Permanent atrial fibrillation in heart failure patients as another condition with increased reverse triiodothyronine concentration

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Abstract

OBJECTIVE: To fully investigate the thyroid hormonal function in patients with the most common arrhythmia – atrial fibrillation.

MATERIALS AND METHODS: 120 patients (aged 55–85 yrs) with symptoms of congestive heart failure exacerbation and no other concomitant disorders (inclusion criteria: normal cardiac troponin T at admission and 12 hours after, normal renal, hepatic and respiratory function; exclusion criteria: inflammatory state, history of myocardial infarction). Depending on the presence of permanent atrial fibrillation (PAF), patients were divided into two groups: PAF (34 females, 26 males) and regular sinus heart rhythm (43 females, 17 males), the groups did not differ in terms of heart rate, blood pressure, presence of overt/subclinical thyroid dysfunction, and medical therapy used. In all subjects thyroid stimulating hormone, free thyroxine, free triiodothyronine, reverse triiodothyronine were measured; echocardiography was performed.

RESULTS: PAF group showed higher FT4 and rT3 (1.41 vs. 1.27 ng/dl, \( p=0.0007 \); 0.61 vs. 0.32 ng/ml, \( p<0.0001 \), respectively). With ROC curve analysis the biochemical thyroid related factor of the highest prognostic value for PAF occurrence (with the highest sensitivity and specificity: 77% and 72%, respectively) was rT3 with the cut-off of above 0.3 ng/ml. Also, a positive correlation between rT3 levels and left ventricular posterior wall diameter was observed (Spearman’s correlation coefficient 0.33, \( p=0.0093 \)).

CONCLUSIONS: PAF is another condition where an increase in rT3 is observed. rT3 concentration above 0.3 ng/ml may be a novel biochemical sign associated with the presence of PAF in patients with chronic heart failure.

Abbreviations:
AF - atrial fibrillation
PAF - permanent atrial fibrillation
FT4 - free thyroxine
FT3 - free triiodothyronine
TSH - thyroid-stimulating hormone
rT3 - reverse triiodothyronine
ECG - electrocardiography
CHD - congestive heart failure
NYHA - New York Heart Association
BP - blood pressure
SBP - systolic blood pressure
INTRODUCTION

Thyroid disorders impact the quality of life in a variety of ways (Sawicka-Gutaj et al. 2015), including the cardiovascular system in particular, and the relationship between thyroid function and cardiovascular diseases has been the subject of numerous studies. Atrial fibrillation (AF) is one of the most common arrhythmias with a prevalence of 0.4–1% in general population, increasing clearly with age (Fuster et al. 2011). The uncoordinated activation of atrial muscular tissue in this supraventricular arrhythmia is presented as the replacement of P waves by fibrillatory wave on ECG (Fuster et al. 2011). In AF, the progression of atrial mechanical function deterioration leads to stroke-related incidents, heart failure and, as a consequence, increased mortality (Schotten et al. 2011). According to the pattern suggested by American College of Cardiology Foundation/American Heart Association, paroxysmal (self-terminating), persistent (not self-terminating) and permanent AF are distinguished depending on the presentation of AF. In permanent AF cardioversion has failed or has not been attempted.

Numerous disorders are known to be the risk factors for the AF development, one of which is the thyroid dysfunction (Gencer et al. 2013). The association of AF with both overt hyperthyroidism and the subclinical thyroid hyperfunction (defined as low thyroid-stimulating hormone (TSH) level with normal concentrations of free thyroxine (FT4) and triiodothyronine (T3)/free triiodothyronine (FT3)) has been proven (Collet et al. 2012). The diagnosis of the underlying thyroid abnormality is of great importance, as an adequate therapy strategy (still discussed in terms of the subclinical thyroid dysfunction) may prevent the patient from the progression of cardiovascular diseases, and thus the development of permanent atrial fibrillation (PAF) and heart failure (Anther et al. 2009; Gencer et al. 2013). Although the alterations of all thyroid hormones concentrations are associated with the well-being of the patient, it is reverse triiodothyronine (rT3) that might be of particular importance for the cardiovascular system. For example, the correlation between elevated (rT3) levels and cardiac muscle function impairment has been observed (Pimentel et al. 2010). rT3 is the product of thyroxin deiodination at the 5 position of the inner ring (Sabatino et al. 2015). In various tissues, this reaction is catalysed by the deiodinases (Sabatino et al. 2015) and leads to the termination of thyroid hormone action (Kohrle 1999).

