Thyroid Status, Cardiac Function, and Mortality in Patients With Idiopathic Dilated Cardiomyopathy

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Context: Previous studies claiming a relationship between thyroid dysfunction and poor prognosis of heart failure (HF) had a major limitation in that they included patients with different etiologies.

Objective: With complete information of thyroid function profile from 458 consecutive patients with idiopathic dilated cardiomyopathy, we tested the hypothesis that thyroid status can independently influence mortality in patients with HF.

Design, Patients, and Outcome Measure: The original cohort consisted of 572 consecutive patients with idiopathic dilated cardiomyopathy, and 458 patients remained at the end of follow-up. All patients took thyroid function tests and other regular examinations in hospital. The risk of mortality was evaluated based on free T_3, TSH, and the whole thyroid function profile, respectively.

Results: The most frequent thyroid dysfunction was subclinical hypothyroidism (n = 41), followed by subclinical hyperthyroidism (n = 35), low-T_3 syndrome (n = 17), and hypothyroidism (n = 12). Logistic analysis showed log-TSH and free T_3 as independent predictors of exacerbated cardiac function (New York Heart Association stages III–IV vs New York Heart Association stages I–II). During the follow-up (17 $\pm$ 8 mo), 111 cumulative deaths occurred. Hypothyroidism was the strongest predictor of mortality [hazard ratio (HR) 4.189; 95% confidence interval (CI) 2.118–8.283)], followed by low-T_3 syndrome (HR 3.147; 95% CI 1.558–6.355) and subclinical hypothyroidism (HR 2.869; 95% CI 1.817–4.532). Subclinical hyperthyroidism showed no significant impact.

Conclusions: We found a clear association between thyroid dysfunction and increased risk of mortality in idiopathic dilated cardiomyopathy with HF. These results suggest that monitoring thyroid function in HF patients is necessary, and further studies on the treatment of HF with thyroid dysfunction are needed. (***J Clin Endocrinol Metab*** **100: 3210–3218, 2015)**

Alteration of thyroid hormone metabolism is frequent in patients with cardiovascular diseases (1, 2), and both clinical and experimental studies have suggested a potential negative impact of thyroid dysfunction on the prognosis of these patients (3–5). In population-based cohort studies (6–8), risk of heart failure (HF) events was increased with abnormalities of the TSH level. As for patients who had already suffered from cardiac diseases, the reduced free T_3 (fT3) level was proven to have a direct link with poor clinical outcome (4).

Changes in thyroid status have not been consistent in heterogeneous populations, and effects of different types

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Abbreviations: AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; fT3, free T_3; fT4, free T_4; HF, heart failure; HR, hazard ratio; IDCM, idiopathic dilated cardiomyopathy; LTS, low-T_3 syndrome; LV, left ventricle; LVEF, LV ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TH, thyroid hormone.

of thyroid dysfunction on clinical outcome have also varied (2, 3, 9, 10). Low-T_3 syndrome (LTS), with decreased fT3 and normal TSH, is commonly viewed as an adaptive response to serious functional impairment. However, comorbid LTS in patients with heart failure has been reported to indicate a particularly poor prognosis (4, 11–13). Subclinical hypothyroidism and subclinical hyperthyroidism are characterized by altered TSH but normal T_3/T_4 levels. With a high prevalence of up to 20% in the elderly, the potential role of subclinical thyroid dysfunction in prognosis of cardiovascular diseases has attracted much attention (6, 7, 9).

As a common final pathway in various heart diseases, HF can be caused by ischemic heart diseases, valvular diseases, cardiomyopathies, etc (14). Prior studies claiming a relationship between thyroid dysfunction and poor prognosis of HF had a major limitation of including patients with different etiologies (12, 15–17). Thus, it remains unclear whether thyroid dysfunction is associated directly with HF progression or aggravates the condition through another underlying pathophysiology. Furthermore, several efforts to identify the impact of thyroid function have focused on the changes of a single hormone instead of the overall thyroid status evaluated by full thyroid function profile mentioned above (6–8, 11, 13, 18). This lack of comprehensive evaluation has resulted in ongoing debate on whether thyroid function should be regularly tested in HF patients.

