Nonthyroidal Illness Syndrome in Cardiac Illness Involves Elevated Concentrations of 3,5-Diiodothyronine and Correlates with Atrial Remodeling

Johannes W. Dietrich^a Patrick Müller^{b, d} Fabian Schiedat^b Markus Schlömacher^c
Justus Strauch^c Apostolos Chatzitomaris^a Harald H. Klein^a Andreas Mügge^b
Josef Köhrle^e Eddy Rijntjes^e Ina Lehmphul^e

^aDepartment of Endocrinology and Diabetes, Medical Hospital I, ^bDepartment of Cardiology and Angiology, Medical Hospital II, and ^cDepartment of Cardiac Surgery, Bergmannsheil University Hospitals, Ruhr University of Bochum, Bochum, ^dHeart Center Bad Neustadt, Clinic for Interventional Electrophysiology, Bad Neustadt an der Saale, and ^eInstitut für Experimentelle Endokrinologie, Charité-Universitätsmedizin Berlin, Berlin, Germany

Key Words

3,5-Diiodothyronine · Reverse triiodothyronine ·
Nonthyroidal illness syndrome · TACITUS · Atrial fibrillation ·
Thyroid hormone

Abstract

Background: Although hyperthyroidism predisposes to atrial fibrillation, previous trials have suggested decreased triiodothyronine (T₃) concentrations to be associated with post-operative atrial fibrillation (POAF). Therapy with thyroid hormones (TH), however, did not reduce the risk of POAF. This study reevaluates the relation between thyroid hormone status, atrial electromechanical function and POAF. **Methods:** Thirty-nine patients with sinus rhythm and no history of atrial fibrillation or thyroid disease undergoing cardiac surgery were prospectively enrolled. Serum concentrations of thyrotropin, free (F) and total (T) thyroxine (T₄) and T₃, reverse (r)T₃, 3-iodothyronamine (3-T₁AM) and 3,5-diiodothyronine (3,5-T₂) were measured preoperatively, complemented by evaluation of echocardiographic and electrophysiological parameters of cardiac function. Holter-ECG and telemetry were used to screen for POAF for 10 days following cardiac surgery.

Results: Seven of 17 patients who developed POAF demonstrated nonthyroidal illness syndrome (NTIS; defined as low T₃ and/or low T₄ syndrome), compared to 2 of 22 (p < 0.05) patients who maintained sinus rhythm. In patients with POAF, serum FT₃ concentrations were significantly decreased, but still within their reference ranges. 3,5-T₂ concentrations directly correlated with rT₃ concentrations and inversely correlated with FT₃ concentrations. Furthermore, 3,5-T₂ concentrations were significantly elevated in patients with NTIS and in subjects who eventually developed POAF. In multivariable logistic regression FT₃, 3,5-T₂, total atrial conduction time, left atrial volume index and Fas ligand were independent predictors of POAF. **Conclusion:** This study confirms reduced FT₃ concentrations in patients with POAF and is the first to report on elevated 3,5-T₂ concentrations in cardiac NTIS. The pathogenesis of NTIS therefore seems to involve more differentiated allostatic mechanisms.

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J.W.D. and P.M. contributed equally to this work.

Introduction

More than 70% of critically ill patients develop a constellation that is marked by reduced concentrations of total (T) and free (F) 3,3',5-triiodo-L-thyronine (T₃, low T₃ syndrome), impaired binding of thyroid hormones (TH) to their plasma proteins and, especially in chronic illness, by thyrotropic adaptation, i.e. diminished thyrotropin (TSH)-release despite decreased or low normal free thyroxine (FT₄) concentrations [1, 2]. This condition is described as nonthyroidal illness syndrome (NTIS), euthyroid sick syndrome or TACITUS (thyroid allostasis in critical illness, tumors, uremia and starvation) and is accompanied by increased mortality and morbidity [3, 4]. Several trials have demonstrated improved surrogate parameters after substitution therapy with T₃ in NTIS [5, 6]. It could not be proven, however, that therapy with T₄ or T₃ ameliorates the overall outcome of affected patients [7, 8]. Today it is still controversial as to whether NTIS represents a form of central hypothyroidism requiring treatment, whether it is simply associated with or results from severe illness, or if it represents an allostatic mechanism that is beneficial by reducing the demand for oxygen, energy and glutathione and by preventing the development of thyroid storm [3, 9–11]. Results from clinical trials and animal experiments suggest possible favorable effects of TACITUS to be restricted to its acute phase, while chronic NTIS could represent a maladaptive response [1]. Of note, up to a third of noncritically ill hospitalized patients may also demonstrate milder forms of NTIS [12].