In our study we aimed to assess the alterations of rT3 levels in patients with PAF and no clinical manifestations of thyroid function impairment, and to investigate whether PAF would be another condition causing rT3 concentrations to increase.

MATERIALS AND METHODS

Patients and data collection

The study cohort comprised 120 patients (43 males, 77 females), aged between 55 and 85 years. The subjects were admitted to the Internal Medicine Department of Public Community Hospital in Drezdenko, Poland, between February 2010 and September 2011, on an emergency basis for symptoms caused by increased blood pressure (BP), which led to the exacerbation of congestive heart failure (CHD) symptoms (NYHA functional class deterioration, from II to III). The fulfillment of the following criteria was required: heart rate 60–100/min; normal cardiac troponin T results at admission and 12 hours after the onset of symptoms to exclude acute coronary syndromes; normal renal, hepatic and respiratory function. Patients in an inflammatory state as well as patients with a history of myocardial infarction were excluded.

The subjects were divided into two homogenic groups. The only distinguishing feature between the groups was of the presence or absence of PAF: the Control Group (60 subjects, 43 females, 17 males; mean age 73.08±4.59 years) – normal sinus heart rhythm; and the Study Group (60 subjects; 34 females, 26 males; mean age 72.80±4.81 years) – AF, defined as an accepted long-standing (over 1 year) AF in which cardioversion has failed or has been foregone (Fuster et al. 2011). The period of time of AF occurrence was determined based on the patient’s medical history and medical records.

Patients were investigated with 12-lead electrocardiography at rest, analyzed for the presence of AF by a single cardiologist. Blood pressure was measured with the use of mercury sphygmomanometer (mean result from 3 morning measurements). Echocardiographic examination was performed with the use of Logic 3, General Electric, USA. Transthoracic echocardiography was performed at 1.5–3.5 MHz frequency, at diastole. Ejection fraction was determined according to the Simpson method. Mean value of three measurements of each parameter was the final result.

All current drug therapies were recorded. Both groups were treated with a similar therapy regimen, one exception was acenocoumarol administered to the Study Group only. Withdrawal of this drug was impossible for ethical reasons, but to our knowledge acenocoumarol does not influence the thyroid function. Aside from this exception, the treatment in both groups included: angiotensin-converting enzyme inhibitors, beta-1 adrenergic receptor antagonists, loop diuretics (furosemide), statins and acetylsalicylic acid, all at standard dosage.
All subjects gave written, informed consent for the study, and the study was approved by the Bioethics Committee of Poznań University of Medical Sciences.

**Laboratory measurements**

Levels of FT3, FT4, TSH were measured using IMMULITE® 1000 Chemiluminescent Technology, Siemens Healthcare Global. The assay sensitivities were as follows: FT3 0.1 pg/ml, FT4 0.3 ng/dl, TSH 0.004 μIU/ml. The rT3 RIA measurements were performed with RIAZEN reverse T3 (ZENTECH SA®, Belgium), radioactivity was measured in a gamma counter (LKB-Wallac CliniGama 1272 Counter, Wallace, Finland), assay sensitivity was 0.009 ng/ml. Subjects were classified according to serum FT3, FT4 and TSH concentrations as follows: overt hyperthyroidism in patients with elevated FT4 and/or FT3, TSH lower than 0.1; subclinical hyperthyroidism for normal FT4 and FT3, serum TSH lower than 0.1; overt hypothyroidism for low FT4, TSH higher than 5.0; subclinical hypothyroidism for normal FT4, TSH higher than 5.0.

**Statistical analysis**

Student’s unpaired t test was used to evaluate differences between groups (age, left ventricle and aorta measurements). The Mann-Whitney U test was used for data not normally distributed (TSH, FT3, FT4, rT3; blood pressure measurements; posterior wall of left ventricle, left atrium, interventricular septum, and efficiency fraction measurements). The thyroid status comparison (overt hyperthyroidism, subclinical hyperthyroidism, overt hypothyroidism, subclinical hypothyroidism) was performed with the use of the Fisher-Freeman-Halton’s exact test. Receiver operator characteristics (ROC) were used to define the cut-off value, specificity and sensitivity and were derived from four-fold tables for the resulting cut-off values. The Spearman’s correlation coefficient was used to assess the degree of correlation between heart echocardiography measurements and rT3 values. All data are presented as mean ± SD unless otherwise specified. A p-value <0.05 was considered statistically significant.

