The upper cervical spine is commonly involved in persons with rheumatoid arthritis (RA),10,16,18,23,24 and the cervical involvements are well known to follow a specific deformation pattern typified as atlantoaxial subluxation (AAS). However, these patterns have been assessed only two-dimensionally, mainly with lateral radiography, even though the deformities occur three-dimensionally with a wider range of variation than was previously thought. Although 2D measurements such as radiography, conventional CT, and conventional MRI4,8,9,22,25,26 have long been used in the evaluation of cervical lesions caused by RA, 2D measurements are limited in their effectiveness for detecting subtle and complex morphological and kinematic changes. The purpose of this study was to elucidate the 3D kinematics of the upper cervical spine in RA and the relationship between 3D morphological changes and decreased segmental rotational motion.

Object. The upper cervical spine is commonly involved in persons with rheumatoid arthritis (RA). Although 2D measurements have long been used in the evaluation of cervical lesions caused by RA, 2D measurements are limited in their effectiveness for detecting subtle and complex morphological and kinematic changes. The purpose of this study was to elucidate the 3D kinematics of the upper cervical spine in RA and the relationship between 3D morphological changes and decreased segmental rotational motion.

Methods. Twenty-five consecutive patients (2 men and 23 women, mean age 63.5 years, range 42–77 years) with RA (the RA group) and 10 patients (5 men and 5 women, mean age 69.9 years, range 57–82 years) with cervical spondylosis and no involvement of the upper cervical spine (the control group) underwent 3D CT of the cervical spine in 3 positions (neutral, 45° head rotation to the left, and 45° head rotation to the right). The segmental rotation angle from the occiput (Oc) to C-2 was calculated for each participant using a voxel-based registration method, and the 3D destruction of articular facets was quantified using the authors’ own parameter, the articular facet index.

Results. The segmental rotation angle was significantly smaller at C1–2 and larger at Oc–C1 in the RA group compared with the control group. The degree of the destruction of the articular facet at C-1 and C-2 correlated with the segmental rotation angle.

Conclusions. In vivo 3D kinematics of the upper cervical spine during head rotation in patients with RA were accurately measured, allowing quantification of the degree of joint destruction for the first time. Joint destruction may play an important role in decreasing segmental motion of the upper cervical spine in RA.

key words • rheumatoid arthritis • upper cervical spine • 3D • voxel-based registration • head rotation • articular facet

Abbreviations used in this paper: AAS = atlantoaxial subluxation; ADI = anterior atlantodental interval; AFI = articular facet index; ICC = intraclass correlation coefficient; Oc = occiput; RA = rheumatoid arthritis; RMSE = root mean square error.

The upper cervical spine is commonly involved in persons with rheumatoid arthritis (RA),10,16,18,23,24 and the cervical involvements are well known to follow a specific deformation pattern typified as atlantoaxial subluxation (AAS). However, these patterns have been assessed only two-dimensionally, mainly with lateral radiography, even though the deformities occur three-dimensionally with a wider range of variation than was previously thought. Although 2D measurements such as radiography, conventional CT, and conventional MRI4,8,9,22,25,26 have long been used in the evaluation of cervical lesions caused by RA, 2D measurements are limited in their effectiveness for detecting subtle and complex morphological and kinematic changes in RA cervical lesions. Because of methodological difficulty, there have been few reports17,20,21 on 3D morphology and kinematics of RA cervical lesions. In addition, there are no published quantitative evaluations of 3D morphological changes or explanations of how those changes affect joint kinematics.

In previous studies, we documented morphological and kinematic changes in the wrist and foot caused by RA, using our own 3D motion analysis method.1,2,14 By comparing persons with RA and persons without RA, we showed that the morphological changes associated with RA could cause abnormal joint kinematics. It is thought
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to be very important for spinal surgeons to have an accurate understanding of the morphological and kinematic changes in the cervical spine in RA, especially when making surgical plans and evaluating patients’ postoperative condition. In the study we report here, we quantified the degree of 3D morphological change in RA cervical lesions for the first time using our own method. The purposes of our study were 1) to quantitatively measure 3D morphological and kinematic changes in the upper cervical spine in persons with RA by comparing their spines with those of persons without RA, and 2) to elucidate the relationship between those morphological and kinematic changes.

