Interobserver variation of single-photon emission computed tomography bone scans in patients evaluated for unilateral condylar hyperactivity

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Objective. This study assessed the quantitative evaluation of the region of interest (ROI) by mean and maximum pixel counts of single-photon emission computed tomography (SPECT) scans in patients with clinical suspicion of unilateral condylar hyperactivity (UCH); the interobserver reliability and the correlation of condylar activity with patient age was determined.

Methods. Two independent observers analyzed 67 bone SPECT scans. Maximum and mean activity values within an ROI on the mandibular condyle were analyzed; a cutoff value of 55% was used to determine the qualitative outcome.

Results. Excellent interobserver agreement was seen for both maximum (kappa 1.0) and mean activity analysis (kappa 0.94). Maximum and mean condylar activities were strongly correlated (r = 0.98). Maximum and mean condylar activity of the normal condyle decreased significantly with increasing age.

Conclusions. Maximum and mean condylar activity levels were highly correlated in patients with mandibular asymmetry. An excellent interobserver agreement was found with either maximum or mean condylar activity. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:399-405)

Unilateral condylar hyperactivity (UCH), also known as condylar hyperplasia, is characterized by excessive pathologic activity resembling growth in one of the mandibular condyles. This excessive activity results in an asymmetric development of the mandible, leading to facial asymmetry. The differential diagnosis of an asymmetric mandible can be subdivided into 2 major categories: cranial base deformations and condylar abnormalities. Examples of cranial base deformities are muscular torticollis, unilateral coronal craniosynostosis, and deformational plagiocephaly. Condylar fracture, condylar hyperactivity, juvenile condylar arthritis, and hemifacial microsomia are examples of an asymmetry based on a condylar abnormality.1 Unilateral condylar hyperactivity is one of the main postnatal causes of facial asymmetry. The precise etiology of this growth anomaly is unknown. Trauma, infections, neoplasms, hormonal and genetic factors, and circulatory problems are some of the suggested causes.2-4 In a recent study, blood flow measurements in the condylar region by using positron emission tomography (PET) scans seemed to rule out hypervascularization as a cause for condylar hyperactivity.3

In patients with clinically progressive mandibular asymmetry and hyperactive growth in the mandibular condyle, a high condylectomy may be indicated to arrest the progression of the condition. It has been demonstrated that the removal of the superior portion of the condyle will stop the growth of the mandible in the hyperactive side and will contribute to stable long-term results.5,6

The findings of semiquantitative bone scintigraphy may predict the presence of an ongoing condylar growth.7,8 In bone scintigraphy, intravenous 99m-technetium–labeled diposphonate (e.g., hydroxyl diposphonate [99m-Tc-HDP]) is administered. It is a method of evaluating bone growth at a single time point. Single-photon emission computed tomography (SPECT) imaging is used to better isolate the activity of the mandibular condyle from that of its adjacent bone, without superimposition of the activity of the normal condyle. SPECT scans of subjects with no suspected UCH show a high correlation of the right and left condylar uptake.5,9,10

Historically, the assessment of UCH was based on measurement of the mean condylar activity in bone SPECT scans. A bone SPECT scan is considered asymmetric if the difference in the regional activity between the right and left condyle is greater than 10%. Thus, a condyle is considered hyperactive when it has a relative activity of 55% or more.9,11,12 Multiple studies using these criteria showed the clinical value of the bone SPECT scan in the evaluation of patients with mandib-
ular asymmetry. There is evidence for the superiority of SPECT imaging compared with planar imaging\(^{13-15}\); however, there is a paucity of data regarding interobserver variability of bone SPECT evaluations of patients with possible UCH.

A recent study of Fahey et al.\(^{10}\) showed that essentially the same information is obtained, irrespective of whether the maximum or mean pixel values are used in the region of interest in condyles of healthy subjects. The clinical significance of maximum versus mean activity levels of bone SPECT scans for the evaluation of patients with mandibular asymmetry has not been defined, however. Differences in quantitative analyses of bone scans may be of importance for the clinical evaluation of patients with UCH. Recent studies have demonstrated an improved interobserver agreement for (semi-) quantitative analyses of fluorodeoxyglucose PET scans, with higher agreement between observers using maximum standardized uptake values (SUVs) instead of mean SUV.\(^{16,17}\) In the present study, we hypothesize that the use of the maximum condylar activity contributes to a higher observer agreement when compared with the use of mean condylar activity.

