# Variability of Quantitative Scintigraphic Salivary Indices in Normal Subjects

George A. Hermann, Frederick B. Vivino, Darryl Shnier, Robert P. Krumm, Valery Mayrin and Jared B. Shore
*Departments of Radiology and Medicine, University of Pennsylvania School of Medicine, Philadelphia; and University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania*

Several quantitative measures of salivary uptake and discharge have been proposed recently in the scintigraphic evaluation of xerostomia. We investigated the scatter of four time-activity curve (TAC)-derived indices in a group of volunteer subjects who met extensive inclusionary and exclusionary criteria of salivary normalcy. **Methods:** Thirty-one adult volunteers underwent dynamic salivary scintigraphy with gustatory stimulation. Any candidates with subjective xerostomia, conditions or medications associated with dry mouth, salivary gland enlargement or pregnancy were excluded from study. All subjects had normal oral exams, xerostomia scores and unstimulated whole-mouth salivary flow rates. After the intravenous administration of $^{99m}$TcO−4, scintigraphy was performed with generation of TACs derived from regions of interest centered about the four major salivary glands and the oral cavity. At 45 min postinjection, hard lemon candy was given for 15 min as a gustatory stimulus. The following functional indices were calculated for each gland: partitioned percentage (PP) of total prestimulated activity, maximum net uptake ratio (NUR) and its time of occurrence ($T_{NUR}$) and percentage stimulated discharge fraction (DF). **Results:** The following ranges were observed: parotid PP, 22%–49%; submandibular PP, 4%–31%; parotid NUR, 2.2–16.0; submandibular NUR, 1.4–16.2; parotid $T_{NUR}$, 8–45 min; submandibular $T_{NUR}$, 2–45 min; parotid DF, 20%–99%; and submandibular DF, 27%–98%. Every subject except one 91-yr-old man showed frequent periodic unstimulated oral transfer of salivary activity with a rising oral TAC and responded to gustatory stimulation. **Conclusion:** So-called quantitative indices may perform poorly in the scintigraphic evaluation of xerostomic patients because the effects of normal simultaneous glandular trapping, uptake, oral discharge and possible vascular washout combine to widen reference limits. Coordinated analysis of oral cavity and glandular activities, glandular index averaging and better temporal resolution may help improve diagnostic performance.

**Key Words:** salivary scintigraphy; quantitative indices; normal variation

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Taplin and his associates (*1*) visualized the major salivary glands with radionuclides more than 30 yr ago, initiating the evolution of modern salivary scintigraphy. Harper et al. (*2*) pioneered the use of $^{99m}$Tc-pertechnetate for clinical imaging in 1964, and the next year Borner et al. (*3*) used this agent specifically for demonstrating salivary glands with a rectilinear scanner. Interest in sequential salivary scintigraphy as a diagnostic tool in the evaluation of xerostomia was stimulated by the widely adopted categorical classification scheme of Schall and his group (*4,5*) during the 1970s and early 1980s.

Recent investigators of xerostomia have, with the help of digital computers, attempted to objectify and refine diagnostic scintigraphy by developing such quantitative indices of salivary function as rate of trapping and uptake, time of maximum activity, uptake ratios and magnitude or rate of stimulated salivary discharge (*6–9*).

However, efficient diagnostic use of numerical benchmarks rests on a thorough distributional account of abnormal and control populations. To date, there have been few studies that evaluate centrality and dispersion of quantitative scintigraphic indices in a well-characterized group of controls. Incident to a study of xerostomic patients, we surveyed a cohort of healthy individuals using a protocol that combined salivary and oral time-activity curve (TAC) analysis with 15-sec temporal resolution.