With complete information of thyroid function profile from a well-characterized population of 458 consecutive patients with HF caused by idiopathic dilated cardiomyopathy (IDCM), we tested the hypothesis that thyroid status can independently influence the mortality of HF patients and evaluated the impact of different types of thyroid dysfunction on HF prognosis.

Materials and Methods

Patients

The original cohort consists of 572 consecutive patients with IDCM who were admitted to the National Center of Cardiovascular diseases (Beijing, China) from January 2010 to October 2011. Of this cohort, 147 patients were admitted due to acute HF and others were admitted for previously known HF or other symptoms caused by chronic heart failure. The diagnosis of IDCM was based on the echocardiographic findings of a large left ventricle (LV) with end-diastolic diameter greater than 56 mm and LV dysfunction with ejection fraction less than 45%. For a differential diagnosis of etiology, regardless of whether it was first-time diagnosis or previously known, patients underwent conventional evaluation including noninvasive and, if necessary, invasive procedure according to international guidelines (19). A duration of at least 6 months without significant evidence of coronary artery disease [>50% luminal stenosis in one or more coronary artery, history of myocardial infarction (MI) or coronary revascularization, or infarct pattern in single-photon emission-computed tomography imaging] was required. Patients with other special types of cardiomyopathies were also excluded, such as hypertensive, metabolic, and alcoholic cardiomyopathies. Of all 572 patients, 194 patients had a first-time diagnosis with HF caused by IDCM, 101 patients had a previously known IDCM, and another 277 patients had a previously known HF and diagnosed as IDCM after admission into our hospital. The study complied with the Declaration of Helsinki. Informed consent was given by all patients before participation in the study, and the protocol was approved by our institutional ethics committee.

For all patients, a detailed medical history was taken with completion of physical examination, blood tests, and 12-lead electrocardiogram. HF was evaluated on the day of discharge with staging based on New York Heart Association (NYHA) functional classification. The main exclusion criteria were as follows: therapy with amiodarone, thyroid hormone (TH), glucocorticoids, and antithyroid medication within 1 month; therapy with radioiodine treatment and thyroid surgery; interventional or surgical procedures performed within the last 3 months before inception; patients who received radiographic contrast medium within 2 weeks before measurements of TH; and patients who underwent heart transplantation. Cumulatively, a total of 458 patients with IDCM were included. The present study is divided into two parts: the first part is about the relationship between TH levels and cardiac function, a cross-sectional study; the second part examines thyroid function status and mortality in IDCM, a longitudinal study. The study disposition is shown in Supplemental Figure 1.

TH measurement and definition of thyroid status

TH status was evaluated before patients were discharged, when HF symptoms could be controlled under regular oral HF medication, instead of the acute phase. Twelve-hour-fasting blood samples were drawn and the serum levels of TH and TSH were measured using a RIA (Immulite 2000; Siemens) in the Department of Nuclear Medicine of Fuwai Hospital. The reference intervals of TH and TSH in our laboratory are as follows: TSH 0.55–4.78 mIU/L; fT3 1.79–4.09 pg/mL; free T_4 (fT4) 0.8–1.88 ng/dL; total T_3 0.65–1.91 ng/mL; total T_4 4.29–12.47 μg/dL.

Patients were categorized according to their thyroid function test results as follows: 1) euthyroidism: TSH, fT3, and fT4 all within reference ranges; 2) LTS: fT3 less than 1.79 pg/mL and TSH and fT4 within the normal ranges but often borderline; 3) subclinical hyperthyroidism: TSH less than 0.55 mIU/L and normal fT3/fT4; 4) subclinical hypothyroidism: TSH greater than 4.78 mIU/L and normal fT3/fT4; 5) overt hyperthyroidism: TSH less than 0.55 mIU/L and elevated fT3 and/or fT4; and 6) overt hypothyroidism: TSH greater than 4.78 mIU/L and decreased fT3 and/or fT4.

Follow-up

Follow-up started at inception with thyroid function testing. We contacted patients by phone every 6 months according to our follow-up schedule. Patients' medical records would be examined if they were readmitted into our hospital. For those who were rehospitalized elsewhere, it was necessary to forward copies of medical records to the study group to get exact information

about medication and etiology. Mean duration of follow-up was 17 months (1–28 mo). End points of the study were cardiac death and all-cause death. Cardiac death was defined by the occurrence of sudden death without an autopsy, cardiac arrest, or death attributable to significant arrhythmia, progressive heart failure, or newly developed MI. All-cause deaths were considered as all deaths from any natural cause. Deaths caused by accidents were regarded as censored data (follow-up censored at the time of death). For patients lost to follow-up, they were censored upon last contact with them.

