Anterior mediastinal tissue volume is correlated with antiacetylcholine receptor antibody level in myasthenia gravis

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ABSTRACT

Objectives: Extended thymectomy is a treatment option for myasthenia gravis (MG), but the surgical indications are controversial. Pathologic features of the thymus can be used to predict surgical outcomes, but there is no reliable method for evaluating these characteristics preoperatively. The purpose of this study was to determine whether anterior mediastinal tissue volume, as measured via 3-dimensional computed tomography (3DCT) volumetry, correlates with serum anti-acetylcholine receptor antibody (AChRab) levels in patients undergoing thymectomy for myasthenia gravis. Therefore, we investigated the relationships among anterior mediastinal tissue volume determined by 3DCT volumetry and AChRab levels.

Methods: The subjects were 28 patients who underwent extended thymectomy and were enrolled retrospectively. We measured volume of the anterior mediastinum and calculated the volumes of more than -30 Hounsfield units (V_{-30}) by using 3DCT volumetry and compared them with perioperative AChRab levels. The significance of their volumes in MG was examined by comparison with 53 patients without MG.

Results: V_{-30} values were related to age and were significantly greater in patients with MG than in patients without MG ($P < .001$). V_{-30} values were correlated positively with preoperative AChRab levels ($\rho = 0.505$, $P = .006$) and inversely with the post/preoperative AChRab ratio ($\rho = -0.453$, $P = .018$). The histologic nonadipose tissue ratio was correlated with the V_{-30} /volume of the anterior mediastinum ($\rho = 0.700$, $P < .001$).

Conclusions: This method for evaluation of the anterior mediastinal tissue volume and AChRab production may be helpful in establishing a treatment plan for MG. (J Thorac Cardiovasc Surg 2018;155:2738-44)

Three-dimensional images of the anterior mediastinum.

Central Message

The preoperative anterior mediastinal tissue volume with 3DCT volumetry is correlated with AChRab production, and may be helpful in establishing a treatment plan for myasthenia gravis.

Perspective

Extended thymectomy is an effective treatment for myasthenia gravis (MG), but prediction of surgical outcomes is challenging. Here, we show that an anterior mediastinal tissue volume of more than -30 HU (V_{-30}) determined preoperatively by 3DCT volumetry is correlated with antiacetylcholine receptor antibody (AChRab) levels. The V_{-30} /preoperative AChRab ratio is a prognostic factor that may be helpful in treatment planning for MG.

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Extended thymectomy is a treatment option for antiacetylcholine receptor antibody (AChRab)-positive myasthenia gravis (MG) and has yielded good results.¹⁻⁵ The pathologic features of the resected thymus, such as the presence of hyperplasia,⁶ germinal center, and active ectopic thymus,^{7,8}

Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms	
3DCT	= 3-dimensional computed tomography
AChRAb	= antiacetylcholine receptor antibody
CT	= computed tomography
HU	= Hounsfield unit
MG	= myasthenia gravis
V ₋₃₀	= volume of tissue with a value more than -30 Hounsfield units
V _{AM}	= volume of the anterior mediastinum

have been used to predict surgical outcomes, but there is no reliable method for evaluating these characteristics preoperatively. The purpose of this study was to determine whether anterior mediastinal tissue volume, as measured with 3-dimensional computed tomography (3DCT) volumetry,

correlates with serum AChRAb levels in patients undergoing thymectomy for MG.

On computed tomography (CT), the normal thymus and thymic hyperplasia exhibit soft-tissue attenuation similar to muscle,⁹ whereas the low-attenuation area of the thymus is increased with aging due to progressive fatty infiltration.⁹ Thymus tissue is likely to play a role in producing AChRAb. Therefore, we hypothesized that the volume of nonadipose soft tissue in the anterior mediastinum may correlate with the antibody production in patients with MG. 3DCT is widely used, and we have frequently used this method in the pulmonary field.¹⁰⁻¹³

PATIENTS AND METHODS

Patient Selection

A retrospective chart review was performed on the medical records for 81 patients with thin-slice CT available, including 28 who underwent

FIGURE 1. A, Three-dimensional images of the anterior mediastinum. The left anterior oblique view is shown on the *left*, the front view is shown in the *center*, and the right anterior oblique view is shown on the *right*. The left and right lateral sides are indicated by *white* and *gray* arrows, respectively. B, A histogram of the volume number with the computed tomography value (Hounsfield units).

extended thymectomy for AChRab-positive MG, 16 patients without MG with thymoma, and 37 individuals who donated lobes for living-donor lobar lung transplantation with available data on preoperative nonenhanced CT. All patients underwent an extended thymectomy at Kyoto University Hospital between January 2000 and February 2015. This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (Reference number: E2504).

