0.5	0.02
Acc (cm/s^2)	1300 ± 390	1180 ± 260	NS
Acc_c (cm/s^2)	45 ± 15	38 ± 9	0.007
EV (cm/s)	73 ± 17	65 ± 12	0.01
EV_c (cm/s)	2.5 ± 0.6	2.1 ± 0.4	0.001
AV (cm/s)	62 ± 19	58 ± 14	NS
AV_c (cm/s)	2.1 ± 0.7	1.8 ± 0.4	NS
E/A ratio	1.2 ± 0.5	1.1 ± 0.3	NS
E/A_c ratio	0.044 ± 0.01	0.038 ± 0.01	NS
EDT (ms)	233 ± 48	235 ± 45	NS
EDT_c (ms)	8 ± 1.5	7.5 ± 1.4	NS

Acc = mean aortic acceleration; AV = late transmitral flow velocity; c = heart rate corrected (Bazett's formula); E/A = E-wave/A-wave; EDT = E-wave deceleration time; EV = early transmitral flow velocity; IVRT = isovolumic relaxation time; LVET = left ventricular ejection time; PEP = pre-ejection period; T4 = thyroxine; Vmax = aortic peak flow velocity.

ratio. The pattern of left ventricular filling before T4 discontinuation (euthyroid phase) was normal in 17 patients, while 3 subjects showed an impaired relaxation pattern; in no case was a pseudonormal or restrictive pattern detected. After T4 withdrawal, the pattern of left ventricular filling was found to have remained unchanged in all cases except in 2 patients who had a normal pattern during the euthyroid phase and showed an impaired relaxation pattern in the hypothyroid phase.

Suga-Sagawa's index showed no significant modification, being normal in all patients during both cardiological evaluations.

Among "hemodynamic" parameters, SVR showed a significant rise, increasing in 16/20 patients and exceeding the normal limits (normal range 700-1600 dynes-s-cm^{-5})[53] in 15 cases at the second evaluation; on the contrary, the stroke index and cardiac index were significantly decreased.

Discussion

Thyroid hormones have complex and not yet well-defined effects on the cardiovascular system. It has been suggested[3,54] that the interaction between triiodothyronine (T3) and specific nuclear receptors induces the synthesis of specific peptide mediators. Their biological effects include an increase in the number and sensitivity of adrenergic receptors[55,56], a rise in the number of sarcoplasmic reticulum Ca^{2+} pumps[57] and an increased production of myosin, with a prevalence of the "fast" V1 against the "slow" V3 isoform[58]. At the cardiac level, these changes improve both myocardial contractility[2] and diastolic relaxation[59]. At the vascular level, these changes cause significant and rapid vasodilation[60], probably through prostacycline-mediated[61] and/or nitric oxide-mediated[62] mechanisms. Thyroid hormone deficiency evidently leads to opposite cardiovascular effects.

In patients with acute hypothyroidism, cardiac functional alterations have been described[8-16], but it is not clear if they are due to a reduction in myocardial contractility (myocardial hypothesis) or to peripheral hemodynamic modifications (vascular hypothesis). Only a few authors[9,14,15] have addressed this aspect, evaluating myocardial contractility by different methodological approaches: Wieshammer et al.[9] studied the variations of the Suga-Sagawa's index in 9 hypothyroid patients who underwent radionuclide ventriculography and simultaneous right heart catheterization; Williams et al.[14] performed an M-mode echocardiogram in 13 hypothyroid mice, measuring the changes in the left ventricular end-systolic pressure/diameter ratio; Bengel et al.[15] investigated 10 patients with acute hypothyroidism, using as a measure of contractility the extent of left ventricular wall thickening as assessed at magnetic resonance. To our knowledge, the present study is the first in which the influences of acute hypothyroidism on myocardial contractility were evaluated by echocardiography in humans.

Systolic function in acute hypothyroidism. In our study, the significant increase in the PEP/LVET ratio and the reduction in $Vmax_c$ and Acc_c (Table III) suggest

left ventricular systolic dysfunction[10], although we cannot exclude that the modifications in these parameters partially derive from the reduced cardiac output due to a decreased peripheral metabolic demand.