Methods

We included in our study 25 consecutive patients (2 men and 23 women, mean age 63.5 years, range 42–77 years) with cervical lesions caused by RA (the RA group), and 10 patients (5 men and 5 women, mean age 69.9 years, range 57–82 years) with cervical spondylosis who had no involvement of the upper cervical spine as an age-matched control group (the control group). There was no significant difference in age between the groups (p = 0.09). All study protocols were approved by our institution’s review board.

Flexion-extension lateral radiographs, obtained with the patient upright, were used for measurement. The anterior atlantodental interval (ADI), the Ranawat value, and the Redlund-Johnell value were measured. AAS was defined as an ADI > 3 mm on flexion lateral radiographs, and AAS was further classified as reducible or irreducible according to whether the ADI was reduced to < 3 mm during extension. Vertical subluxation for female study participants was defined as the presence of a Ranawat value of < 13 mm or a Redlund-Johnell value of < 32 mm. For male participants, it was defined as Ranawat value of < 13 mm or a Redlund-Johnell value of < 37 mm. Subaxial subluxation was defined as the distance between the posterior borders of adjacent vertebral bodies of > 3 mm. Radiographic classification identified 11 cases of reducible AAS, 13 cases of irreducible AAS, 17 cases of vertical subluxation, and 9 cases of subaxial subluxation (Table 1).

Acquisition of 3D CT

We obtained 3D CT scans for 3 positions for each study participant using a commercial CT system (Light-Speed VCT, GE Healthcare) with the following parameters: slice thickness 0.625 mm, pixel size 0.352 mm, tube rotation speed 0.5 seconds, beam collimation 40 mm, beam pitch 0.9, tube current 50 mA, and voltage 120 kV. Participants were placed in a neutral position supine on the CT table, and also with their head rotated 45° to the left and then 45° to the right. Those who could not rotate their head to 45° were excluded from the study. A support device was used to keep the head at the correct rotation point (Fig. 1). To reduce radiation exposure, scans done in positions other than neutral were performed with a lower tube current (15 mA). Total exposure was 60 dose-length products, which is less than that specified for routine CT by our hospital. CT data were transferred via a digital imaging and communications in medicine network into a computer workstation, where image processing was performed using Virtual Place software (M series, Medical Imaging Laboratory).

Motion Analysis

We conducted motion analysis as described in our previous reports.11–13,15 First, each vertebra was semiautomatically extracted using intensity threshold techniques. Second, segmented images of the vertebrae in the neutral position were superimposed over images of other positions using voxel-based registration. As a result of the registration, the spatial migration of each vertebra was expressed by a matrix. Third, segmental motions at occiput (Oc)–C1 and C1–2 were calculated by converting the matrix obtained by the registration into a matrix representing relative motion with respect to the inferior adjacent vertebra. The results were expressed in 6 degrees of freedom by Euler angles, with the sequence of pitch (X), yaw (Y), roll (Z), and translations, using a previously defined coordinate system.11–13 The rotation angle was calculated as the sum of the right (–RY) and left (+RY) rotation angles. The accuracy of the method described here was 0.13° in axial rotation, as previously described in detail.6

Evaluation of 3D Morphology

In our study, we defined the articular facet index (AFI) for the first time to assess the severity of joint destruction objectively. First, we chose 3 points free of RA invasion in each 3D bone model, from the occiput to C-2. At C-1 and C-2, the points were the volume centroids of the bilateral transverse processes and a posterior arch. At the occiput, the points consisted of the bilateral posterior border of the base of the occipital condyle and the center of the anterior arch of the foramen magnum. Then we created planes passing through these 3 points. Second, we chose 200 points on each right and left articular facet and measured the minimum distance (in mm) between these points and the plane. The mean value of these distances was calculated as the height of the articular facet. However, the mean value had to be corrected by the size of each vertebra for valid comparisons. Finally, the AFI was

| TABLE 1: Radiographic classification of study participants with rheumatoid arthritis |
|---------------------------------|----------------|
| Classification                  | No. of Participants |
| reducible AAS                   | 5               |
| reducible AAS + VS              | 3               |
| reducible AAS + VS + SS         | 3               |
| irreducible AAS                 | 2               |
| irreducible AAS + VS            | 6               |
| irreducible AAS + VS + SS       | 5               |
| SS                              | 1               |