The objectives of this study were to establish the interobserver correlation in measuring the mean and maximum pixel counts of the mandibular condyle, to evaluate the interobserver correlation in classifying condylar images as normal or hyperactive with both mean and maximum measurements, to compare the quantitative evaluation of SPECT scans by mean and maximum methods, and to determine if there is a correlation of condylar activity with patient age using mean and maximum pixel counts in both normal and hyperactive mandibular condyles.

### MATERIAL AND METHODS

#### Subject selection

In the period 2009 to 2010, 67 patients (37 women and 30 men) received regular bone SPECT scans at the VU University Medical Center for the clinical evaluation of progressive mandibular asymmetry and suspected UCH. The patients’ ages ranged between 11 and 40 years (mean 19.9 ± 7.5).

#### Bone scintigraphy

Bone scintigraphy with SPECT acquisition was performed 4 hours after intravenous administration of 600 MBq 99m-Tc–HDP.

SPECT imaging was performed on a double-headed gamma camera (ECAM camera; Siemens, Chicago, IL) with a low-energy, high-resolution collimator. Imaging was acquired into a SPECT matrix size of 128 × 128, through a 180° rotation, with 32 positions, 40 seconds per view, and a 15% energy window centered at 140 keV. Standard Esoft software (Siemens Medical Solutions, Malvern, PA, USA) was used to analyze regions of interests (ROIs).

#### Data analysis

An experienced nuclear medical physician and a resident of the oral and maxillofacial surgery department independently performed retrospective analyses of the bone SPECT scans of selected patients. An ROI was drawn around the condylar region on the standard axial SPECT images (Fig. 1).\(^{14}\) To ensure comparable sizes of the left and right sides, the ROI was copied to the

### Table I. The average mean and maximum pixel counts of 3 consecutive transversal regions of interest of the patient in Fig. 1

<table>
<thead>
<tr>
<th></th>
<th>Hyperactive</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>72.00</td>
<td>35.67</td>
</tr>
<tr>
<td>Mean</td>
<td>62.25</td>
<td>31.73</td>
</tr>
</tbody>
</table>
contralateral condyle. The activities of 3 consecutive transversal ROIs were determined, whereby in the ROI, the mean and maximum pixel values were determined in a group of contiguous pixels. To determine the relative activity of each condylar region, the following equation was used: (counts per pixel in ipsilateral region)/(counts per pixel in ipsilateral region + counts per pixel in contralateral region) \times 100%.

The SPECT scan was considered significantly positive (asymmetric) if the difference between the activities in the ipsilateral and contralateral condyles was greater than 10%, that is, a relative activity of the hyperactive condyle of more than 55%.9,14

Statistical analysis
Correlation analysis was used to determine if there was a relation between the maximum and mean condylar activities in the ROIs of observers 1 and 2, between the mean and maximum condylar activities in an ROI, and between the age and condylar activity. Bland-Altman plots were used to further assess the between-method differences. Correlations were considered significantly different from 0 by using a 2-tailed P value of less than .05. An intraclass correlation coefficient for the contiguous pixels counts was calculated to assess the conformity between the 2 observers. The kappa estimate was used to evaluate the correlation between the 2 observers for the qualitative outcome by using the cutoff value of 55%.

RESULTS
Interobserver variation
The correlation analysis showed a strong relation between the rating of condylar activity by observer 1 and observer 2 on the side of the highest condylar uptake, this strong relation was present for both the maximum and mean condylar activity analysis; Pearson r value for maximum pixel count was 1.00 and the r value for mean pixel count was 0.98 (see Fig. 2, A and B).

Tables II shows the agreement of both observers on a qualitative scale with a cutoff value of 55% or higher. A relative activity of more than 55% was indicated as a positive SPECT scan and thus a hyperactive condyle. The qualitative classification showed 100% agreement between the observers when the maximum condylar activity was used, resulting in a kappa score of 1.00. The classification using the mean condylar activity resulted in an interobserver agreement with a kappa score of 0.94.

Table III demonstrates more detailed information on the clinical effects between maximum and mean activity analysis. Observer 1 classified 2 condyles as hyperactive with the mean pixel count but normal with the maximum count; this observer also classified 2 other condyles as normal with the mean values but reclassified them as hyperactive based on the maximum count.

