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Red cell distribution width — a new marker for exacerbation of heart failure in patients with hypothyroidism following radioiodine therapy

Rozpiętość rozkładu objętości erytrocytów — nowy marker zaostrzenia niewydolności krążenia u pacjentów z niedoczynnością tarczycy po leczeniu jodem promieniotwórczym

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Abstract

Introduction: Cardiovascular diseases constitute a major cause of health problems and death in developed countries across the world. The increased value of the index of distribution of red blood cell volume (RDW) may be a prognostic marker in patients diagnosed with chronic heart failure (CHF). Hypothyroid patients present higher RDW values compared to healthy controls. Taking into consideration that RDW might be affected by both thyroid status and CHF, we decided to determine the effect of concomitant hypothyroidism following radioiodine therapy (RIT) and CHF on haematological parameters.

Material and methods: Patients with toxic nodular goitre and heart failure with concomitant anaemia were included. Patients underwent treatment with radioiodine before the planned heart transplant or pacemaker implantation (combined ICD/CRT-D). After RIT patients were divided into the three subgroups: with overt hypothyroidism (TSH ≥ 10 μIU/mL, Group I), subclinically hypothyroid patients (TSH 4.3–9.0 μIU/mL, Group II), and with high-normal level of TSH (2.6–4.2 μIU/mL, Group III).

Results: Significant correlation between TSH and RDW was observed ($r = 0.46$; $P < 0.0001$) after RIT, whereas no correlation between serum TSH levels and TIBC and Fe was observed. In Group I significant correlation between TSH and RDW ($r = 0.48$; $P = 0.002$) after RIT was observed, whereas in two other subgroups there was no significant correlation.

Conclusions: Subclinical hypothyroidism or high-normal levels of TSH did not affect RDW in a significant manner in the studied population. Our results demonstrate that overt hypothyroidism may contribute to deterioration of CHF, as reflected in changes of RDW value.
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Key words: *RDW, hypothyroidism, heart failure, radioiodine therapy*

Streszczenie

Wstęp: Choroby sercowo-naczyniowe stanowią główną przyczynę problemów zdrowotnych i zgonów w krajach wysoko uprzemysłowionych na całym świecie. Podwyższona wartość rozpiętości rozkładu objętości erytrocytów (RDW) może stanowić marker prognostyczny u pacjentów z przewlekłą niewydolnością serca (PNS). Pacjenci z niedoczynnością tarczycy mają wyższe wartości RDW w porównaniu z osobami zdrowymi. Biorąc pod uwagę, że RDW może być zmienione zarówno przez stan czynnościowy tarczycy, jak i PNS, autorzy niniejszej pracy postanowili ustalić wpływ współistniejącej niedoczynności tarczycy spowodowanej terapią jodem promieniotwórczym (RIT) i PNS na parametry hematologiczne.

Materiały i metody: Włączono pacjentów z wolem guzkowym toksycznym, PNS oraz towarzyszącą niedokrwistością. U pacjentów przeprowadzono RIT przed planowanym przeszczepieniem serca lub implantacją urządzenia resynchronizującego lub defibrylatora (ICD/CRT-D). Po RIT pacjentów podzielono na 3 podgrupy: z jawną niedoczynnością tarczycy (TSH ≥ 10 μIU/mL — grupa I), z subkliniczną niedoczynnością (TSH 4,3–9,0 μIU/mL — grupa II) oraz z TSH w górnej granicy normy (2,6–4,2 μIU/mL — grupa III).

Wyniki: Zaobserwowano istotną korelację między TSH i RDW ($r = 0{,}46$; $P < 0{,}0001$) po RIT, podczas gdy nie zaobserwowano korelacji między stężeniem TSH i stężeniem żelaza oraz TIBC. W grupie I zaobserwowano istotną korelację między TSH i RDW ($r = 0{,}48$; $P = 0{,}002$) po RIT, jakkolwiek w dwóch pozostałych podgrupach nie zaobserwowano istotnej korelacji.