Iodothyronines have strong effects on cardiac function, including heart rhythm [13–15]. Congestive heart failure and atrial fibrillation (AF) are classical consequences of thyrotoxicosis included in two scoring systems for estimating the probability of thyroid storm [16]. Even subclinical hyperthyroidism is associated with increased risk for AF [17] and a prolonged total atrial conduction time (TACT) [18], an independent predictor of AF [19].

However, AF may also occur after cardiac surgery. Postoperative AF (POAF) contributes significantly to increased morbidity, mortality and costs, and frequencies of up to 60% have been reported [20–22].

The exact mechanism leading to new-onset POAF remains uncertain. In addition to surgery-associated factors (like inflammation, oxidative stress and increased sympathetic drive), preexisting factors, including ion channel alterations, interstitial impairments, myocardial apoptosis and fibrosis, may provide pathophysiological substrates of POAF [19, 23, 24].

Despite the well-known arrhythmogenic potential of iodothyronines, their role for the pathogenesis of POAF is less well understood. Two trials unexpectedly revealed low preoperative FT₃ concentrations and subclinical hypothyroidism to predict POAF [25, 26]. However, experimental substitution therapy with TH in order to prevent POAF resulted in conflicting results [27].

In this prospective study we assessed the frequency of new-onset POAF in a series of patients who underwent cardiac surgery. TACT, concentrations of B-type natriuretic peptide (BNP), serum apoptosis markers and iodothyronine metabolites were measured preoperatively in all patients. We hypothesized that preoperative markers for thyroid status predict the risk for development of POAF.

Methods

Design of the Investigation and Patient Population

This cohort covers a subset of the population of a previous trial that evaluated the prognostic value of TACT for the onset of POAF [24]. After approval by the local institutional ethics committee on human study of the Ruhr University of Bochum (Bochum, Germany) we prospectively enrolled 39 noncritically ill patients who underwent cardiac surgery (coronary artery bypass graft, CABG, and/or aortic valve replacement, AVR).

The inclusion criteria were: (1) preoperative sinus rhythm (SR), and (2) elective CABG and/or AVR. The exclusion criteria were: (1) any history of AF or atrial flutter; (2) moderate or severe mitral valve disease; (3) prior cardiac surgery; (4) poor echocardiographic imaging quality; (5) any history of thyroid disease; (6) concentrations of TSH or FT₄ outside their respective reference ranges; (7) an insufficient amount of preoperative serum aliquots, and (8) any antiarrhythmic medication pre- or perioperatively with the exception of β -blocking agents and verapamil. All patients had received iodinated radiocontrast agents in coronary angiography 3–5 weeks preoperatively.

The main outcome measure of the investigation was serum concentration of FT₃ in patients with and without POAF. Secondary outcome measures were concentrations of other hormones involved in thyroid homeostasis (total and free T₄, TSH), total T₃ and nonclassical TH [3,5-diiodothyronine (3,5-T₂), 3,3',5'-triiodothyronine (reverse, rT₃) and 3-iodothyronamine (3-T₁AM)]. In order to get exploratory information on pathophysiological processes, derived parameters of thyroid homeostasis were calculated, including thyroid's secretory capacity (SPINA-GT), total deiodinase activity (SPINA-GD), FT₃/rT₃, 3,5-T₂/FT₃ and 3,5-T₂/rT₃ ratios [3, 28–32] (see online suppl. methods for a detailed description; see www.karger.com/doi/10.1159/000381543 for all online suppl. material). Concentrations of serum BNP and Fas ligand were determined to serve as markers for myocardial remodeling and apoptosis.

Detection of POAF was based on documentation of AF episodes by continuous telemetry for the first 3 postoperative days followed by 7 days via Holter-ECG monitoring. POAF was defined as any episode of AF lasting 30 s or longer.