Table II. Agreement between categorical assessment by observer 1 and observer 2 using mean or maximum activity with a cutoff value of 55%; the resulting Cohen’s kappa value is 0.94 and 1.00 for the mean and maximum activity, respectively

<table>
<thead>
<tr>
<th>Normal</th>
<th>Asymmetric</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pixel count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Observer 2</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Maximum pixel count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Observer 2</td>
<td>32</td>
<td>35</td>
</tr>
</tbody>
</table>

Therefore, a total of 4 (6%) of 67 patients were reclassified in this way. Observer 2 classified 2 condyles as hyperactive with the mean count and normal with maximum values; however, there were 4 condyles identified as normal with the mean count and hyperactive with the
maximum count, resulting in disagreements in 6 (9%) of 67 patients. In the patients who were reclassified when using a different method, the mean percentage on the side with the highest uptake was 55.4% (±0.97).

**Mean versus maximum condylar activity**

The correlation analysis showed that there was a strong correlation between the mean condylar activity and the maximum condylar activity (Fig. 3). Pearson $r$ correlation coefficients were greater than 0.99 for both the side with the highest uptake and for the side with the lowest uptake. Additionally, a Bland-Altman plot (i.e., the difference between the mean and maximum condylar activities plotted against their means) with 95% limits of agreement was used to further assess the between-method differences. Fig. 4, A and B, shows the Bland-Altman plot for both the maximum and mean activity analysis of the 2 observers with 95% limits of agreement. From this plot, we observe that for the maximum condylar activity analysis values are largely clustered around the difference $= 0$ line, with 2 (3%) of 67 of the points lying beyond the ±1.96 SD lines. The Bland-Altman plot of the mean condylar activities depicts that 6 (9%) of 67 of the points are beyond the ±1.96 SD lines. The last Bland-Altman plot (Fig. 4, C) represents the difference between the maximum and mean percentages on the side with the highest uptake, independent of the size of the measurements.

**Correlation of condylar activity with patient age**

The mean and maximum pixel counts of the mandibular condyle on the side with the lowest uptake are plotted as a function of age in Fig. 5, A and B, respectively. The correlation analysis showed a fair negative relation of both the mean and maximum pixels counts with age, with Pearson $r$ correlation coefficients of −0.526 and −0.498, respectively (both significant with $P < .01$). This negative relation is not seen when the condylar activity of the hyperactive side was plotted as a function of age. Fig. 5, C and D, shows these functions with Pearson $r$ correlation coefficients of −0.079 and −0.082 (both nonsignificant with $P$ values of .675 and .662 respectively).

**DISCUSSION**

In the workup of patients with mandibular asymmetry, the presence or absence of hyperactivity in the condyle resembling growth, influences the treatment plan. Bone SPECT scan is an important diagnostic tool for the evaluation of the activity of the condylar growth center in patients with UCH. In the present study, the impact of 2 methods of bone SPECT analysis was evaluated and the interobserver variation in a relatively large population of patients with suspected UCH was assessed. A high correlation between the maximum and mean condylar activities was found. Also, interobserver agreement was high for both the maximum and mean condylar activity; however, in a minority of patients, comprising fewer than 10% of the evaluated patients, the classification of patients changed from abnormal to normal, or vice versa, using maximum activity instead of mean activity. Typically, this applies for patients with marginal differences at the cutoff level.

A recent study of Fahey et al. showed that the mean and maximum activities in an ROI in the mandibular condyles of healthy subjects are highly correlated. In the present study, this high level of correlation was confirmed in patients with a suspected UCH, with Pearson $r$ correlation coefficients greater than 0.99.

We hypothesized that the use of the maximum condylar activity contributes to a higher observer agreement when compared with the use of the mean condylar activity. Our results partially support this hypothesis. Comparing the analysis of the 2 observers, the maximum condylar activity resulted in a higher Pearson $r$
correlation coefficient and a higher intraclass correlation coefficient as compared with the mean condylar activity. Furthermore, Cohen’s kappa showed a perfect agreement between the 2 observers when the maximum activity was used, with a higher observer agreement as compared with the mean activity analysis. However, we also found an excellent agreement as expressed by a kappa value of 0.93 when the mean condylar count rate was used; the differences between the 2 methods were small. The Bland-Altman plots for the maximum versus mean condylar activities showed a smaller confidence interval for the maximum activity analysis, favoring the use of maximum condylar activity. The slightly better results of the maximum pixel counts can be explained by the possible variation between observers in drawing and placement of the condylar ROI. The mean condylar activity may be affected when the surrounding bone tissue is incorporated in the ROI; moreover, differences in size between the left and right condyles may influence the mean activity because a similar ROI size for the left and right sides in an individual patient is used. In contrast, the maximum pixel value does not critically depend on the size and exact placement of the ROI if the maximum pixel resides within the ROI. Apparently, the theoretical variation associated with the mean activity analysis is limited, given the high correlation between maximum and mean condylar activities that were calculated.