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Wnioski: Subkliniczna niedoczynność tarczycy, jak i wartości TSH w górnej granicy normy nie wpływały na RDW w sposób istotny w grupie badanej. Wyniki wskazują, że jawna niedoczynność tarczycy może przyczynić się do zaostrzenia PNS odzwierciedlonej zmianą wartości RDW. **(Endokrynol Pol 2018; 69 (3): 235–240)**

Słowa kluczowe: *RDW, niedoczynność tarczycy, niewydolność serca, terapia jodem promieniotwórczym*

Introduction

Cardiovascular diseases constitute a major cause of health problems and death in developed countries across the world [1, 2]. The overall five-year survival rate in heart failure (HF) is approximately 25–28% [3, 4]. Results presented in recent publications demonstrate that the increased value of the index of distribution of red blood cell volume (RDW, red cell distribution width) may be a prognostic marker in patients diagnosed with heart failure [5], but still the left ventricular ejection fraction (LVEF) is considered to have the strongest prognostic value. Moreover, other parameters, e.g. increased left ventricular volume, increased left ventricular filling pressure, restrictive mitral inflow, and pulmonary hypertension, may be taken into account [6–8]. As compared with 2008, the new 2012 ESC guidelines call for RDW to be included as a useful prognostic factor in patients with chronic heart failure (CHF) [9].

Recent studies have shown that CHF is often accompanied by anaemia, and its occurrence is associated with a poor prognosis and increased mortality [10–21]. It was also demonstrated that anaemia can occur in as much as 50%, or even more patients with CHF, while the incidence increases with a higher NYHA functional class, age of the patient, and in the case of concomitant renal failure [22–24]. Iron deficiency anaemia accompanied by elevated RDW may be associated with a number of cardiovascular diseases, i.e. hypertension, myocardial infarction, and heart failure [25–28]. In certain conditions, RDW was found to be a useful parameter determining prognosis [29–32]. On the other hand, in a euthyroid group RDW was a parameter that was demonstrated to be negatively correlated with thyroid hormones concentration [33]. Hypothyroid patients present higher RDW values compared to healthy controls [34]. Concordant findings were presented by Aktas et al. [35], who demonstrated that higher RDW value was the only haematological index significantly different in patients with Hashimoto's thyroiditis in comparison to the control group with no evidence of thyroid disease.

Taking into consideration that RDW might be affected by both thyroid status and CHF, we decided to determine the effect of concomitant hypothyroidism following radioiodine therapy (RIT) on haematological parameters in a group of CHF patients. The aim of our study was to assess whether hypothyroidism after radioiodine therapy is associated with exacerbation of CHF, as reflected by changes in RDW value.

Material and methods

Material

Consecutive patients with a toxic nodular goitre and heart failure with concomitant anaemia admitted to the Endocrine Department in Poznan were included. They were on medications prescribed according to current therapeutic guidelines [9]. It is a retrospective study of patients treated between January 2014 and May 2015.

Toxic nodular goitre was diagnosed on the basis of suppressed TSH levels measured by sensitive assay, elevated serum free thyroid hormone levels, nodules on thyroid ultrasound examination, and undetectable levels of anti-TSH receptor antibodies. The diagnosis of hypothyroidism was based on the following criteria: decreased free thyroid hormone levels and elevated TSH. Anaemia was defined as haemoglobin (Hgb) < 12 g/dL in women and < 13 g/dL in men, according to the World Health Organisation (WHO) criteria.

Exclusion criteria were:

— significant heart valve dysfunction, recent surgical treatment for valvular heart disease;
— coronary revascularisation (PCI or CABG) within the last three months;
— concomitant active neoplastic process;
— concomitant active inflammation (e.g. infective endocarditis);
— end-stage renal disease (ESRD) (eGFR < 15 mL/ /min/kg);
— liver failure;
— advanced anaemia (HGB < 6.5 mmol/L);
— blood transfusion.