Table 1. Clinical characteristics of the study population

	Without POAF (n = 22)	With POAF (n = 17)	p value	Without NTIS (n = 30)	With NTIS (n = 9)	p value
Age, years	64.5±2.4	69.5±2.6	n.s.	64.8±2.2	72.9±1.5	<0.01*
Sex			n.s.			n.s.
Female	3	4		7	0	
Male	19	13		23	9	
Body surface area, m ²	2.0±0.0	2.0±0.1	n.s.	2.0±0.0	2.1±0.1	n.s.
Body mass index	28.9±0.7	28.7±1.4	n.s.	28.7±0.8	27.7±1.8	n.s.
Operative parameters						
CABG	17	12	n.s.	22	7	n.s.
AVR	5	3	n.s.	7	1	n.s.
CABG and AVR	0	2	n.s.	1	1	n.s.
Duration of surgery, min	211±20	192±23	n.s.	203±16	209±63	n.s.
Aortic cross clamp time, min	63±9	97±19	n.s.	79±12	65±14	n.s.

Data are reported as n or mean ± SEM. * Significant after correction for multiple testing. See online supplementary table 1 for additional, nonsignificant parameters. n.s. = Not significant.

A single expert cardiologist blinded to the results of echocardiography and laboratory investigations diagnosed POAF and performed transthoracic echocardiography in all patients 1 day before surgery. All patients provided written informed consent.

Preoperative Echocardiography and TACT

Transthoracic echocardiography was performed 1 day before surgery using a GE Vivid 7 echocardiograph device according to standards of the American Society of Echocardiography. Maximal and minimal left-atrial volume (LAV_{max} and LAV_{min}) were measured from the apical 4-chamber view in the ventricular end-systole just before opening or after closure of the mitral valve, respectively, via the single-plane area-length method. Subsequently, LAV_{max} was indexed for body surface area to provide the left-atrial volume index (LAVI). Left atrial ejection fraction (LA-EF) was calculated as:

$$LA-EF = \frac{LAV_{max} - LAV_{min}}{LAV_{max}} \times 100\%.$$

In order to estimate the TACT, the tissue Doppler imaging (PA-TDI) interval was assessed twice per patient by measuring the time interval between the onset of the P wave in lead II of the ECG to the peak A' wave of the lateral atrial wall on tissue Doppler tracing. Both results were averaged to calculate the mean PA-TDI interval. See the online supplementary methods section for information on additional cardiovascular parameters.

Blood Sampling and Laboratory Analysis

Fasting blood samples were obtained in the morning before the intake of medication 1 day presurgery. After centrifugation (2,800 rpm, 20 min), serum aliquots were stored at -80°C until analyzed.

Concentrations of TSH, FT₄, TT₄, FT₃, TT₃ and BNP were determined with a fully automated chemiluminescence-based system (DxI800, Beckman-Coulter, Krefeld, Germany). Serum concentrations of Fas ligand (Fas) and TRAIL, both members of the

tumor necrosis factor superfamily, were measured using commercially available ELISA kits (R&D Systems, Minneapolis, Minn., USA). Inter- and intra-assay coefficients of variation (CV) were <10 and <5%, respectively.

The 3,5-T₂ concentrations were detected in a single batch of assays with a novel antibody-based chemiluminescence immunoassay with a working range between 0.2 and 10 nmol/l (detection limit 0.2 nM; intra-assay variation <10%, interassay variation <13%), as recently described [33]. The method to quantify 3-T₁AM concentrations was modified from a previously published immunoassay [34] (detection limit 0.93 nM; intra- and interassay variation <13%). rT₃ concentrations were determined with a commercially available RIA (ZenTech RIAZEN Reverse T₃; Radim, Freiburg, Germany; detection limit 0.014 nM, intra- and interassay variation <9%) according to the manufacturer's instructions. The antibody-bound radiolabelled tracer was counted in a gamma counter (1277 Gammamaster, LKB Wallac, Turku, Finland). Intra-assay CV was 8.7%. Analyses were performed in duplicates. Results were excluded from further analysis if the CV exceeded 20%. Patients were classified as presenting NTIS if they exhibited low-T₃ syndrome or low-T₄ syndrome, i.e. if concentrations of FT₃, TT₃ or TT₄ were reduced below their respective reference ranges in the absence of thyroid disease.

Statistical Analysis

Depending on the class of analyzed data and possible direction of causality, distributions were compared with multivariable logistic regression, two-sample t test, Wilcoxon's rank sum test or χ^2 test. For multivariable logistic regression, parameters were selected that differed between patients with and without POAF in an a priori t test with p < 0.1. Predictors that gave reason to expect multicollinearity (total TH and parameters calculated from TH) were not included in the logistic regression. For each predictor the variance inflation factor (VIF) was calculated to deliver a measure for possible multicollinearity.

