Association of Thyroid Function with Early/Mid-term Aorta-Related Adverse Events and Readmissions after Thoracic Endovascular Aortic Repair

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The prognosis of patients after thoracic endovascular aortic repair (TEVAR) is affected by several clinical characteristics. This study aimed to evaluate whether thyroid hormones predicts early (30 days) and mid-term (12 months) aorta-related adverse events (ARAE) and readmissions (ARAR) in patients after TEVAR. A total of 338 continuous patients who underwent TEVAR were included and stratified based on quartile of free thyroxine (FT4) levels examined before surgery. The relationship of FT4 levels with early or mid-term ARAE and ARAR were assessed using univariate and multiple logistic regression analysis. The incidence of ARAE and ARAR were 2.7% and 4.1% within 30 days, and 8.9% and 13.5% within 12 months, respectively. After adjusting for confounders, the lowest FT4 quartile group were noted to be at significantly greater risk than the highest FT4 quartile group in early (OR 10.105, 95% CI 1.103 to 92.615, \(P=0.041\)) and mid-term (OR 5.687, 95% CI 1.708 to 18.935, \(P=0.005\)) ARAR, but not significantly different in early (OR 2.097, 95% CI 0.228 to 19.307, \(P=0.513\)) and mid-term (OR 0.695, 95% CI 0.207 to 2.332, \(P=0.556\)) ARAE. Thus, patients with low-normal FT4 levels after TEVAR are at greater risk of ARAR, but not ARAE, in both the early and the mid-term follow-up periods.

Thoracic endovascular aortic repair (TEVAR) has been increasingly applied to treat a variety of aortic diseases1,2. Nevertheless, it is still a young technology with several unknowns, including the risk factors for the prognosis of patients after TEVAR. Thyroid hormones play important roles in the development and functioning of the circulatory system. Several studies have demonstrated that overt thyroid disorders, or even subclinical dysfunction, are associated with cardiovascular disease3–7. Blood pressure and heart rate, which can be affected by thyroid hormones, are associated with the prognosis of patients after TEVAR8,9.

It is unclear whether thyroid hormone levels are related to aortic diseases and whether thyroid hormones could provide valuable predictive information for patients after TEVAR. The aim of this study was to investigate the influence of thyroid hormones on aorta-related adverse events (ARAE) and readmissions (ARAR) during the early (30 days) and mid-term (12 months) follow-up periods after TEVAR.

Methods

Study population. A retrospective study was conducted on prospectively collected data of aortic disease patients undergoing TEVAR from January 2004 to December 2015 at Wuhan Asia Heart Hospital. Participants who had a medical history of aortic disease, Marfan syndrome or other connective tissue disease, cancer, renal insufficiency, and clinical hyperthyroidism or hypothyroidism were excluded. Participants who were scheduled to have or who underwent surgical procedures within 30 days of study enrolment were also excluded.

The methods in the study were in accordance with relevant guidelines and the Declaration of Helsinki. Written informed consent was obtained from all participants. All procedures were approved by the Ethics Committee of Wuhan Asia Heart Hospital and the Ethics Committee of The First Affiliated Hospital of Shantou University Medical College.

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Procedures. All subjects routinely received a contrast-enhanced computed tomography (CT) scan before a TEVAR procedure. The indications for the TEVAR procedure were aortic dissection (AD), intramural hematoma (IMH), aortic aneurysm (AA), penetrating aortic ulcer (PAU), and traumatic aortic lesions. Successful procedures were defined as technically accurate placement of the stent graft at the intended target location without endoleak.

Subjects were classified into the acute group (≤14 days), the sub-acute group (15–90 days), and the chronic group (>90 days), based on the time interval from symptom onset date to procedure date.

Diagnostic criteria. Concentrations of serum free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were measured on fasting, morning samples using 2 different assays. Hyperthyroidism and hypothyroidism were defined as serum TSH < 0.45 μU/L and TSH > 19.9 μU/L, respectively. All participants were stratified by quartiles based on of FT4 levels.

Persistent or unrelenting pain despite having received maximal medical therapy was considered as refractory pain. Refractory hypertension was defined as persistent hypertension despite having received ≥3 different classes of antihypertensive therapies at best recommended or maximum tolerated doses. Rupture or impending rupture was defined as extravasation of fresh blood outside the thoracic aorta or concomitant hemothorax documented by preoperative CT.