Statistical analysis

Statistical analysis was assessed with SPSS statistical package for Windows 18.0. Parametric variables were expressed as mean ± SD, and categorical variables were given as number and percentage. To optimize the statistical analysis model, variables with skewed distribution were transformed to their natural logarithm. Differences between groups were evaluated by a one-way ANOVA or a χ^2 test. To adjust for the traditional risk factors, a multivariable linear regression analysis was performed while evaluating the relationship between left ventricular ejection fraction (LVEF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and thyroid function parameters. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of each thyroid status compared with the euthyroidism group, adjusting for other potential confounders. Kaplan-Meier analysis was used to study cumulative survival of different groups. A value of $P < .05$ was considered statistically significant.

Results

Baseline characteristics of the study population

Baseline characteristics of the study population are shown in Table 1. Patients with IDCM were divided into six groups according to their thyroid status as mentioned above (euthyroidism, subclinical hyperthyroidism, LTS, subclinical hypothyroidism, overt hyperthyroidism, and overt hypothyroidism). We excluded patients with overt hyperthyroidism (n = 3) for their use of antithyroid medication and performed statistics with the other five groups. The most frequent thyroid dysfunction was subclinical hypothyroidism (n = 41, 9%), followed by subclinical hyperthyroidism (n = 35, 7%), LTS (n = 17, 4%), and overt hypothyroidism (n = 12, 3%). Follow-up duration

Table 1. Baseline Characteristics of Study Population According to Thyroid Status

	Total (n = 458)	Euthyroid (n = 353)	Subclinical Hyperthyroidism (n = 35)	LTS (n = 17)	Subclinical Hypothyroidism (n = 41)	Overt Hypothyroidism (n = 12)
Age, y	51 (14)	51 (14)	52 (10)	52 (13)	48 (14)	49 (15)
Female, n, %	131 (29)	101 (29)	7 (20)[a]	5 (29)	12 (29)	6 (50)[a]
Follow-up, mo	17 (8)	18 (7)	18 (8)	13 (10)[a]	13 (9)[a]	10 (10)[a]
Blood pressure						
Systolic, mm Hg	111 (17)	112 (17)	111 (20)	104 (18)	107 (16)	103 (16)
Diastolic, mm Hg	70 (12)	71 (12)	70 (12)	64 (12)	70 (11)	71 (12)
NT-proBNP	2494 (1821)	2319 (1749)	2317 (1703)	3896 (2369)[a]	3128 (1835)[a]	3942 (1679)[a]
LVEF	32 (10)	33 (10)	32 (7)	31 (10)[a]	28 (8)[a]	28 (7)[a]
Smoking, n, %		162 (46)	19 (54)	10 (58.8)	17 (41.5)	3 (25)[a]
Comorbidities, n, %[b]						
Atrial fibrillation	75 (16)	57 (16)	3 (9)[a]	3 (18)	9 (22)	3 (25)
Diabetes mellitus	85 (19)	61 (17)	10 (29)	6 (35.3)	8 (19.5)	0 (0)[a]
Dyslipidemia	168 (37)	133 (38)	8 (23)	6 (35)	15 (37)	6 (50)
Anemia	77 (17)	52 (15)	5 (14)	3 (18)	11 (27)	6 (50)[a]
Renal dysfunction	111 (24)	84 (24)	5 (14)	5 (29)	12 (29)	5 (42)[a]
Medications, n, %						
ACEi/ARB	285 (62)	222 (63)	24 (69)	7 (41.2)	27 (65.9)	5 (41.7)
β-Blocker	379 (83)	292 (83)	32 (91)	12 (70.6)	34 (82.9)	9 (75)
Aldosterone antagonists	354 (77)	282 (80)	27 (77)	12 (70.6)	27 (65.9)	6 (50)
Diuretics (loop or thiazides)	384 (84)	296 (84)	33 (94)	13 (76)	33 (80)	9 (75)
NYHA class, n, %						
I–II	105 (23)	92 (26)	7 (20)	2 (12)	2 (5)	2 (17)
III–IV	353 (77)	261 (74)	28 (80)	15 (88)	39 (95)	10 (83)
TSH, mIU/L	3.37 (7.15)	2.00 (1.06)	0.36 (0.16)[a]	1.74 (1.33)	8.59 (4.91)[a]	36.75 (24.24)[a]
fT3, pg/mL	2.70 (0.57)	2.80 (0.47)	2.72 (0.48)	1.45 (0.30)[a]	2.72 (0.53)	1.48 (0.25)[a]
fT4, ng/dL	1.32 (0.29)	1.35 (0.26)	1.39 (0.29)	0.99 (0.36)[a]	1.34 (0.28)	0.71 (0.16)[a]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. The data are presented as n (percentage) or mean (SD).