* AAS = atlantoaxial subluxation; SS = subaxial subluxation; VS = vertical subluxation.
calculated by dividing the height of the articular facet by the square root of the cross-section area (in mm$^2$) of each vertebra at the planes already described (S) (Fig. 2): AFI = height of articular facet/$\sqrt{S}$.

A low AFI means a decrease in the thickness of the lateral mass; thus, the AFI is thought to reflect the severity of joint destruction.

Reproducibility of the AFI

To assess the reproducibility of measurement of the AFI, two authors (T.S. and Y.N.) independently calculated the AFI for 10 patients in the control group for the caudal side of the articular facet of C-1 twice, with 1 week elapsing between the measurements. Intraobserver and interobserver intraclass correlation coefficient (ICC) and root mean square error (RMSE) were assessed. For intraobserver reproducibility of measurement of the AFI, the mean ICC and RMSE were 0.926 and 0.01, respectively. For interobserver reproducibility, the mean ICC and RMSE were 0.845 and 0.02, respectively.

Statistical Analysis

Statistical analyses were performed with Microsoft Excel 2007 for Windows with the add-in program Statcel 2 (OMS Ltd.). The data were analyzed using the non-parametric Mann-Whitney U-test. A p value < 0.05 was considered to indicate statistical significance. Correlation analyses were performed using the Spearman rank-correlation coefficient. ICC was calculated using SPSS for Windows (version 21.0, IBM). Mean values are presented with SDs.

Results

Morphological Analysis: Value of AFI

The mean AFI at the occipital articular facet was $0.14 \pm 0.02$ (0.13 ± 0.02 in men, 0.15 ± 0.02 in women) in the control group and 0.13 ± 0.02 (0.15 ± 0.02 in men, 0.12 ± 0.02 in women) in the RA group. The mean AFI on the cranial side of the C-1 articular facet was $0.18 \pm 0.03$ (0.20 ± 0.03 in men, 0.17 ± 0.03 in women) in the control group and 0.18 ± 0.03 (0.17 ± 0.02 in men, 0.18 ± 0.04 in women) in the RA group. The mean AFI on the caudal side of the C-1 articular facet was $0.15 \pm 0.03$ (0.15 ± 0.03 in men, 0.15 ± 0.04 in women) in the control group and 0.09 ± 0.04 (0.08 ± 0 in men, 0.09 ± 0.04 in women) in the RA group. The mean AFI on the cranial side of the C-2 articular facet was $0.27 \pm 0.02$ (0.27 ± 0.02 in men, 0.27 ± 0.03 in women) in the control group and 0.22 ± 0.05 (0.22 ± 0.01 in men, 0.22 ± 0.05 in women) in the RA group. There was no significant difference at the occipital articular facet or on the cranial side of the C-1 articular facet, but there were significant differences on the caudal side of the C-1 articular facet and the cranial side of the C-2 articular facet (Table 2). With respect to comparison of findings in women in both groups, there was a significant difference at the occipital articular facet (p = 0.04), but the same tendency was seen in other articular facets compared with overall analysis of data for men and women.

Kinematic Analysis

Head Rotation. The mean angle of axial rotation of the head was $89.4^\circ \pm 3.3^\circ$ in the control group and $87.2^\circ \pm 8.5^\circ$ in the RA group (not a significant difference, p = 0.69).