The impairment in left ventricular performance may theoretically result from variations in contractility, afterload, preload or heart rate, which are the major determinants of systolic function[27]. It is of interest that SVR increased significantly well beyond physiological limits and furthermore, LVEDV significantly decreased, probably because of the reduced circulating volume, which is known to be often associated with acute hypothyroidism[9,63]. On the contrary, no significant change was found in the Suga-Sagawa's index that remained within normal limits. Finally, heart rate was significantly decreased (Table II) but, as previously described[64], this decrease was probably not sufficient to adversely affect the contractile function (Bowditch's or *treppe* phenomenon[65]). These findings suggest that acute hypothyroidism may induce left ventricular systolic dysfunction both by increasing the afterload (peripheral vasoconstriction) and by decreasing the preload. These changes occur earlier than the impairment in myocardial contractility. The well-known[2-4] negative inotropic effects probably develop later, during chronic hypothyroidism, and this may explain their absence in our patients. These data are in agreement with the results obtained by Wieshammer et al.[9] in humans, but are discordant with those of other authors[14,15] who report a reduction in myocardial contractility. With regard to this, it should be emphasized that the data of Williams et al.[14] were obtained in an experimental model and not in humans; furthermore, in the study of Bengel et al.[15], the contractility was evaluated by measuring left ventricular systolic wall thickening at magnetic resonance which is not considered a proven methodological approach.

With regard to the absence of a significant modification in left ventricular fractional shortening and LVEF (Table II), also described by previous authors[9-11], it should be emphasized that the decrease in preload tends to reduce both the left ventricular end-diastolic as well as the end-systolic dimensions, whereas the increase in afterload leads to opposite effects. In our patients the balanced effects of the reduced preload and increased afterload altogether may have determined a reduction in both the end-diastolic and end-systolic dimensions (Table II); left ventricular fractional shortening and LVEF, equally sensitive to left ventricular diastolic and systolic dimensional variations, showed no significant modification.

Diastolic parameters in hormone withdrawal. The positive influences of thyroid hormones on myocardial diastolic relaxation are known[59]. In our experience IVRT, E/A ratio, EDT and AV showed no significant changes, whereas only EV decreased significantly (Table III); moreover, the pattern of left ventricular filling was found to have changed in only 2/20 patients. On the whole, according to the established criteria[31,32,66], these findings do not suggest a clear alteration in left ventricular diastolic function. Besides, the observed change in EV is probably due to a preload reduction rather than to a true modification in myocardial diastolic properties[12,67]. Our data regarding diastolic function are in agreement with those of Grossmann et al.[12]. On the contrary, a significant increase in IVRT has been reported by Kahaly et al.[10], who consider it as an index of impaired diastolic relaxation. However, it should be emphasized that the patients investigated by Kahaly et al. were evaluated using a different study protocol (first evaluation during the hypothyroid phase, only 5 weeks after total thyroidectomy; second evaluation during the euthyroid phase, after replacement therapy). Furthermore, it is possible that the well-known consequences of chronic thyroid hormone deficiency on diastolic relaxation[2-7] did not fully develop in our patients because of the short observation period.

Effect on cardiac mass. The observed rise in left ventricular wall thickness and mass is not likely to be due to an increase in the cellular component, since it has not been proved that acute thyroid hormone deficiency is associated with myocardial cell hypertrophy. On the contrary, it has been documented that hypothyroidism is generally associated with both an increased collagen and glycosaminoglycan synthesis as well as an increased capillary permeability, resulting in protein extravasation to the interstitium (myxedema)[68-70]. It is therefore possible that these phenomena begin to develop in the early stages of hypothyroidism and that the observed increase in myocardial mass is due to the increase in the interstitial component.

Interestingly, the left ventricular wall thickness increased significantly only at the level of the interventricular septum (not at the posterior wall), resulting in asymmetric left ventricular hypertrophy. This phenomenon, already observed by previous authors[10,71], has not yet been clearly explained.

In conclusion, in our study acute thyroid hormone deficiency was associated with echocardiographic parameter modifications suggesting left ventricular systolic dysfunction, due to both pre- and afterload changes rather than to an impaired myocardial contractility. The systolic time intervals were suggestive of acute alterations in systolic function, whereas the left ventricular fractional shortening and LVEF did not change significantly. On the whole, the parameters of left ventricular diastolic filling showed no significant change. LVM and wall thickness increased, whereas the volumes were reduced.

Further data on the left ventricular function in acute hypothyroidism may be obtainable by using more recent and sensitive methods such as pulsed tissue Doppler, already profitably employed in patients with primary overt[72] or clinically latent hypothyroidism[73].

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