Treatment protocol and serial evaluation

The study group consisted of 82 patients (42 males and 40 females), aged 25–89 years. (mean age 55 ± 15 years) with toxic nodular goitre and chronic heart failure due to left ventricular systolic dysfunction (LVEF < 45%, NYHA functional class ≥ II) with concomitant anaemia. Patients underwent treatment with radioiodine before the planned heart transplant or pacemaker implantation (combined ICD/CRT-D). The diagnosis of CHF was based on the criteria of the European Society of Cardiology [7].

All of the patients were assigned to radioiodine therapy [22 mCi = 800 MBq] alone. Clinical and laboratory assessments were performed at baseline as well as twice, one and after six months following radioiodine treatment. Clinical evaluations were performed by

Table I. *The comparison of the number of patients, age, and sex distribution as well as laboratory findings in three groups of patients with overt (G-I) and subclinical (G-II) hypothyroidism as well as high-normal TSH concentration, evaluated before and after radioiodine therapy*

Tabela I. *Porównanie liczby pacjentów, rozkładu wieku i płci, jak również wyników badań laboratoryjnych w trzech grupach pacjentów z jawną (G-I) i subkliniczną (G-II) nadczynnością tarczycy, oraz wysokiego normalnego stężenia TSH, oceniane przed i po terapii radiojodem*

	G-I	G-II	G-III	G-I vs G-II (P-values)	G-I vs G-III (P-values)	G-II vs G-III (P-values)
Before radioiodine therapy						
Total no. of patients	38	24	20	NS	NS	NS
No. of F:M	21:17	10:14	9:11	NS	NS	NS
Age (years)	71	66	64	NS	NS	NS
TSH [μIU/mL] range: 0.27–4.2	0.1 ± 0.2^{1a}	0.0 ± 0.0^{1b}	0.0 ± 0.0^{1c}	NS	NS	NS
RDW-CV (%) range: 11.0–16.0	16.9 ± 0.6^{2a}	16.6 ± 0.6^{2b}	16.7 ± 0.6^{2c}	NS	NS	NS
TIBC [μg/dL] range: 250–400	363.1 ± 48.0^{3a}	384.3 ± 49.4^{3b}	378.0 ± 48.2^{3c}	NS	NS	NS
Fe [μg/dL] range: 37–145	28.8 ± 5.3^{4a}	28.5 ± 5.6^{4b}	29.6 ± 3.9^{4c}	NS	NS	NS
After radioiodine therapy						
TSH [μIU/mL] range: 0.27–4.2	18.6 ± 16.4^{1a}	6.8 ± 1.3^{1b}	3.2 ± 0.8^{1c}	< 0.001	< 0.001	0.006
RDW-CV (%) range: 11,0–16,0	17.6 ± 0.8^{2a}	17.0 ± 0.5^{2b}	16.9 ± 0.6^{2c}	0.02	0.003	NS
TIBC [μg/dL] range: 250–400	365.2 ± 52.2^{3a}	388.2 ± 45.4^{3b}	348.1 ± 47.4^{3c}	NS	NS	NS
Fe [μg/dL] range: 37–145	28.5 ± 4.5^{4a}	29.7 ± 5.3^{4b}	29.7 ± 3.9^{4c}	NS	NS	NS

$^{2a}P = 0.0001$, $^{2b}P = 0.004$, ^{2c}P = NS
^{3a}P = NS, $^{3b}P < 0.0001$, ^{3c}P = NS
^{4a}P < NS, $^{4b}P < 0.0001$, $^{4c}P < 0.0001$
Data are given as mean ± S.D. The reference ranges for serum TSH and other parameters in our laboratory were as follows: TSH: 0.27–4.2 μIU/mL, RDW-CV (red blood cell distribution width — coefficient of variation): 11.0–16.0%, TIBC (Total Iron Binding Capacity) 250–400 μg/dL, Fe (iron concentration) 37–145 μg/dL.

the same physician. None of the patients received antithyroid drug therapy during and after the follow-up. L-thyroxine (50–100 μg/day) was given to patients when hypothyroidism occurred.