[a] $P < .05$ for comparison with euthyroid group.

[b] Comorbidities included the following: anemia, hemoglobin less than 12 g/dL in women, less than 13 g/dL in men; renal dysfunction, estimated glomerular filtration rate less than 60 ml/min per 1.73 m^2.

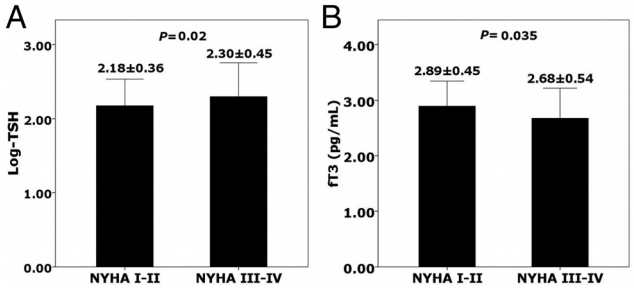


Figure 1. Comparison of log-TSH (A) and fT3 (B) in patients with NYHA I–II and NYHA III–IV.

for the three types of hypothyroidism was much shorter than that in the euthyroid group. Slight, but significant, differences were also detected for LVEF, NT-proBNP, TSH, fT3, and fT4. Patients with LTS, in which low fT3 level was present, had higher levels of NT-proBNP. A slight, but significantly decreasing, trend could be detected with respect to LVEF across the listed thyroid status categories. No significant difference was found with regard to age and blood pressure (BP).

The relationship between thyroid hormone levels and cardiac function

To achieve a normal distribution, we applied logarithmic transformation to TSH values, thus converting it into log-TSH.

When we compared TH levels in patients with different NYHA classes, lower fT3 and higher log-TSH were found in NYHA III–IV patients compared with those with NYHA I–II ($P = .035$ and $P = .02$, respectively; shown in Figure 1). However, no difference was detected between NYHA classes in terms of fT4. After adjusting for potential confounders (age, gender, smoking status, BP, fasting blood glucose, total cholesterol), and low-density lipoprotein), fT3 showed a significant correlation with LVEF ($r = 0.244$, $P < .001$), NT-proBNP ($r = -0.358$, $P < .001$), and systolic BP ($r = 0.290$, $P < .001$). On the other hand, fT4 and TSH had no significant relationship with LVEF, NT-proBNP, and BP. Additionally, a univariate and multivariate logistic analysis showed that log-TSH and fT3 were significantly associated with an exacerbated cardiac function (NYHA III–IV vs NYHA I–II; Table 2).

Thyroid status and mortality

During follow-up (17 ± 8 mo), there were 111 cumulative deaths, of which 87 were determined as cardiac, whereas the others were due to stroke (n = 5), malignancy (n = 8), or other known or unknown reasons (n = 11). To evaluate the prognostic value of thyroid function parameters for survival time, we performed a Kaplan-Meier plot and a Cox proportional regression survival analysis based on fT3, TSH, and overall thyroid function profile.

Table 2. Predictors of Exacerbated Cardiac Function (NYHA III–IV vs NYHA I–II) by Logistic Regression

Variables	Odds Ratio	95% CI	*P* Value
Univariate regression			
Log-TSH	1.975	1.161–3.357	.012
fT3	0.447	0.289–0.691	<.001
Renal dysfunction	2.463	1.339–4.529	.004
Age	1.011	0.995–1.026	.177
Male	0.998	0.616–1.616	.994
Diabetes mellitus	0.886	0.551–1.535	.665
Dyslipidemia	0.713	0.457–1.112	.136
Anemia	1.278	0.694–2.356	.431
Multivariate regression[a]			
Log-TSH	2.189	1.217–3.938	.009
fT3	0.483	0.301–0.775	.003
Renal dysfunction	2.045	1.077–3.882	.029

Abbreviations are listed in Table 1.