Follow-up. All subjects were followed up by 3 clinical cardiologists at 30 days, 3 months, 6 months, and 12 months from the completion of the TEVAR procedure. Symptoms, medications, laboratory measurements, electrocardiogram and imaging tests (ultrasonic cardiogram and contrast-enhanced CT, depending on medical criteria) were collected by electronic data capture and telephone interviews. Early (30 days) and mid-term (12 months) ARAE and ARAR were the primary outcomes of our study.

ARAR was defined as aorta-related death, progression of aortic disease, organ failure or lower limb ischemia, aortic expansion of >5 mm, or endoleak. ARAR was defined as readmissions associated with any aorta-related complications, such as progression of aortic disease, organ failure or lower limb ischemia, surgical requirement, or occurrence of similar symptoms upon aortic disease onset without other diseases identified by a comprehensive clinical examination.

Statistical analysis. Continuous variables were presented as means ± standard deviations or medians (quartile 1 to quartile 3). Categorical variables were shown as counts and percentages. Analysis of variance, Kruskal-Wallis test, and Chi-square test were used to compare the difference in normal continuous variables, non-normal continuous variables and categorical variables, respectively. The relationship between thyroid hormones and 30-day or 12-month ARAE and ARAR were assessed using univariate and multiple logistic regression analysis. Candidate covariates for multivariable modelling were selected based on p-value (P < 0.1) in univariate logistic regression analysis. Odds ratios (ORs) were presented with 95% confidence interval, and a two-tailed P ≤ 0.05 was considered statistically significant. All data analyses were performed using the statistical software Statistical Product and Service Solution (SPSS 19.0 for Windows, Chicago, Illinois, USA).

Data availability statement. All raw data and analysis code are available from the corresponding author on reasonable request.

Results
Demographics. Three hundred and thirty-eight subjects (mean age 56.5 years, 276 males, 62 females) were included: 221 patients with AD, 78 patients with IMH, 32 patients with AA, and 7 patients with PAU. There were 182 subjects in the acute phase, 85 subjects in the sub-acute phase, and 71 subjects in the chronic phase.

The clinical and operative procedure characteristics of subjects stratified by FT4 levels are shown in Table 1 and Table 2, respectively. None of the parameters were significantly different among the 4 levels. The medians (Q1–Q3, ng/dl) of the FT4 quartiles were 0.82 (0.76–0.86), 0.95 (0.92–0.98), 1.12 (1.07–1.17), and 1.35 (1.28–1.49), respectively.

Univariate analysis and multiple logistic regression analysis at early follow-up. All 338 patients completed 30 days of follow-up, and the incidence of patients with ARAR was 4.1%. The univariate analysis indicated that there were 3 variables (other than thyroid hormones) associated with early ARAR, including glomerular filtration rate (GFR), cerebrovascular diseases (CVD), and operative procedure. Multiple logistic regression showed that, FT4 levels (OR 0.079, 95% CI 0.004 to 1.074, P = 0.105) were not associated with 30-day ARAR when FT4 was analyzed as a continuous variable. When all participants were stratified into quartiles based on FT4 levels, the lowest FT4 quartile group were at significantly greater risk of 30-day ARAR (OR 10.105, 95% CI 1.103 to 92.615, P = 0.041) compared to the highest FT4 quartile group. There was no significant association between 30-day ARAR and neither FT3 (OR 3.288, 95% CI 0.780 to 13.839, P = 0.203) nor TSH OR 0.508, 95% CI 0.242 to 1.064, P = 0.45). Besides FT4, GFR (OR 0.972, 95% CI 0.946 to 0.999, P = 0.044) was another multivariable predictor of ARAR. The results of multivariable logistic analyses for ARAR within 30 days are shown in Table 3.

The incidence of patients with early ARAE was 2.7%. Operative procedure and blood transfused were variables significantly associated with ARAE on univariate analysis. The results of multiple logistic regression analysis showed that FT4 (OR 0.543, 95% CI 0.022 to 13.697, P = 0.711) was not associated with 30-day ARAE when FT4 was analyzed as a continuous variable. When all participants were stratified by quartiles of FT4, no significant associations were noted between 30-day ARAE and the lowest FT4 quartile group (OR 2.097, 95% CI 0.228 to 19.307, P = 0.513), FT3 (OR 3.168, 95% CI 0.688 to 14.587, P = 0.139), and TSH (OR 1.016, 95% CI 0.692 to 1.491, P = 0.937).
**Univariate analysis and multiple logistic regression analysis at mid-term follow up.** A total of 288 patients (85.2%) were followed-up with regard to 12-month ARAR; the percentage of patients that encountered ARAR was 13.5%. Potential risk factors for mid-term ARAR identified by univariate analysis were gender, tobacco abuse, peripheral arterial disease (PAD), CVD, GFR, and stage of aortic diseases. After adjustment for these factors, FT4 (OR 0.114, 95% CI 0.018 to 0.705, \( P = 0.019 \)) was noted to be significantly associated with 12-month ARAR when FT4 was analyzed as a continuous variable. When all participants were stratified by quartiles of FT4, no significant associations were noted between 12-month ARAR and the lowest FT4 quartile group (OR 0.695, 95% CI 0.207 to 2.332, \( P = 0.556 \)).