Table 2. Echocardiographic, procedural characteristics and results of preoperative blood samples in the study population comparing subjects with and without POAF and with and without NTIS

Parameter (reference range [51–53])	Without POAF (n = 22)	POAF (n = 17)	p value	Without NTIS (n = 30)	NTIS (n = 9)	p value
Preoperative transthoracic echocardiogram						
LA-EF, %	53.2±3.6	45.3±2.2	n.s.	48.9±2.9	52.8±2.7	n.s.
LAVI, ml/m ²	25.9±2.3	33.2±3.0	n.s.	26.6±2.1	37.4±2.9	<0.01*
PA-TDI interval (<152), ms	120.3±2.3	152.5±3.6	<1e-7*	130.9±3.5	145.7±7.3	n.s.
Preoperative laboratory parameters						
Fas, ng/l	66.2±3.6	90±7.0	<0.05	76.3±5.4	74.7±5.2	n.s.
TSH (0.4–4.3), mIU/l	1.10±0.13	1.46±0.19	n.s.	1.23±0.14	1.35±0.22	n.s.
FT ₄ (7.6–16.1), pmol/l	11.7±0.4	11.7±0.3	n.s.	11.5±0.2	12.3±0.8	n.s.
FT ₃ (4.0–5.7), pmol/l	5.0±0.2	4.4±0.1	<0.01*	5.0±0.1	3.9±0.1	<1e-5*
TT ₄ (64–154), nmol/l	105±3	104±4	n.s.	101±3	115±3	<0.05*
TT ₃ (1.1–2.8), nmol/l	1.80±0.09	1.53±0.11	n.s.	1.80±0.07	1.32±0.15	<0.05*
rT ₃ (0.14–0.54), nmol/l	0.46±0.02	0.50±0.04	n.s.	0.47±0.02	0.52±0.03	n.s.
3,5-T ₂ (0.20–0.37), nmol/l	0.37±0.04	0.53±0.06	<0.05	0.39±0.04	0.59±0.07	<0.05*
3-T ₁ AM, nmol/l	14.5±0.7	14.5±0.9	n.s.	14.2±0.5	15.5±1.8	n.s.
Calculated parameters						
SPINA-GT (1.4–8.7), pmol/s	3.7±0.3	3.1±0.3	n.s.	3.5±0.3	3.3±0.5	n.s.
SPINA-GD (20–60), nmol/s	40.6±1.7	35.1±1.6	<0.05	40.6±1.3	30.3±1.8	<0.001*
FT ₃ /rT ₃	11.8±0.9	8.7±0.6	<0.05	11.5±0.7	7.9±0.6	<0.001*
3,5-T ₂ /FT ₃	0.08±0.01	0.13±0.02	<0.05	0.08±0.01	0.15±0.02	<0.01*

Data are reported as mean ± SEM. Reference ranges are reported where available. * Significant after correction for multiple testing. See online supplementary table 1 for additional, nonsignificant parameters. n.s. = Not significant.

Where not otherwise specified, data are presented as the mean value ± standard error of the mean (SEM) for normally distributed continuous data, as the median (interquartile range) for nonnormally distributed data, or as percentages for count data. $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Thirty-nine patients undergoing cardiac surgery were included in the analysis. Their mean age was 67 ± 2 years, and 7 patients were women. In the total group, 29 patients underwent CABG alone, 8 patients AVR and 2 patients CABG and AVR. The basic clinical characteristics of the study population are reported separately for POAF and NTIS in table 1. There was no association between anthropometric measures, parameters of patient history and medication with POAF (see online suppl. table 1). Likewise, most variables were identical in patients with and without NTIS, apart from the fact that patients with NTIS were slightly older (table 1).

Biomarkers for POAF

In all subjects serum concentrations of Fas were 76 ± 4.5 ng/l and significantly higher in patients with POAF versus patients who maintained SR (table 2). In addition, the PA-TDI interval was significantly longer at baseline compared to patients who maintained SR. In the total study population PA-TDI was 134.3 ± 3.3 ms.

Phenotype of NTIS

Nine of the 39 included patients demonstrated NTIS as defined by reduced concentrations of TT₃ or FT₃, or of TT₄. Concentrations of 3,5-T₂ were 0.45 ± 0.04 nmol/l in all subjects, but significantly increased in patients with NTIS (table 2; fig. 1). As expected, patients with NTIS demonstrated a reduced SPINA-GD and FT₃/rT₃ ratio, but also an increased 3,5-T₂/FT₃ ratio (table 2). Unlike age, no association of NTIS with sex, underlying disease, 3-T₁AM concentration, CRP or creatinine was observed.