[a] In the multivariate analysis, only variables found to be significant were shown.

Survival analysis based on fT3 level

Taking the lower limit of the reference interval of fT3 (1.79 pg/mL) as the cutoff, patients are divided into a low-T3 level group (n = 29) and a normal-T3 level group (n = 429) for Kaplan-Meier curves (Figure 2). In a survival analysis, the potential risk factors for HF listed in Table 1 were put into the model. Univariate model showed a low fT3 as a strong predictor of cumulative death (HR 3.18, 95% CI 1.96–5.16, $P < .001$; Table 3). By multivariate analysis, low fT3 was still the strongest predictor for worse outcome, whereas anemia and age were also independent predictors. Although sex is considered an important impact factor in HF mortality, it did not show a significant predictive effect in a univariate analysis or an effect on the result after stratifying the multivariate analysis for it.

Survival analysis based on TSH level

Of all 458 patients, 385 patients had normal TSH, 53 patients had elevated TSH (>4.78 μIU/L), and 20 patients had suppressed TSH (<0.55 μIU/L). Kaplan-Meier curves according to the cutoff values of TSH are shown in Figure 2. In a univariate analysis, suppressed TSH showed no significant impact on prognosis (HR 0.833, 95% CI 0.406–1.711, $P = .619$; Table 3), whereas worse outcome was observed in patients with elevated TSH (HR 3.315, 95% CI 2.242–4.903, $P < .001$; Table 3). By multivariate analysis, elevated TSH was still the strongest predictor, with age and anemia also showing slight but significant correlation with mortality. Again, sex did not affect survival.

Survival analysis based on the complete thyroid function profile

As mentioned above, thyroid status, which included complete thyroid profile information, was put into the

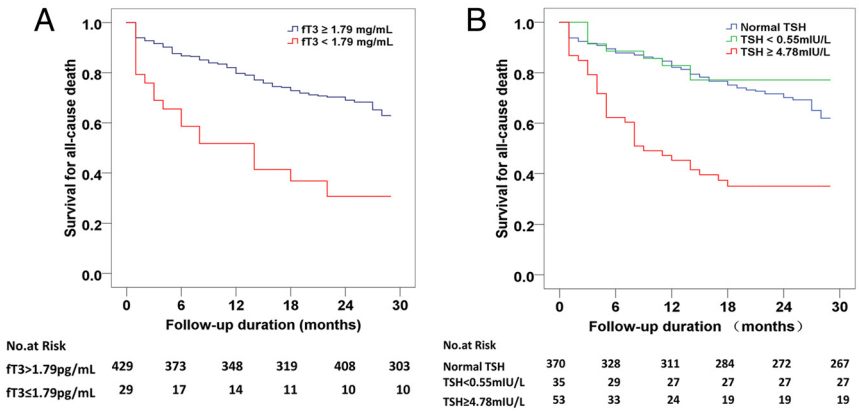


Figure 2. Kaplan-Meier survival curves according to the cutoff values of fT3 (A) and TSH (B) in patients with idiopathic dilated cardiomyopathy.

survival analysis. Kaplan-Meier survival curves for cumulative death in different thyroid dysfunction subgroups are shown in Figure 3. With the euthyroid group as the reference, significant differences in mortality were observed among different subgroups (log-rank test, $P = .006$). In a univariate analysis, except for subclinical hyperthyroidism, all the other thyroid dysfunction groups showed negative impact on the survival (Table 3). By a multivariate analysis with the risk factors mentioned above, hypothyroidism was the strongest predictor of mortality (HR 4.189; 95% CI 2.118–8.283), followed by LTS (HR 3.147; 95% CI 1.558–6.355) and subclinical hypothyroidism (HR 2.869; 95% CI 1.817–4.532). Again, subclinical hyperthyroidism showed no impact (Table 3).