## MATERIALS AND METHODS

### Subjects

The group consisted of 31 volunteers (25 women, 6 men; age range 18–91 yr; median age 48 yr) who provided informed consent for study approved by our institutional review board. Each volunteer confirmed a lack of oral discomfort or xerostomia by marking a pair of 100-mm visual analog scales, first before study entrance and again at the time of imaging (*10*). Subjects were excluded if they had a history of head or neck irradiation or surgery, connective tissue disease or other systemic illnesses known to cause xerostomia, were taking any medications known to influence salivary gland function or were pregnant. The volunteers underwent measurement of whole mouth unstimulated salivary flow by sialometry (*11*). Each also had an oral examination that scored the effect and severity (0–3+) of drying of the lips, tongue, buccal mucosa and throat and then was asked to seal a standard gummed 24-cm business envelope. Results were summed and tabulated on a semiquantitative 20-point xerostomia scale. Candidates continued in the study if their oral xerostomia score was <2 and their unstimulated whole salivary flow exceeded 0.3 ml/min.

### Scintigraphy

Ten to 15 min after drinking 12 oz water, the fasting subject received an intravenous injection of 5.6 MBq (150 μCi)/kg $^{99m}$Tc-pertechnetate to a maximum of 555 MBq (15 mCi). Dynamic salivary scintigraphy in the Waters projection with a high-resolution collimator, a photopeak of 140 keV and a symmetric 15% window began 1.5 min later. Images were digitally recorded in a 64 × 64 × 16 matrix with ×1.85 zoom. Two hundred forty 15-sec frames were obtained during 60 min. At 45 min, hard lemon candy provided 15 min of gustatory stimulus. The subject afterward ingested 400 mg of aqueous potassium perchlorate and was encouraged to increase fluid intake for several hours.

### Data Processing

We reviewed cinematic sequences and selected optimal salivary and oral frames. Regions of interest (ROIs) were drawn manually around the four major salivary glands. An oral ROI was also generated to record the frequency, magnitude and evolution of spontaneous and stimulated salivary secretion. Counts per second of each ROI were plotted against time. Background correction was performed by subtracting the first frame, dominated by pretrapping

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For correspondence or reprints contact: George A. Hermann, MD, Presbyterian Hospital, 39th and Market St., Philadelphia, PA 19104.

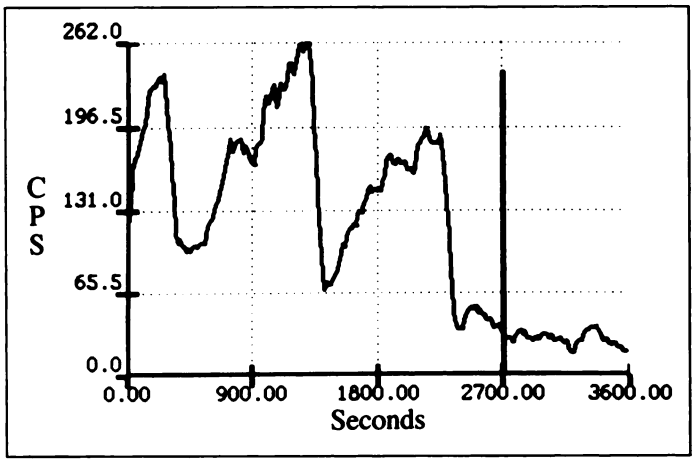


**FIGURE 1.** Time-activity curve of the right submandibular gland in a 51-yr-old normal female. The vertical line marks the gustatory stimulus at 45 min. Scintigraphic indices: PP, 12%; NUR, 3.4; $T_{NUR}$, 22 min; and DF, 36%. Three episodes of spontaneous discharge interrupt uptake, with little remaining glandular activity at the time of gustatory stimulus.

vascularity, from succeeding frames. One volunteer showed functional or anatomic absence of the right submandibular gland. Its background-corrected ROI comprised 2% of unstimulated pansalivary counts. Changes in minor residual uncorrected blood background during imaging were monitored by a crescentic scalp ROI, avoiding choroid, and averaged −49% (n = 18). This activity was useful in screening for poor injection technique and extravasation, but it was not used in subsequent calculations. All TACs were corrected for physical decay and smoothed with a six-point moving average kernel that reduced noise without significantly compromising temporal resolution. Processing time averaged 15 min/case.