The patients were divided into the three following groups:

— group I (G-I) comprised 38 patients (F:M ratio was 1.4:1) with overt hypothyroidism (TSH ≥ 10 μIU/mL) with average age 71 years;
— in group II (G-II) there were 24 (F:M ratio 1:1.4) subclinically hypothyroid patients (TSH 4.3–9.0 μIU/mL) with average age 66 years;
— group III (G=III) comprised 20 patients (F:M ratio 1:1.2) with high-normal level of TSH 2.6–4.2 μIU/mL. The average age in this group was 64 years (Table I).

Assays

TSH, RDW (red blood cell distribution width), TIBC (Total Iron Binding Capacity), and Fe (iron concentration) were determined in serum by radioimmunoassay (RIA) using an automated system (Cobas Immuno602 — Roche Diagnostics). The reference ranges for serum TSH, RDW, TIBC, and Fe concentrations in our laboratory were as follows: TSH: 0.27–4.2 μIU/mL, RDW-CV: 11.0–16.0%, TIBC 250–400 μg/dL, and Fe 37–145 μg/dL.

Statistical analysis

The calculations were performed using StatSoft Statistica 12 software package. The level of significance was set at $\alpha = 0.05$. A result was considered statistically significant when $P < \alpha$. Continuous variables were presented as mean ± SD, whereas in the case of categorical variables, n and % were also given. For all the variables under scrutiny, the compatibility of their distributions with the normal distribution was checked (Lilliefors test). To compare variables between the groups, due to the lack of the compatibility with the normal distribution, the Mann-Whitney test or the Kruskal-Wallis test were applied. In addition, to determine which groups differ from one another, the Dunn's multiple comparisons test was used. To assess whether changes in levels of the analysed parameters have changed as a result of treatment, the t-Student test for dependent samples (in the case of compliance with the normal distribution) or the Wilcoxon test (in the case of non-normal distribution) were used. In order to investigate the effect of TSH on the RDW levels, Fe, and TIBC, due to the incompatibility with the normal distribution, we calculated R_S (Spearman's rank-order correlation coefficient).