Survival analysis considering cardiac death

As we have mentioned, of all the 111 cumulative deaths, 87 were determined as cardiac. The frequency of cardiac death was much higher in the groups with overt hypothyroidism, subclinical hypothyroidism, and LTS than those with subclinical hyperthyroidism and euthyroidism (58.3%, 48.8%, 41.2% vs 20.0%, 22.7%). In the Cox survival analysis with euthyroidism as the reference, overt hypothyroidism, subclinical hypothyroidism, and LTS were predictors for cardiac death in a univariate model (Supplemental Table 1). In a multivariate model, overt hypothyroidism was still the strongest predictor of cardiac death (HR 3.736; 95% CI 1.681–8.302). and an approximately 2-fold increased risk of cardiac death was displayed in groups with subclinical hypothyroidism (HR 2.671; 95% CI 1.624–4.394) and LTS (HR 2.723; 95% CI 1.245–5.956). Subclinical hyperthyroidism showed no significant impact.

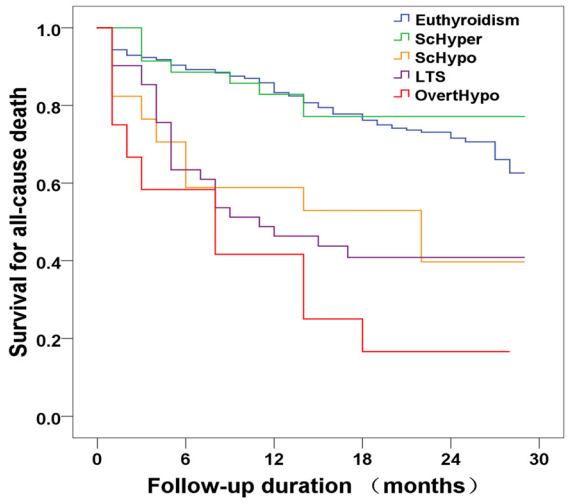
Table 3. Hazard Ratios for All-Cause Mortality in Univariate and Multivariate Survival Analysis

Variables	Hazard Ratio	95% CI	*P* Value
Analysis based on fT3			
Model 1[a]			
Low T_3	3.181	1.960–5.163	<.001
Model 2[b]			
Low T_3	3.160	1.921–5.199	<.001
Analysis based on TSH			
Model 1[a]			
Elevated TSH	3.315	2.242–4.903	<.001
Suppressed TSH	0.833	0.406–1.711	.619
Model 2[b]			
Elevated TSH	2.828	1.902–4.206	<.001
Suppressed TSH	0.883	0.426–1.827	.737
Analysis based on the whole thyroid function profile			
Model 1[a]			
Subclinical hyperthyroidism	0.881	0.428–1.815	.732
LTS	2.634	1.328–5.224	.006
Subclinical hypothyroidism	3.049	1.942–4.788	<.001
Overt hypothyroidism	5.565	2.885–10.733	<.001
Model 2[b]			
Subclinical hyperthyroidism	0.973	0.469–2.018	.941
LTS	3.147	1.558–6.355	.001
Subclinical hypothyroidism	2.869	1.817–4.532	<.001
Overt hypothyroidism	4.189	2.118–8.283	<.001

Elevated TSH was defined as TSH greater than 4.78 μIU/L, and suppressed TSH was defined as TSH less than 0.55 μIU/L. Cox survival analysis was taken with the euthyroid group as the reference.

[a] Model 1 was unadjusted.

[b] Model 2 was adjusted for age, sex, anemia, renal dysfunction, dyslipidemia, smoking, and diabetes mellitus.



No.at Risk						
Euthyroidism	353	318	302	275	264	259
ScHyper	35	29	27	27	27	27
LTS	17	10	9	9	8	8
ScHypo	41	26	19	17	17	17
OvertHypo	12	7	5	2	2	2

Figure 3. Kaplan-Meier plot showing survival curves stratified by thyroid function subgroup (euthyroidism served as reference). OvertHypo, overt hypothyroidism; ScHyper, subclinical hyperthyroidism; ScHypo, subclinical hypothyroidism.