Methods

The total volume of the anterior mediastinum including anterior mediastinal and pericardial adipose tissue but excluding the volume of thymoma is defined as V_{AM} . The mediastinal tissue volume with a value of more than -30 Hounsfield units (HU) was calculated to eliminate adipose tissue,^{10,11} and this value is referred to as V_{-30} (Figure 1, A and B). Anterior mediastinal 3DCT volumetry was performed with 0.5-mm axial slices of nonenhanced CT images with Synapse 3D imaging software (Fujifilm Corp, Tokyo, Japan), as we previously reported.¹⁰⁻¹³ The anterior mediastinal region was manually segmented by tracing the edge of the area (Video 1). In cases in which a thymoma was present, the tumor volume was excluded from the anterior mediastinal volume, and the final volume was defined as V_{AM} . V_{AM} and V_{-30} were measured repeatedly by one author blinded to perioperative data, outcome, and all information except the study ID number of each patient and were confirmed by another author blinded to the same information.

Variables and Anterior Mediastinal Volumes

Age, sex, and the presence of thymoma were compared between the MG and non-MG groups. Clinical information for patients with MG included preoperative performance status, Myasthenia Gravis Foundation of America stage, AChRab levels preoperatively and at the earliest postoperative measurement (after a mean of 24.0 [range, 10-58] days), and presence of thymoma.

The volume of tissue with a value measuring more than -30 HU was calculated to eliminate adipose tissue,^{14,15} and this value is referred to as V_{-30} (Figure 1, A and B). The V_{-30} values of patients without MG (16 patients with thymoma with normal AChRab and 37 healthy individuals who donated lobes for living-donor lobar lung transplantation between 2009 and 2011) were compared with those of patients with MG. For patients with MG, the relationship between V_{-30} values and perioperative AChRab levels was also investigated. In one case with a MG crisis just after an operation, the AChRab levels were excluded from the post/preoperative AChRab ratio evaluation.

Pathohistologic Examination of the Resected Thymus in All Patients With MG

Resected tissue (excluding adipose tissue) from 28 patients who received extended thymectomy was examined histologically. Two board-certified pathologists examined 5 to 7 slices with hematoxylin-eosin staining in each specimen. We evaluated the characteristic histology including thymic hyperplasia. The histologic volume ratio excluding adipose tissue was calculated by the proportional average in each slide.

Statistical Analysis

Age and preoperative height, weight, body mass index, and body surface area were summarized as mean (standard deviation). Other continuous variables were summarized as median (ranges). Categorical variables were summarized as counts and proportions. For continuous variables, differences in patients' characteristics between the MG and non-MG groups were compared with the Student *t* test or Wilcoxon rank sum test. For binary variables, they were compared by with the χ^2 test. Spearman rank correlations were used to evaluate the associations between the 2 variables. The difference in V_{-30} values between the MG and non-MG groups was estimated via multiple regression analysis

VIDEO 1. Anterior mediastinal 3DCT volumetry was performed with 0.5-mm axial slices of nonenhanced computed tomography images with Synapse 3D imaging software (Fujifilm Corp, Tokyo, Japan). The anterior mediastinal region was manually segmented by tracing the edge of the area. In cases in which a thymoma was present, the tumor volume was excluded from the anterior mediastinal volume, and the final volume was defined as V_{AM} . The anterior mediastinal volume obtained by 3DCT volumetry is defined as V_{AM} . The volume of tissue with a value of more than -30 HU was calculated to eliminate adipose tissue, and this value is referred to as V_{-30} . 3CDT, 3-Dimensional computed tomography. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)32425-X/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)32425-X/fulltext).