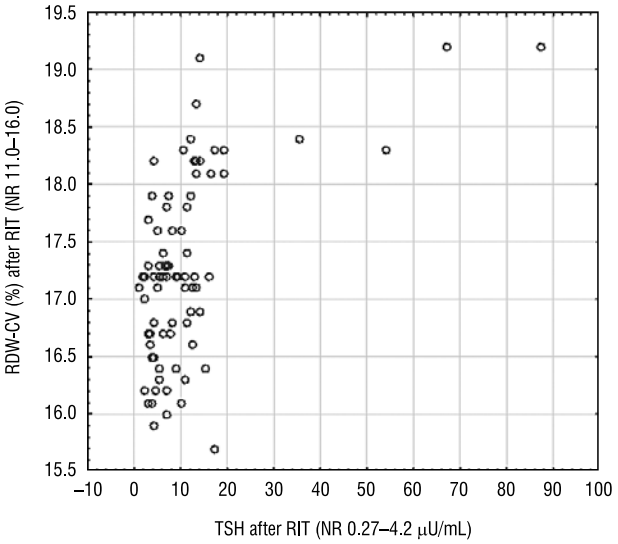

Figure 1. *Relationship between TSH levels and RDW in all patients*

Rycina 1. *Związek między stężeniem TSH i RDW u wszystkich pacjentów*

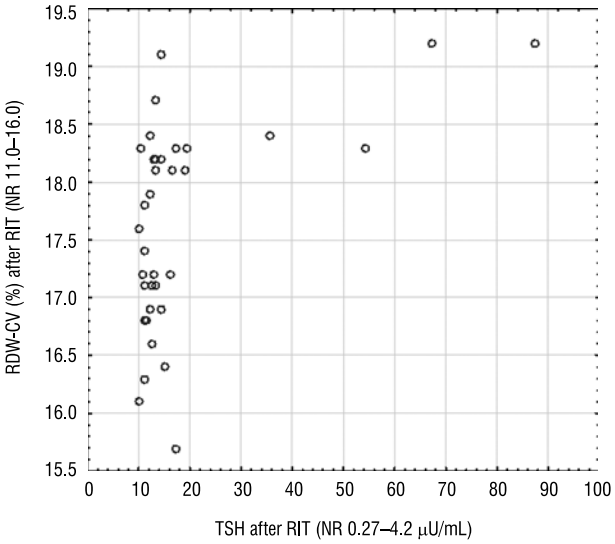

Figure 2. *Correlation between TSH and RDW after RIT (r = 0.48; P = 0.002)*

Rycina 2. *Współzależność między TSH i RDW po terapii RIT (r = 0,48; P = 0.002)*

Results

A comparison of the levels of all the parameters between female and male patients ($P = 0.24$; Mann-Whitney test) did not report any significant differences.

Before RIT, no significant relationships between serum TSH levels and RDW (r = –0.06; $P = 0.55$), TSH and TIBC (r = 0.05; $P = 0.62$), and Fe (r = –0.17; $P = 0.12$) were observed.

A significant correlation between TSH and RDW was observed (r = 0.46; $P < 0.0001$) after RIT, whereas no correlation between serum TSH levels and TIBC (r = –1.69; $P = 0.09$), and Fe (r = –1.2; $P = 0.23$) was observed.

Relationships between TSH, RDW, and Fe in all analysed subgroups (I, II, III).

Group I

In Group I, with high level of serum TSH, a significant correlation between TSH and RDW (r = 0.48; $P = 0.002$) after RIT (Fig. 2) was observed. Before RIT, no correlation between TSH and TIBC was observed (r = 0.17; $P = 0.9$), as well as TSH and Fe (r = –0.09; $P = 0.58$) was found. Similarly, after RIT there were no relationships between TSH and TIBC (r = –0.13; $P = 0.42$), or between TSH and Fe (r = –0.00; $P = 0.99$).

Group II

In Group II, before RIT, no correlation between TSH and RDW (r = –0.00; $P = 0.97$), TIBC (r = –0.11; $P = 0.59$), and Fe (r = –0.10; $P = 0.61$) was observed as well as after RIT between TSH and RDW (r = 0.05, $P = 0.81$), TSH and TIBC (r = 0.11; $P = 0.59$), or TSH and Fe (r = –0.16; $P = 0.45$).

Group III

In Group III, no correlation between TSH and RDW was observed (r = –0.13; $P = 0.57$), TSH and TIBC (r = –0.02; $P = 0.92$) was observed before and after RIT — TSH and RDW (r = –0.03, $P = 0.87$), TSH and TIBC (r = 0.13; $P = 0.55$), TSH and Fe (r = –0.01; $P = 0.96$).

A correlation between TSH and Fe (r = –0.45; $P = 0.04$) was observed before RIT.

Discussion

Recent research has proved that anaemia occurs frequently in patients with CHF and it deteriorates the prognosis and increases [10–13, 15, 16, 19, 21]. According to various studies, anaemia can occur in up to 60% of patients with HF, and the probability of its occurrence increases with the NYHA failure class, age of the patient, and especially if there is concomitant renal failure [22–24]. Despite the documented relationship between anaemia and prognosis in HF, it is still unclear whether anaemia is only a reflection of the severity of the disease or a concomitant pathological condition that affects the deterioration of the prognosis and incidence of complications.

The aetiology of anaemia in HF is multifactorial and not fully elucidated [36–39]. Persistent use of aspirin and anticoagulants, malnutrition, intestinal malabsorption, cardiac cachexia, and renal impairment may adversely contribute to its development in patients with HF [24, 40],