**RESULTS**

The cohort comprised 120 subjects. The difference of mean age between the Control Group and the Study Group was not significant, p = 0.7420 (mean±SD: 73.08±4.59 years, 72.80±4.81 years, respectively). No significant difference was observed in blood pressure values between Control and Study Groups (mean±SD): SBP – 141.7±21.6 vs. 144.2±25.4, respectively, p = 0.0977; DBP – 85.7±10.9 vs. 88.9±17.1, respectively, p = 0.9469.

Furthermore, the comparative analysis of the prevalence of overt/subclinical hyperthyroidism/hypothyroidism in the cohort showed no significant difference between the control and study group, p = 0.0521 (Table 1). Then, we compared the values of hormone concentration between the groups. As shown in Table 2, hormone levels did not differ except for higher FT4 and rT3 in the PAF patients.

After demonstrating different rT3 and FT4, we searched for any possible associations between these hormones and cardiac anatomy. To do this, we compared numerous echocardiographic data with hormone levels. As the result, we showed that the thickness of posterior wall of left ventricle was the only parameter which correlated with rT3 value in subjects of the Study Group. No other significant correlations were observed. (Table 3).

Eventually, knowing that rT3 was higher in PAF, we aimed to evaluate if any cut-off level that would be specific for PAF might be found. We were able to calculate this as we had two similar groups where only the presence of PAF was the differentiating factor. For this purpose, ROC curve analysis was used, and in order not to omit any other parameter, we performed this analysis for all the hormones examined (data not shown). With this test, we demonstrated that only rT3 had the highest predictive value (area under the ROC curve = 0.79, p = 0.0001) for PAF occurrence, with the optimal cut-off value of 0.3 ng/ml (sensitivity: 77%, specificity: 72%). (Figure 1)
DISCUSSION

In this study, we investigated the relationships between thyroid function and the most common cardiac arrhythmia, i.e., atrial fibrillation. The complex actions of thyroid hormones in terms of altering the cardiovascular hemodynamics (Davis & Davis 2002) and thus the association between the concentrations of thyroid hormones and the overall heart condition have been the subject of numerous studies (Gammage et al. 2007; Frost et al. 2004; Fazio et al. 2004; Sgarbi et al. 2003; Ozturk et al. 2012). Here however, we compared the levels of TSH, FT3, FT4 and rT3 in the strictly selected groups of patients with the exacerbation of CHD symptoms and no clinical manifestations of thyroid alterations. Importantly, and in contrast to most other studies, we created two almost identical study groups, where the only differential factor was the presence of PAF. This approach enabled us to achieve the results presented above.

The novel finding of our study is the observation of significantly higher concentrations of rT3 in patients with permanent AF (Study Group) in comparison with Control Group ($p<0.0001$). Among the other thyroid hormones we investigated in the study, the difference in FT4 levels between the two groups of patients, higher in those suffering from permanent AF ($p=0.0007$), is a result coherent with the observations of increased AF prevalence in patients with thyroid hyperfunction. The correlation between the prevalence of AF and overt hyperthyroidism has been proven (Gammage et al. 2007; Fazio et al. 2004; Sgarbi et al. 2003), whereas the association of AF and subclinical hyperthyroidism alongside the necessity of subclinical hyperthyroidism treatment, have been a subject of considerable debate (Sgarbi et al. 2003; Yang et al. 2012; Schultz et al. 2011). The levels of TSH, FT3 and FT4 have been examined thoroughly; to date however, the available clinical data on the concentration of rT3 in patients with AF is scarce.

Taking into consideration the paucity of clinical data on the rT3 concentration in AF patients, we attempted to take a more far-sighted approach. On account of permanent AF being a condition deteriorating the general state of the organism (Anter et al. 2009), we sought the relation between rT3 and presence of severe diseases. An evident relationship of elevated rT3 levels and

![Fig. 1. ROC curve analysis of rT3 cut-off values for the determination of the occurrence of persistent atrial fibrillation.](image-url)
severe body conditions as well as impaired physical function has been proven (van den Beld et al. 2005). What is more, serum rT3 concentration was confirmed to increase with age and the setting of non-thyroidal disease, and might reflect a catabolic state of the human body (van den Beld et al. 2005).

The relationship between AF and heart failure has been established suggesting the mutual impact of both of these diseases. The reduction in cardiac output due to shorter diastolic filling time (not completely compensated for by increased diastolic filling in longer cycles), the loss of effective atrial contraction are only some aspects leading to the myocardial dysfunction (Anter et al. 2009). Permanent AF as a long-lasting state of arrhythmia leads to the deterioration of myocardial function and, in particular in the elderly patients, enhances the systolic and diastolic dysfunction of the left ventricle (Wysokiński & Zapolski 2005).