with the volume of anterior mediastinum, thymoma, and age as covariates. All *P* values were 2-sided, and *P* < .05 was considered statistically significant. Statistical analyses were performed with JMP 12 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients

The MG group consisted of 28 patients, including 14 with thymoma, and the non-MG group consisted of 53 patients, including 16 with thymoma and 37 donors for living-donor lobar lung transplantation. The distribution of sex, age, and rate of thymoma did not differ significantly between the 2 groups (Table 1). The background of the 28 patients with MG who underwent extended thymectomy is summarized in Table 2. The distribution of the preoperative performance status score was 0, 85.7%; 1, 7.1%; 2, 3.6%; 3, 0.0%; and 4, 3.6% and that of the pretreatment Myasthenia Gravis Foundation of America stage was I, 43.6%; IIa, 38.2%; IIb, 0%; IIIa, 1.8%; IIIb, 9.1%; IVa, 0%; and IVb, 1.8%. The median postoperative AChRab level was significantly lower than the preoperative level (17.0 vs 23.0 nmol/L, *P* < .001). The median post/preoperative AChRab ratio was 0.65 (range, 0.16-3.44). The approach for extended thymectomy was median sternotomy in 9 patients, bilateral video-assisted thoracoscopic surgery in 16 patients, and robotic-assisted thoracoscopic surgery in 1 patient.

TABLE 1. Background characteristics of patients and values of V_{AM} and V_{-30}

Variables	MG group (n = 28)	Non-MG group (n = 53)	P value
Age, y, mean $\pm$ SD	45.8 $\pm$ 3.0	47.8 $\pm$ 2.2	.596*
Sex, male, n (%)	14 (50.0)	26 (49.1)	.936†
Thymoma, n (%)	14 (50.0)	16 (30.2)	.079†
V_{AM} , mL, median (range)	47.5 (14.4-205.3)	43.6 (2.8-209.1)	.076‡
V_{-30} , mL, median (range)	12.2 (2.7-45.8)	4.5 (0.7-23.2)	<.001‡

MG, Myasthenia gravis; SD, standard deviation; V_{AM} , volume of the anterior mediastinum; V_{-30} , volume of tissue with a value more than -30 Hounsfield units. *Student *t* test. † χ^2 test. ‡Wilcoxon rank sum test.

Preoperatively, 5 patients were treated with plasma exchange, 6 with intravenous immunoglobulin, and 5 with steroid pulse therapy. Postoperative plasma exchange was performed in 2 patients, and steroid pulse therapy was administered in 15 patients. Eight resected specimens (28.6%) showed thymic hyperplasia, and 3 (10.7%) had an atrophic thymus.

V_{-30} Values of Patients With MG Were Significantly Greater Than Those of Patients Without MG

The median V_{AM} and V_{-30} values were 47.5 mL (range, 14.4-205.3) and 12.2 mL (range, 2.7-45.8) in the MG group and 43.6 mL (range, 2.8-209.1) and 4.5 mL (range, 0.7-23.2) in the non-MG group on Synapse 3D (Table 1 and Figure 2). V_{-30} values were associated with age in the non-MG group but not with V_{AM} and the presence of thymoma. The median V_{-30} was significantly greater in patients with MG ($P < .001$).

TABLE 2. Background characteristics of all patients with MG (n = 28)

Variables	Number
Preoperative PS, 0/1/2/3/4	24/2/1/0/1 (85.7%/7.1%/3.6%/0%/3.6%)
Preoperative height, cm, mean $\pm$ SD	163.5 $\pm$ 9.4
Preoperative weight, kg, mean $\pm$ SD	59.2 $\pm$ 10.9
Preoperative BMI, kg/cm ² , mean $\pm$ SD	22.1 $\pm$ 3.1
Preoperative body surface area, m ² , mean $\pm$ SD	1.63 $\pm$ 0.18
Preoperative MGFA, I/IIa/IIIa/IIIb/IVb	7/14/0/3/3/1 (43.6%/38.2%/1.8%/9.1%/5.5%/1.8%)
Preoperative AChRab, nmol/L, median (range)	23.0 (0.8-340)
Postoperative AChRab, nmol/L, median (range)	17.0 (1.0-350)
Post/preoperative AChRab ratio, median (range)	0.65 (0.16-3.44)

PS, Performance status; SD, standard deviation; BMI, body mass index; MGFA, Myasthenia Gravis Foundation of America; AChRab, antiacetylcholine receptor antibody.