**Discussion**

This study showed that among subjects who underwent TEVAR, those who had low-normal levels of FT4 were at increased risk of ARAR compared to those with high-normal levels of FT4 in both early and mid-term follow-up.

The entire circulatory system and thyroid are closely linked by their embryological anlage. The metabolic functions and the effects of thyroid hormones on the heart and vasculature have been discussed in several studies. Thyroid hormones function in the maintenance of normal vascular remodeling. When the secretion of thyroid hormones is disordered, the altered blood coagulability and endothelial dysfunction will affect the remodeling of the damaged aorta, resulting in increased risk in developing aorta-related clinical symptoms and possible readmission.

In spite of this, the relationship between subclinical hypothyroidism and cardiovascular diseases has not been fully elucidated. One of the most common cardiovascular manifestations of hypothyroidism is hypertension,
which results from increasing systemic vascular resistance. Hypertension can be aggravated by hypothyroidism4. At the same time, hypertension can also lead to poor prognosis for patients after TEVAR10,16. Therefore, lower levels of thyroid hormones may cause patients to be at a higher risk of readmission.

Lower levels of FT4, even within the normal range, can influence increased arterial stiffness, coronary artery calcification, atherosclerosis, cardiac pump performance, and C-reactive protein4,17-20. These clinical characteristics are also predictive factors of the adverse outcomes in patients after TEVAR21–23. Owing to the aforementioned effects of thyroid hormones on the overall vascular system, it is reasonable to find an association between low-normal levels of FT4 and increased risk of ARAR in patients after TEVAR.

In addition to reflection of the negative feedback of T4 and T3, TSH also embodies other influences, such as drugs and non-thyroidal disease24. FT3 and FT4 levels are differentially associated with some cardiovascular risk markers in euthyroid subjects25. Therefore, it is plausible that the levels of FT4 reflect a more sensitive index of cardiac “thyroid status”. This could explain why in this study, FT4, but not TSH and FT3, was an independent predictor of aortic readmission. Similar findings on the relationship of thyroid hormones and cardiovascular diseases were also reported in previous studies9,25.

Monitoring both ARAE and ARAR could provide additional information than monitoring only one of these parameters. Some researchers have found an inverse relationship between the risk of adverse events and the risk of readmission. In other words, patients who are at higher risk of readmission are at lower risk of adverse events.

Table 2. Population operative characteristics stratified by FT4. AD, aortic dissection; IMH, intramural hematoma; AA, aortic aneurysm; PAU, penetrating aortic ulcer; TEVAR, thoracic endovascular aortic repair; FT4, free thyroxine.

Table 3. Multiple logistic regression analysis for 30-day aorta-related readmissions. FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; FT4, free thyroxine; GFR, glomerular filtration rate; CVD, cerebrovascular diseases; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; OR, odds ratio; CI, confidential interval.
| OR  | 95% CI    | P value |
|-----|-----------|---------|
| Gender |            |         |
| Tobacco abuse |    |         |
| None | Reference |         |
| Current | 1.293 | 0.476–5.12 | 0.614 |
| Former | 1.466 | 0.428–5.013 | 0.542 |
| PAD | 0.983 | 0.447–2.163 | 0.967 |
| CVD | 3.161 | 1.392–7.177 | 0.006 |
| GFR | 0.987 | 0.97–1.005 | 0.160 |

Table 4. Multiple logistic regression analysis for 12-month aorta-related readmissions. PAD, peripheral arterial disease; CVD, cerebrovascular diseases; GFR, glomerular filtration rate; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; FT4, free thyroxine; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; OR, odds ratio; CI, confidential interval.

Conclusions

This study showed that, in comparison to patients with high-normal FT4 levels, patients with low-normal FT4 levels had greater risk of experiencing ARAR after TEVAR during the early and mid-term follow-up periods. In contrast, risk of ARAE was not significantly different in patients with differing FT4 levels. These findings need to be further verified in larger clinical studies before they can provide remarkable contributions to the prognostic assessment of patients after TEVAR.

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