The total population showed a significant negative correlation between concentrations of FT₃ and 3,5-T₂, but a positive correlation between 3,5-T₂ and rT₃ (fig. 2). SPINA-GD inversely correlated with 3,5-T₂ concentra-

Fig. 1. Distribution of preoperative 3,5-T₂ concentrations in patients with and without POAF (**a**) and with and without NTIS (**b**). * $p < 0.05$.

Fig. 2. Correlation of preoperative concentrations of 3,5-T₂ with those of FT₃ (Spearman's rho -0.38 , $R^2 = 0.13$, $p < 0.05$; **a**) and rT₃ (Spearman's rho 0.30 , $R^2 = 0.12$, $p < 0.05$; **b**) in patients who developed POAF and those who maintained SR, respectively.

tions, age, BNP concentrations and the PA-TDI interval (online suppl. fig. 1).

NTIS and Its Association with Atrial Remodeling and Transduction

LAVI was 29.1 ± 1.9 ml/m² in the overall group, was not different between patients who eventually developed POAF and those who did not, but was significantly elevated in patients with NTIS (table 2). No differences were observed with respect to LA-EF and LV-EF. Concentrations of FT₃ and TT₃ as well as calculated deiodinase activity inversely correlated with the PA-TDI interval (online suppl. fig. 1, 2).

POAF and Thyroid Function

Seven out of the 17 patients (41%) who eventually developed POAF demonstrated NTIS prior to surgery, as compared to 2 of the 22 patients (9%) who remained in SR ($p < 0.05$). In patients with POAF, serum concentrations of FT₃ were significantly decreased and 3,5-T₂ concentrations were increased at baseline (table 2). In addition, the SPINA-GD and FT₃/rT₃ ratios were decreased, while the 3,5-T₂/FT₃ ratio was increased compared to the group of patients who maintained SR (table 2).

In the model of multivariable logistic regression, FT₃ and 3,5-T₂ were independent predictors of POAF, together with the PA-TDI interval, LAVI and Fas (table 3). VIF values suggested low multicollinearity.

Fig. 3. Relation between age, TACT and preoperative concentrations of FT₃ (a) or 3,5-T₂ (b) and POAF.

Table 3. Model of multiple logistic regression analysis with respect to the risk of POAF

	B	SE	Wald	d.f.	p value	OR (95% CI)	VIF
PA-TDI interval	2.361	0.040	3,562.0	1	<1e-12	10.6 (9.8 to 11.4)	1.15
LAVI	-0.217	0.030	51.3	1	<1e-4	0.81 (0.76 to 0.85)	1.16
FT ₃	-5.935	0.571	107.9	1	<1e-5	2.6e-3 (8.6e-4 to 8.1e-3)	1.11
3,5-T ₂	-43.150	3.075	196.9	1	<1e-8	1.8e-19 (4.4e-22 to 7.5e-17)	1.86
Fas	1.563	0.037	1,760.0	1	<1e-10	4.78 (4.44 to 5.14)	1.80

Variables were chosen by a priori selection, as described.

Discussion

In this study we analyzed the association between preoperative thyroid status, TACT and the development of POAF. The main findings were: (1) patients who develop POAF have decreased basal FT₃ concentrations and increased 3,5-T₂ concentrations; (2) preoperative reduced FT₃ concentrations reflect markers of impaired outcome, first of all age and PA-TDI interval; (3) basal 3,5-T₂ concentrations positively correlate with rT₃ concentrations but inversely correlate with FT₃, and (4) preoperative NTIS is associated with increased atrial remodeling and increased 3,5-T₂ concentrations.

Thyromimetic actions at cardiomyocytes, mainly attributed to T₃, are able to destabilize the heart rhythm. This effect results from upregulation of β1-adrenoceptors

by TH [35, 36], direct actions at cardiac potassium [37] and sodium channels [38], hypermetabolism and a plethora of other mechanisms [14, 39]. It is therefore not astonishing that hyperthyroidism, even in its subclinical form, facilitates the development of AF [17].