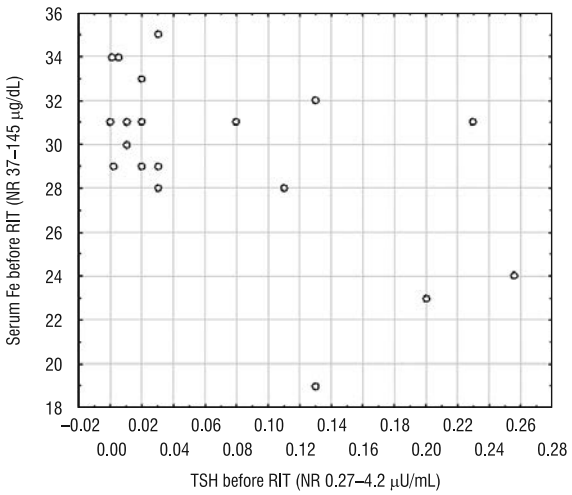

Figure 3. *Relation between serum TSH and Fe levels before RIT*
Rycina 3. *Związek między TSH w surowicy krwi oraz stężeniem Fe przed terapią RIT*

as well as persistent therapy with ACE-I/ARB [41, 42]. On the other hand, anaemia in the case of thyroid dysfunction is caused mainly by the depression of bone marrow function due to reduced erythropoietin secretion [33, 43]. The erythropoietin production is further decreased in patients with concomitant chronic kidney disease [44]. Anaemia in hypothyroidism might also be related to iron, folates, or B12 deficiency or accompanying diseases i.e. coeliac disease, pernicious anaemia or atrophic gastritis, autoimmune haemolytic syndrome, or soft tissue rheumatic disorders [45].

In patients with anaemia and HF, elevated levels of inflammatory cytokines, such as TNF-alpha and IL-6, have been observed [46–48]. These cytokines are responsible for blocking iron in the reticuloendothelial system (mononuclear phagocyte system) and thus make it unavailable for erythropoiesis. It has also been demonstrated that patients with anaemia and HF present a similar constellation of parameters of iron metabolism to patients with anaemia associated with a chronic disease (ACD), i.e. reduced levels of iron, normal or reduced levels of TIBC, and elevated levels of ferritin.

In our study we attempted to determine whether the thyreometabolic state, particularly hypothyroidism, exerts any influence on exacerbation of heart failure. To the best of our knowledge, our study is the first to demonstrate a significant negative impact of hypothyroidism on haematological parameters in a group of patients with CHF. The present study has proven that after RIT an increase in TSH level is followed by a significant increase in RDW levels in the whole group ($r = 0.46$; $P < 0.0001$) as well as in subgroup I (Group I, $r = 0.48$; $P = 0.002$), whereas slightly increased TSH levels do not correlate with increased RDW levels (Group II and III). The results clearly show that overt hypothyroidism (Group I) is accompanied with a greater risk of higher RDW being a marker for myocardial insufficiency. Therefore, it is important to continuously monitor thyroid functional state in these patients to prevent development of overt hypothyroidism (TSH > 10 IU/mL). RDW seems to be a useful, cheap, and easy to assay marker; however, it is still an underestimated marker in clinical practice.

A major limitation of our study is the lack of evaluation of BNP and CRP in plasma and an echocardiogram necessary to assess the clinical status of the patient, particularly with respect to heart failure and inflammation overlapping with hypothyroidism and anaemia. What is more, unfortunately data on RDW values assessed in the studied group after euthyroidism is restored were not available. However, we might speculate that adequate hormonal replacement therapy with L-thyroxine brings back the risk in CHF patients to the level found in euthyroid subjects with CHF. Hyperthyroid patients treated with RIT are at relatively high risk of hypothyroidism [49]. However, it should be interpreted as neither a complication nor a side effect, but instead as an indicator of the efficacy of RIT therapy and the desired therapeutic effect. Hypothyroidism following RIT can quickly be managed with L-thyroxine, and euthyroidism can be promptly restored. However, our study demonstrates that high vigilance must be maintained when monitoring patients following RIT with heart failure because a decline in thyroid hormonal production might deteriorate the course of CHF and worsen the final prognosis. Thus, it is important for practitioners to regularly asses the thyroid function following radioiodine administration to prevent development of overt hypothyroidism. Subclinical hypothyroidism or high-normal levels of TSH seemed not be a factor affecting RDW in a significant manner, at least in the studied population. In conclusion, our results demonstrate that concomitant overt hypothyroidism may contribute to deterioration of CHF, as reflected in changes of RDW value.

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