The *P* values of V_{AM} and the presence of thymoma were relatively small ($P = .076, .079$). We performed the multiple regression analysis in which V_{-30} values were response variables and age, presence of thymoma, and V_{AM} were covariates considering their results of univariate analysis and clinical information. The result showed that V_{-30} remained significantly greater in patients with MG compared with that in patients without MG ($P < .001$; 95% confidence interval, 2.54-5.73) (Table 3).

Correlations of V_{-30} With Pre- and Postoperative AChRab Levels in Patients With MG

V_{-30} values were significantly and positively correlated with preoperative AChRab levels ($\rho = 0.505, P = .006$; 95% confidence interval, -0.59 to 0.12) and inversely correlated with post/preoperative AChRab ratios ($\rho = -0.453, P = .018$; 95% confidence interval, -0.22 to 0.50) (Figure 2). They were moderate correlations. V_{AM} values did not show these correlations ($P = .167, .510$). Spearman rank correlations were used to evaluate the associations between the 2 variables with correlation coefficient (ρ), and rated as $\rho \geq 0.2$, weak correlation, $\rho \geq 0.4$, moderate correlation; and $\rho \geq 0.6$, strong correlation.

Correlations of V_{-30} With Pre- and Postoperative AChRab Levels in Patients Without Thymoma

The relationship between V_{-30} and AChRab levels was examined in 14 patients with MG without thymoma. V_{-30} was significantly and strongly correlated with the post/preoperative AChRab ratio ($\rho = -0.631, P = .015$; 95% confidence interval, -0.50 to 0.56) and had a borderline correlation with preoperative AChRab levels ($\rho = 0.477, P = .085$; 95% confidence interval, -0.72 to 0.27) (Figure 3).

Correlation Between V_{-30} and Histology of the Resected Specimen in Patients With MG

Histologic examination showed thymic hyperplasia in 9 patients (32.1%), atrophic thymus in 3 patients (10.7%), and thymoma in 14 patients (50.0%). The histologic volume ratio of cells in the whole anterior mediastinal volume was calculated and compared with the V_{-30}/V_{AM} ratio

FIGURE 2. The median V_{AM} and V_{-30} values were 47.4 mL (range, 14.4-205.3) and 12.2 mL (range, 2.7-45.8) in the MG group and 43.6 mL (range, 2.8-209.1) and 4.5 mL (range, 0.7-23.2) in the non-MG group on Synapse 3D. V_{AM} , Volume of the anterior mediastinum, V_{-30} , volume of tissue with a value more than -30 Hounsfield units; MG, myasthenia gravis.

measured by 3DCT volumetry. The histologic volume ratio was strongly correlated with the V_{-30}/V_{AM} ratio ($\rho = 0.700$, $P < .001$; 95% confidence interval, 0.32-0.81). Preoperative AChRab levels in patients with thymic hyperplasia were significantly greater than those in patients without thymic hyperplasia ($P = .040$), but there was no significant difference in V_{-30} values between these groups ($P = .878$). Preoperative AChRab levels were not associated with the presence of thymoma ($P = .854$).

DISCUSSION

The aim of this study was to investigate the significance of the anterior mediastinal tissue volume determined with 3DCT volumetry and the relationship between the volume and clinical data. Mediastinal tissue volumes with a value of more than -30 HU were of significance in patients with MG, and these volumes were correlated with serum AChRab levels and pathologic features.

The remission or improvement rate of MG after extended thymectomy is reported to be 75% to 81%,¹⁻³ and this procedure is an effective treatment option for AChRab-positive MG.^{4,16,17} However, surgical treatment has been associated with poor outcomes in elderly patients,¹⁸⁻²⁰ which is probably because the pathologic features were associated with the clinical outcomes described in previous articles.^{2,3,17} However, there is no method to evaluate features of the thymus preoperatively.⁹ Thus, we

have developed a new technique to evaluate anterior mediastinal tissue on CT using 3DCT volumetry.