Therefore, considering the role of rT3 in cardiac muscle dysfunction itself, several studies linked the heart condition with alterations in rT3 concentrations. A state of sick euthyroid syndrome (SES), defined as low FT3, normal TSH and elevated rT3 concentrations, has been shown to be associated with alterations in cardiac index, filling pressures of the ventricles and functional impairment of myocardial muscle (Opasich et al. 1996). A relationship between SES and the heart failure functional class (NYHA) has been the subject of research, the result presenting a positive correlation of rT3 value and functional classes II, III and IV (Pimentel et al. 2010). A study on rats with congestive heart failure showed a significant increase in rT3 levels and a significant decrease in FT3 levels (Baubab et al. 2005).

The analysis of thyroid hormones serum levels (FT3, FT4, TSH and rT3) in patients with myocardial infarction at the time of admission, investigated the thyroid hormone levels for association with subsequent mortality, and proved the result to be an increase of 1-year mortality by rT3 levels >0.41 nmol/L (hazard ratio = 3.0, p = 0.005) (Friberg et al. 2001).

A state of elevated rT3 in patients with atrial fibrillation is additionally observable when treated with amiodarone (Jabrocka-Hybel et al. 2015). Amiodarone, the most common antiarrhythmic drug worldwide (frequently used in the handling of atrial fibrillation), can lead to both hypo- and hyperthyroidism (Narayana et al. 2011). Its actions interfere with the iodothyronine deiodinases and cause an early rise in rT3 (also a rise in FT4, and a fall in FT3) (Jabrocka-Hybel et al. 2015). Three months into the therapy, a steady state of rT3 remaining at the upper end or marginally elevated is achieved (Jabrocka-Hybel et al. 2015).

All this to some extent allocates the role of elevated rT3 concentration in heart condition deterioration. Yet in our study, we did not observe differences in FT3, nor TSH levels, between the two groups (p = 0.5797, p = 0.6631, respectively). In this setting, it is not the sick euthyroid syndrome that could be diagnosed here.

Bearing in mind the finding of rT3 increasing in permanent AF, we made an attempt to measure its predictive value for the occurrence of this disease. With the use of ROC curve, we established the cut-off value for rT3 to be 0.3 ng/ml. To our knowledge, this is the first report on this issue. Few studies have addressed similar problems by now. For example, Gammage et al. (2007) examined the variations in thyroid hormones in relation to the presence of AF on ECG and, similarly to our study, did not observe differences in TSH levels, but reported a difference in FT4 levels. However, rT3 levels were not measured by these authors. In this study the hypothesis of FT4 being a more sensitive indicator of cardiac ‘thyroid status’ than TSH was introduced (Gammage et al. 2007). This is in line with our results, as we also observed significantly higher FT4 levels in the Study Group. Now, we add to this issue that the increased rT3 value observed in our patients with permanent AF could also become a sensitive indicator of the incidence of deleterious arrhythmias such as permanent AF.

Our novel approach also included examining the correlations between rT3 and echocardiography parameters in both groups. Despite the clear difference in rT3 values between the two groups, a simple general mathematical correlation between echocardiography parameters and rT3 values was not found. The only parameter to show a positive correlation with rT3 value was left ventricular posterior wall diameter (LVPWd) (Spearman’s correlation coefficient 0.33, p = 0.0093). Interestingly, a Chinese study which analyzed LVPWd, among other echocardiography parameters, such as left atrial diameter and tricuspid insufficiency in patients with paroxysmal atrial fibrillation, recognized this parameter to be one of the risk factors for paroxysmal AF (Xu et al. 2011). In permanent AF, the subtle, potential relations of the coexistence of elevated rT3 in correlation with LVPWd might require further investigation.

Obviously, our study had some limitations. Perhaps the main limitation is the relatively small number of patients enrolled. However, this was explained by the strict enrollment criteria we used, thus decreasing the number of participants significantly.

In conclusion, we demonstrate here that permanent atrial fibrillation in patients suffering from heart failure is another condition where an increase of rT3 is observed. Furthermore, our finding of the rT3 concentration cut-off value of above 0.3 ng/ml as being highly specific for PAF in these patients, might be of interest when seeking biochemical background to this arrhythmia but certainly requires confirming in larger cross-sectional and observational studies.

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