Different analyzing methods have been used in the evaluation of bone SPECT scans in patients with UCH. Saridin et al. summarized these and showed that determining the differences in the percentile activities in the ROIs of both condyles was the best quantitative method of analysis. There was no benefit from calculation of the ratios using a reference bone (i.e., the cervical spine or clivus). Two other studies determined the bone uptake values with SPECT scans in condyles of individuals without temporomandibular joint disorder. Kajan et al. found a mean difference between the percentage uptake of the right and left condyles of 2.1%, with a maximum difference of 6.2%. These results are in line with those of Fahey et al. In the present study, a SPECT scan was considered asymmet-

Fig. 4. A, Bland-Altman plot of the difference of the mean values measured by observer 1 and observer 2 as a function of their averages on the side with the highest uptake. B, Bland-Altman plot of the maximum values measured by observer 1 and observer 2 on the side of the highest uptake. C, Bland-Altman plot of the maximum and mean percentages on the side with the highest uptake.
ric if the difference between the hyperactive and normal condyles exceeded 10%. This is a conservative approach and is in line with the evaluation used in several different studies.9,14 When using this cutoff value, high interobserver agreement values for both the mean and maximum pixel count methods were obtained; however, 6% to 9% of the patients were classified differently by an observer using 1 of the 2 methods of analysis. Hence, using either maximum or mean counts may influence the final decision-making process regarding the use of condylar surgery in a minority of the patients. Especially in patients marginally meeting the criteria of positive bone scan (e.g., a relative condylar activity—just more or less than 55%) might be prone to a reclassification from abnormal to normal (or vice versa) if another method for activity analysis is used. Indeed, the patients who were reclassified using maximum instead of mean activity levels had an average relative activity of 55.4%, which is only just above the cutoff value of 55.0%. Future follow-up studies are needed to evaluate if patients with a relative activity of the hyperactive condyle in close proximity of 55% may benefit from an emphasis in the decision making for condylar surgery, on the patient history and the clinical assessment.

One of the secondary objectives of this study covers the influence of the patient’s age on condylar activity. A study of Cisneros and Kaban8 showed that the ratio of the condylar uptake with the fourth lumbar vertebra decreases in a linear fashion with increasing age. The present study also shows that there is a negative linear relation between the condylar activity in the nonaffected (normal) condyle and increasing age. Apparently, there is a gradual decrease of bone activity within the normal mandibular condylar region with an increasing age. In contrast, both mean and maximum condylar activity levels showed no significant decrease of bone

![Fig. 5. A and B, Condylar uptake on the side with the lowest uptake measured with mean and maximum pixel count plotted against age. The correlation analysis showed Pearson r correlation coefficients of −0.526 and −0.498, respectively, resulting in a fair negative relation of both the mean and maximum pixels counts with age. C and D, Condylar uptake on the side with the highest uptake in patients classified as “hyperactive.” The correlation analysis showed Pearson r correlation coefficients of −0.079 and −0.082 (both nonsignificant with P values of .675 and .662, respectively).](image)
activity for the faster-growing condyle, implying that abnormal condylar bone growth of older patients may not be that different from younger patients. However, in a recent histology study we showed that younger patients with UCH had a thicker cartilage layer compared with older patients with UCH. On the other hand, both older and younger patients with UCH showed cartilage islands with a low frequency in their condyles. An increased cartilage thickness and the presence of cartilage islands are considered typical features of hyperactive condyles. Additionally, an increased number of cartilage islands may reflect the hyperactivity of the condylar growth center. We found no association between age and bone activity. Hence, the importance of age in the development of UCH remains unclear. Further studies are necessary to explore the possible interrelation of cartilage layer thickness, number of cartilage islands, bone activity, and age in patients with UCH.

Finally, it is important to realize that despite the indispensability of the bone scanning techniques in the present diagnostic pathway of patients with UCH, the outcomes of this technique present only a snapshot of relative growth rates of the condyles, and yield no information on future bone growth. It is unknown if repeated bone scans will be superior to single bone scans in identifying a persisting condylar growth. At this moment, the combination of bone SPECT results, patient history, and clinical information are essential for the final diagnosis of progression of the disease in UCH.

In summary, we found excellent interobserver agreement for the analysis of bone SPECT scans with either maximum or mean condylar activity levels. Maximum and mean condylar activity levels were highly correlated in patients with mandibular asymmetry. Both methods can be recommended for the analysis of mandibular bone SPECT scans.

REFERENCES