TABLE 2: Articular facet index

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Group (n = 10, 20 joints)</th>
<th>RA Group (n = 25, 50 joints)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lateral mass of Oc</td>
<td>0.14 ± 0.02</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>articular facet of C-1 (cranial side)</td>
<td>0.18 ± 0.03</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>articular facet of C-1 (caudal side)</td>
<td>0.15 ± 0.03*</td>
<td>0.09 ± 0.04*</td>
</tr>
<tr>
<td>articular facet of C-2 (cranial side)</td>
<td>0.27 ± 0.02*</td>
<td>0.22 ± 0.05*</td>
</tr>
</tbody>
</table>

* p < 0.01.
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**Segmental Rotation Angle at Upper Cervical Spine During Head Rotation.** The mean segmental rotation angle at Oc–C1 was 3.3° ± 1.6° (3.3° ± 1.8° in men, 3.3° ± 1.6° in women) in the control group and 4.8° ± 4.2° (1.9° ± 2.5° in men, 5.1° ± 4.3° in women) in the RA group (not a significant difference). However, the segmental rotation angle at C1–2 was 54.5° ± 5.4° (56.8° ± 5.0° in men, 52.1° ± 5.1° in women) in the control group and 29.1° ± 18.0° (29.7° ± 7.5° in men, 29.4° ± 18.2° in women) in the RA group (a significant difference, p < 0.01, Fig. 3 left). In patients with RA, there was a weak inverse correlation between the rotation angle at Oc–C1 and the angle at C1–2 (rs = –0.21) (Fig. 3 right). With respect to comparison of women in both groups, the same tendency was seen compared with overall analysis of men and women.

**Correlation Between Articular Facet Destruction and 3D Kinematics in the Upper Cervical Spine.** At the occipital articular facet, the AFI did not correlate with the segmental rotation angle (rs = –0.13). Yet the AFI did correlate with the segmental rotation angle on the cranial and caudal sides of the C-1 articular facet (rs = 0.58 and 0.59, respectively) and with the cranial side of the C-2 articular facet (rs = 0.74) (Figs. 4 and 5).

**Discussion**

Regarding the morphological changes of RA in the cervical spine, there have been several previous reports based on cadavers or 2D images from data obtained by radiography, CT, and MRI. Eulderink and Meijers performed pathological analysis using the cervical spines of cadavers with RA and reported that bony ankylosis of the articular facet was demonstrated in 15% of spines at Oc–C1 and in 10% at C1–2. Iizuka et al. reported that joint destruction was demonstrated in 17% of patients at Oc–C1, 4% of patients at C1–2, and 4% of patients at both Oc–C1 and C1–2 in sagittal and coronal views on CT. In those studies, the authors reported on the occurrence of joint destruction in the upper cervical spine in patients with RA, but minute morphological evaluation was not done. In addition, joint destruction was determined only by visual assessment. It is generally thought that in persons with RA, the more severe joint destruction is, the more severe the depression of the articular facet. For more objective evaluation, we developed a method for quantifying the severity of joint destruction: the AFI, which is an indicator of the extent of depression of the articular facet. We observed a significant decrease in the AFI in the RA group at C1–2, but no significant difference at Oc–C1. These results suggest that joint destruction is milder at Oc–C1 than at C1–2. From a mechanical viewpoint, this is a reasonable conclusion, considering the fact that the segmental motion of Oc–C1 is much smaller than that of C1–2. The AFI was calculated from the mean value of the minimum distance between 200 points on the articular facet and the plane passing through 3 points free of RA invasion. This index is the only method that can express the severity of joint destruction three-dimensionally as a single value with good reproducibility. The joint destruc-

![Fig. 3. Left: The mean segmental rotation angle at Oc–C1 was greater in the RA group than in the control group but the difference was not significant (NS). However, the mean angle at C1–2 was significantly smaller in the RA group than in the control group. Error bars represent 1 SD. **p < 0.01. Right: There was a weak inverse correlation between the segmental rotation angle at Oc–C1 and the angle at C1–2 in patients with RA (rs = –0.21).](image-url)
tion best detected by the AFI is that associated with homogeneous decrease of the lateral mass. However, the AFI cannot detect morphological changes such as localized depression of the articular surface or an indented articular surface. In our study, most joint destruction involved homogeneous depression of the lateral mass. Given these morphological findings, the AFI could be a useful indicator for assessing the severity of joint destruction of the cervical spine in RA. However, there is not yet an equivalent index for use in 2D image analysis. It is anticipated that the newly emerging technique of 3D image analysis will make measuring the AFI easy and quick.