Discussion

In the present study consisting of 458 patients with IDCM, TH levels are correlated with cardiac function and thyroid dysfunction showed predicting value for negative prognosis. Lower level of fT3 and higher level of TSH were observed in the NYHA III-IV group. By logistic regression analysis, we demonstrated a prognostic value of fT3 and log-TSH for exacerbated cardiac function. Both low fT3 and elevated TSH were identified as risk factors for mortality in HF. Based on complete information of thyroid function profile, we found LTS, subclinical hypothyroidism, and overt hypothyroidism as the predictors of cumulative deaths, whereas subclinical hyperthyroidism had no impact. The down-regulation of thyroid function occurs frequently in cardiac diseases and has been traditionally regarded as a common adaptive response to lower metabolic consumption. However, important changes in cardiac structure and function have been reported in our previous animal experiment (5) and clinical studies involving patients with overt and subclinical hypothyroidism (11, 20–23).

The link between TH levels and cardiac function, as expressed by LVEF and NT-proBNP, was also addressed by several observational studies (10, 24, 25), but the complex relationship between thyroid status and the prognosis of HF has not been clear. Kozdag et al (12) reported that the fT3 to fT4 ratio less than 1.7 was a predictor of mortality in 111 patients with dilated cardiomyopathy, but the authors did not investigate the differences among subgroups of thyroid dysfunction. Also, the cohort consists of both ischemic and nonischemic etiology, thus rendering an important confounder. Iervasi et al described an increased risk of mortality in patients with low fT3 among 573 Italians with different cardiac diseases, whereas in the multivariate analysis, dilated cardiomyopathy, independent of THs, was a predictor of cumulative deaths (4). Other studies claiming a relationship between thyroid dysfunction and risk of mortality in HF were also limited by either study size or heterogeneity of etiology (10, 13, 16, 22, 26). In the present study, we took a well-characterized cohort to overcome the shortcomings mentioned above.

In this particular population, the percentage of LTS (3.7%) was much lower than that in patients with cardiovascular diseases of unselected origin (3, 4). Iervasi et al (3, 4) reported that the prevalence of LTS could be 30%, whereas that of subclinical hyperthyroidism is only 3.14% in populations containing different kinds of cardiovascular diseases. However, a study focusing on HF and thyroid function reported that the proportions of LTS and subclinical hyperthyroidism are 1.75% and 9.27%, respectively (27). This proportion is similar to that in our study (3.71% and 7.64%, respectively). Furthermore, we compared the present study with our previous study focusing on acute MI (28). It also showed that the proportions in acute MI were different from those in IDCM. Based on these previous studies, we think that the proportions of thyroid dysfunction could change with different types of cardiovascular diseases.

There are several interesting findings in our baseline data (Table 1). The first one is that the prevalence of current smokers was significantly lower in the hypothyroid group, which was also observed in a large-population-based study reported by Asvold et al (29). This suggests that smoking may have reversible effects on thyroid function. We also found that anemia and renal dysfunction were much more prevalent in the hypothyroid groups. In our previous review (30), we concluded that renal dysfunction was a strong independent predictor of increased risk of anemia in HF, so it is not difficult to understand the simultaneous high prevalence of these two diseases. However, further study is needed to explore whether renal dysfunction, as an independent predictor for exacerbated cardiac function (Table 2), could impact the thyroid status in HF. The most surprising and unexpected finding in baseline is that the prevalence of atrial fibrillation (AF) was lower among those with subclinical hyperthyroidism. After reviewing other studies carefully, we found that the usage of β-blocker in our cohort was more frequent than other cohorts (80% vs 44%) (3). We believe the difference may explain this situation because high usage of β-block-

ers can blunt the potential pathophysiological effects of subclinical hyperthyroidism, such as increased heart rate and adrenergic overstimulation, thus reducing the prevalence of AF induced by subclinical hyperthyroidism. Additionally, it has been revealed recently that both hypothyroidism and hyperthyroidism can increase AF inducibility (31). These findings are different from our general view that only hyperthyroidism is associated with AF and may explain the relatively high prevalence of AF in the hypothyroid group: because the mechanisms of AF induced by hypo- or hyperthyroid status were dramatically different, high usage of β-blockers were not protective of AF induced by hypothyroidism.