The transition of AChRab level has been suggested to be an index of clinical improvement of MG after surgery.²¹ AChRab is derived from thymic tissue, and its secretion is stimulated by thymocytes or lymphocytes,^{1,19,21} which suggests that the AChRab level may be associated with specific tissues producing antibodies. Therefore, we also investigated relationships among AChRab levels, anterior mediastinal volumes, and tissue features in a specific CT value range on CT images.

Extended thymectomy for MG is a recognized surgical method for removal of the anterior mediastinal tissue, including the anterior mediastinal fat inferiorly, inferior aspect of the thyroid gland superiorly, and inside than each phrenic nerve laterally.^{3,4,20} The CT value for intrathoracic adipose tissue has been found to be less than -30 HU,^{14,15} and other studies suggest that a hyperplastic gland shows soft-tissue attenuation, except for adipose tissue.^{18,22} The germinal center was described to exist in ectopic site of patients with MG.⁷ With reference to these studies, we used a value of more than -30 HU (V_{-30}) to exclude adipose tissue on 3DCT volumetry, and we assumed that the V_{-30} of the thymus reflected the production of AChRab. Interestingly, in our study, body weight and body mass index were correlated with V_{AM} ($P = .005$ and $< .001$, respectively) but not V_{-30} .

V_{-30} showed a positive correlation with the preoperative AChRab level and an inverse correlation with the post/preoperative AChRab ratio. These results indicate that the V_{-30} value reflects the thymic function of AChRab production. The inverse correlation between V_{-30} and the post/preoperative AChRab ratio also suggests that V_{-30} reflects the ability for local antibody production. V_{-30} was also strongly correlated with the histologic volume, which supports the reliability of V_{-30} as a reflection of the actual

TABLE 3. Characteristics of propensity-matched patients

Variables	Estimation	P value	95% CI
MG	8.27	<.001	5.09 to 11.46
V_{AM}	0.08	<.001	0.04 to 0.11
Thymoma	3.17	.075	-0.32 to 6.66
Age	-0.19	<.001	-0.30 to -0.09

CI, Confidence interval; MG, myasthenia gravis; V_{AM} , volume of the anterior mediastinum.

FIGURE 3. V_{-30} was significantly and positively correlated with the preoperative AChRAb level ($\rho = 0.505$, $P = .006$) (A) and inversely correlated with the post/preoperative AChRAb ratio ($\rho = -0.453$, $P = .018$) (B). AChRAb, Antiacetylcholine receptor antibody; V_{-30} , volume of tissue with a value more than -30 Hounsfield units.

thymus volume. The ability to produce AChRAb in the thymus is the basis for choice of extended thymectomy for MG, although it is appropriate to regard MG as a systemic disease because other sites may also produce AChRAb.^{23,24} Establishment of the volume of the lesion associated with MG or the thymic contribution to MG may help to determine treatment strategy for MG and to elucidate the etiology of MG.

Study Limitations

This study has several limitations. First, it was conducted in a single institution with a limited number of patients and was retrospective in nature. A long-term investigation was needed because MG is a very rare disease, but the length of the study period caused the development of radiologic imaging to become a limitation. Greater reliability would have been obtained using the same CT device over a shorter study period. We also only analyzed patients for whom thin-slice CT was available, which leads to a selection bias. In addition, postoperative AChRAb levels were not measured at a fixed time, and the presence of thymoma may have influenced the levels of AChRAb; however, we suspect that the effect would be negligible and thymoma is also taken into account in making propensity-matched groups. Prospective and/or multi-institutional studies are required to validate the findings of this study.

CONCLUSIONS

Anterior mediastinal volumes of more than -30 HU on CT were positively correlated with preoperative AChRAb levels and inversely correlated with post/preoperative AChRAb ratios. Quantification of the anterior mediastinal

tissue volume using 3DCT volumetry may help with the development of a treatment plan for MG.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: myasthenia gravis, antiacetylcholine receptor antibody, 3-dimensional computed tomography volumetry, extended thymectomy, prognostic factor