In this cohort, however, we observed decreased FT₃ concentrations to be associated with AF, similar to a small number of previous reports [25, 26]. FT₃ concentrations and SPINA-GD activity inversely correlated with age and PA-TDI interval, two markers of impaired prognosis. Thus, the most plausible explanation for these associations might be that the more severely ill patients, presenting a mild form of NTIS, are faced with increased risk of POAF. This assumption is also supported by the fact that patients with NTIS were not only older, but also presented significantly higher LAVI, suggesting left atrial remodel-

eling. However, even after correction for these confounders in multiple logistic regression, reduced FT₃ levels remained a predictor for POAF.

Unlike FT₃, concentrations of 3,5-T₂, an active TH metabolite and suggested product of 5'-deiodination of T₃, were significantly increased in the NTIS group. Additionally, 3,5-T₂ positively correlates with rT₃ concentrations and inversely correlated with T₃ concentrations. Serum concentrations of 3,5-T₂ were significantly elevated in patients who eventually developed POAF. Increased 3,5-T₂ concentrations have been previously described in patients with liver cirrhosis and brain tumors [40]. However, to the best of our knowledge, this is the first study to describe elevated 3,5-T₂ concentrations in cardiac disease.

These results suggest that elevated 3,5-T₂ concentrations are part of the metabolic signature of NTIS. However, interpretation of these findings on a mechanistic basis is not straightforward. Recently, nonlinear associations of serum 3,5-T₂ concentrations with altered microvascular damage parameters and glucose metabolism were observed in a subpopulation of the Study of Health in Pomerania (SHIP-2 and SHIP-Trend) [41, 42].

Usually, it is assumed that low-T₃ syndrome results from decreased phenolic ring 5'-deiodination of T₄ to T₃, mainly resulting from downregulated type 1 deiodinase (D1) [43]. Since PTU-sensitive D1 has been proposed to catalyze the conversion of T₃ to 3,5-T₂ in vivo [44–47], one may suggest that plasma concentrations of the 3,5-T₂ should also be decreased in NTIS and not increased as observed in this cohort. A possible explanation of these unexpected results could be that deiodination rates generating T₃ and its sequential product 3,5-T₂ differ and/or that their deiodination occurs in different tissues to a variant extent. In cells, where D1 activity is downregulated deiodination of T₃ may stop at the T₃ stage, while it may be upregulated in tissues that form 3,5-T₂. This hypothesis requires the assumption of additional transport and control mechanisms that determine both the rate and local extent of deiodination. In addition to impaired 5'-deiodination of T₄ to T₃, enhanced inactivation of T₄ by type 3 deiodinase (D3) generating rT₃ has also been observed in the liver and various other cells activated during inflammation and infection [2]. This combination might explain in part the shift of the T₃/T₄ and T₃/rT₃ ratios observed in NTIS. However, elevated D3 activity in combination with decarboxylation would also degrade 3,5-T₂ to 3-T₁AM, although in this study, we did not observe changes in 3-T₁AM serum concentrations. The serum TH metabolite profile observed in NTIS might be further influenced by tissue-specific uptake or efflux of

TH metabolites [1, 48] in addition to altered deiodinase activities.

It could be hypothesized that POAF might result from increased 3,5-T₂ concentrations in the more severely ill patients. However, in multivariable logistic regression, i.e. after correction for other explanatory variables including FT₃, LAVI, PA-TDI and Fas, 3,5-T₂ was a negative predictor of POAF. This suggests a complex interaction of multiple factors predisposing for POAF (fig. 3) and 'high-3,5-T₂ syndrome' not to be the cause but a consequence of other, still to be identified factors in the pathogenesis of NTIS. Since VIF is low for all parameters, the results are not explained by multicollinearity.

This investigation is faced with certain limitations. First of all, its pure observational design limits possible causal attributions. The limited number of included patients, a consequence of strict inclusion and exclusion criteria, may result in low statistical power. Calculated parameters like SPINA-GD or the FT₃/rT₃ ratio may provide valuable physiological insights, as they did in previous trials on NTIS [30–32, 49, 50], but they are also faced with limitations, since hormone concentrations also depend on tissue distribution and elimination. Therefore, future interventional trials with enhanced methodology and a larger number of included patients are necessary to provide more details on these associations or cause-effect relationships involved in NTIS and POAF.

Elevated 3,5-T₂ serum concentration in combination with reduced FT₃ may represent a new, potentially clinically relevant predictive marker in cardiac illness. 3,5-T₂ might be a valuable indicator of T₃ metabolism, and its elevations in NTIS could explain why patients with low-T₃ syndrome substituted with T₄/T₃ do not benefit from exogenous TH administration.

Disclosure Statement

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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