In the present study, we found that not only the prevalence of AF but also the mortality in subclinical hyperthyroidism was lower than expected. Recently pooled data of six prospective cohorts were analyzed in an attempt to evaluate the association between subclinical thyroid dysfunction and HF events (6). Increased risk was observed in patients with subclinical hyperthyroidism. In another study enrolling 3121 cardiac patients, subclinical hyperthyroidism was reported as a predictor of mortality (3). These results are not comparable with our findings for four reasons: first, participants in a population-based study mostly were at low risk of cardiovascular diseases; second, the predictive value of subclinical hyperthyroidism in the second study disappeared when considering nonischemic subgroup analysis, indicating that ischemic etiology, which had been ruled out of our study, could be a confounder; third, as mentioned above, usage of β-blockers in our cohort was more frequent than the Italian cohort (80% vs 44%), thus blunting the potential pathophysiological effects of subclinical hyperthyroidism, such as increased heart rate, adrenergic overstimulation, etc (32); and fourth, amiodarone can induce hyperthyroidism (33, 34) and the exclusion of amiodarone administration in our cohort might contribute to the lower incidence of subclinical hyperthyroidism.

LTS and overt hypothyroidism, both with low serum TH levels, were associated with negative prognosis. Biologically active T_3 influences several important genes encoding for structural and functional proteins of the myocardium and also has extensive nongenomic actions on ion pumps and enzymes (1, 2, 15). In our previous animal experiment with a hypothyroid rat model, we observed that expression of sarcoendoplasmic reticulum Ca^{2+}-ATPase-2a and α-myosin heavy chain were reduced, whereas phospholamban and β-myosin heavy chain were increased with decreased levels of THs. These are typical changes of myocardial function proteins in the HF process (5).

Noteworthy, our study showed subclinical hypothyroidism as an independent predictor of mortality. Although population-based studies have suggested that subclinical hypothyroidism is an important risk factor for HF events, its role in advanced HF remained controversial. Frey et al (16) recently reported that subclinical thyroid dysfunction had no prognostic impact in a German cohort of 758 HF patients, whereas Silva-Tinoco et al (35) found that patients with subclinical hypothyroidism had more hospitalization and were associated with poor prognostic factors. The much lower prevalence of thyroid dysfunction in the German cohort (13%) compared with the study by Silva-Tinoco et al (27%) and our present study (23%) might explain why predictivity of subclinical hypothyroidism was not detected.

The complex relationship between hypothyroidism and cardiac diseases has been a chicken-egg debate for a long time. In 2005 we first reported that low thyroid function could lead to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction, resembling the pathological changes in IDCM (5). Although this causal relationship may not apply in the clinical setting much of the time, because hypothyroidism is usually not detected until after HF, it suggests that hypothyroidism plays an important role in the progression of IDCM. Importantly, animal studies suggest cardiac tissue hypothyroidism may be present in heart diseases in the background of a normal serum hormone profile (36–38). Because such data are not available from patients with heart diseases, it is not yet clear how extensive or early cardiac tissue hypothyroidism occurs in cardiac patients. More work in patients is clearly needed to better understand the interaction between thyroid dysfunction and LV function. Hopefully more investigators will exploit the potential of obtaining tissue samples before and after from left ventricular assist device transplant patients to better understand the role of thyroid dysfunction in heart failure, as in the recent study by Adamopoulos et al (39).

Despite strong evidence supporting our results, this study has several limitations. The first one is the unavoidable limitation of trying to classify thyroid function in seriously ill patients due to the bidirectional relationship between HF and thyroid hormone levels. Because exacerbated HF (n = 147) could cause nonthyroidal illness, thyroid dysfunction detected during hospitalization might be transient. In other words, TH levels could change over time, especially the most sensitive one: TSH. This might explain the relatively normal fT4/fT3 levels in subclinical hyperthyroid group. Because multiple thyroid tests were available in only 20% of the initially evaluated patients, the present study could not resolve this ambiguity. The second limitation is that only drugs administrated at the time of inception or shortly before were reported, so we

cannot exclude that some patients may have been treated earlier with amiodarone, with a potential long-lasting effect on thyroid function. Finally, we did not have access to the medical records of patients who underwent heart transplant and had to exclude them from the present study. However, strengths of the present study include the well-characterized IDCM cohort with a high level of adherence to recommended HF drugs, complete information of thyroid function profile, and the exclusion of drug administration that might affect thyroid profile.

In conclusion, we found a clear association between an increased risk of mortality in HF caused by IDCM and thyroid dysfunction (LTS, subclinical hypothyroidism, and overt hypothyroidism). Monitoring thyroid function is necessary for patients with IDCM, and further study is warranted to investigate whether reversing low thyroid function can benefit these patients.

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