There have been few studies of the kinematic changes in the cervical spine in RA. Iai et al. measured 3D segmental motion of the upper cervical spine in RA, including rotation, by tracking the bony landmarks of each vertebra on biplanar roentgenograms, and they reported that the segmental rotation angle of persons with RA involving the upper cervical spine was larger at Oc–C1 and smaller at C1–2 compared with the angle in healthy persons. However, their method presented major difficulties in precisely identifying the same reference points on sequential separate views of the same vertebra. Recently, Takatori et al. assessed the relationship between morphological change and kinematics during head flexion using dynamic CT, and they reported that movement of the upper cervical spine increased with C-2 unilateral mass collapse and decreased with a continuous bony lesion between the atlas and the odontoid process. Although the accuracy of their measurements was much greater than any researchers had ever obtained before, their kinematic study was performed only during head flexion and their morphological study was performed using only visual assessment. Because the upper cervical spine has the largest segmental motion during head rotation, we hypothesized that the pathological changes of RA could be best detected during this motion. In our study, the segmental rotation angle in the RA group was greater than that in the control group at Oc–C1, but the difference was not significant. However, the segmental rotation angle was significantly smaller in the RA group than in the control group at C1–2. These results are similar to those of Iai et al. Furthermore, our study showed a weak inverse correlation between the segmental rotation angle at Oc–C1 and the angle at C1–2. This finding caused us to speculate that the segmental rotation angle might decrease at C1–2 and increase in compensation at Oc–C1 in persons with RA. We also quantitatively elucidated the relationship between morphological and kinematic changes for the first time. The AFI both at C-1 and at C-2 correlated with the segmental rotation angle. Because of that finding, we speculated that destruction of the articular facet might play an important role in the decrease of the segmental rotational motion of the upper cervical spine in RA.

Piecing together all of our findings, we speculated that the rotational motion at C1–2 might initially be reduced by destruction of the articular facet and that joint contracture at C1–2 might promote a compensatory increase in rotational motion at Oc–C1 with the progression of RA.

Fig. 4. Correlation between the segmental rotation angle and the AFI at Oc–C1. The AFI correlated with the segmental rotation angle at the cranial side of the articular facet of C-1 (rs = 0.58).
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Our study had some limitations. First, data were not obtained from true real-time imaging in the upright position. Second, increased segmental motion caused by ligament laxity and ligament rupture could not be detected because our study was performed with the head fixed only at 45° of rotation. Third, the selection of study participants with RA was somewhat biased toward those with more severe disease. Fourth, there was a difference in the male-to-female ratios for the control group versus the RA group. Although there was a significant between-groups difference in the AFI at the occipital articular facet in women, the segmental rotation angle and the AFI at other articular facets showed the same tendency compared with overall analysis when analyzed for women alone. In addition, the AFI is contingent on the size of each vertebra, and it was thought not to be affected by the difference in size of vertebrae between men and women. Therefore, we think that the difference in male-to-female ratios had little effect on our study results. Despite all of these limitations, no other approaches have provided the kind of information provided by our study, and our findings thus represent a step toward a better understanding of the effects of RA on the cervical spine.

Conclusions

We accurately measured in vivo 3D kinematics of the upper cervical spine in RA during head rotation, quantified the degree of destruction of the articular facet for the first time using our own parameter, termed the AFI, and elucidated the relationship between the destruction of the articular facet and segmental rotational motion. The segmental rotation angle was significantly smaller at C1–2 in the RA group than in the control group. The AFI at C1–2 was significantly smaller in the RA group than in the control group and correlated with the segmental rotation angle at C-1 and C-2. In persons with RA, the destruction of the articular facet may play an important role in decreasing segmental rotational motion in the upper cervical spine.

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Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Sugiura, Nagamoto. Acquisition of data: Sugiura, Nagamoto. Analysis and interpretation of data: Sugiura, Nagamoto. Drafting the article: Sugiura. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manu-
References


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