### Derivation of Quantitative Indices

Figure 1 shows a typical submandibular TAC. The area under the curve integrates its counts during the unstimulated portion of the study. These counts are divided by total salivary counts during the same period and multiplied by 100 to give the partition percentage (PP). The net uptake ratio (NUR) is maximum counts at time $T_{NUR}$ divided by initial postinjection counts. The discharge fraction (DF) = (1 − minimum poststimulus counts/maximum counts at 43–45 min) × 100.

### Statistical Analysis

Index statistics were expressed as medians, percentiles and range because much of the data were non-Gaussian (*12*). To evaluate the effect of interoperator processing bias on imprecision, paired independent examiners calculated TAC indices after drawing 40 salivary ROIs. A two-tailed Wilcoxon's signed rank test was used with the null hypothesis of no operator-associated differences between index medians. A p value of $<0.05$ was considered significant. Scatter plotting and linear least-squares regression assessed the relationship of age and scintigraphic index.

## RESULTS

### Interoperator Imprecision and Effects of Age

Operator differences in PP, NUR, $T_{NUR}$ and DF medians averaged 0, 0.5, 1.5 and −0.7, respectively, with all p values $>0.05$. There was negligible distributional expansion that was attributable to interoperator bias.

Mild positive and negative parotid and submandibular correlations of PP, NUR, $T_{NUR}$ and DF with subject age were noted, but scatter was great and no $r^2$ exceeded 0.09. Age was, therefore, not a significant contributor to observed index variability. Insufficient data precluded evaluation of sex association.

**TABLE 1**
Median Values, 5th-95th Percentiles and Ranges of Normal Scintigraphic Indices of Salivary Function (n = 31)

| Index | Median | $PCTL_{5-95}$ | Minimum | Maximum |
|---|---|---|---|---|
| PP (%) | | | | |
| RP | 34 | 23–43 | 22 | 43 |
| LP | 32 | 24–44 | 23 | 49 |
| RS* | 15 | 6–26 | 4 | 26 |
| LS | 19 | 7–27 | 6 | 31 |
| NUR | | | | |
| RP | 7.3 | 3.2–13.7 | 3.0 | 14.0 |
| LP | 6.9 | 2.7–15.9 | 2.2 | 16.0 |
| RS* | 4.4 | 1.7–10.5 | 1.4 | 10.8 |
| LS | 4.7 | 1.8–15.9 | 1.4 | 16.2 |
| $T_{NUR}$ (min) | | | | |
| RP | 43 | 17–45 | 10 | 45 |
| LP | 42 | 8–44 | 8 | 45 |
| RS* | 28 | 5–44 | 2 | 45 |
| LS | 34 | 5–44 | 3 | 45 |
| DF (%) | | | | |
| RP | 88 | 36–98 | 20 | 98 |
| LP | 85 | 45–98 | 35 | 99 |
| RS* | 86 | 32–97 | 27 | 98 |
| LS | 86 | 43–98 | 36 | 98 |

*n = 30.
PCTL = percentile; RP = right parotid; LP = left parotid; RS = right submandibular; LS = left submandibular.

### Scintigraphic Index Variability

Table 1 displays the range of scintigraphic salivary indices in normal individuals, which, in the case of the left submandibular NUR, exceeded 11-fold. Partition percentages of parotid and submandibular pairs were closely balanced, as previously noted (*13*). The parotids accounted for ~67% of total prestimulated salivary activity. The median NUR of the parotids was 1.6 times that of the submandibulars and occurred significantly later. Scatter plots confirmed that parotid and submandibular NURs increased as $T_{NUR}$ was delayed. However, both indices varied widely, and Figure 2 offers a probable explanation. Periodic unstimulated salivary discharge punctuated 30 of 31 submandibular uptake curves throughout the resting interval and, not discounting swallowing, caused roughly reciprocal glandular and oral activities. There were two types of normal unstimulated parotid behavior. One or both parotids of 15 subjects

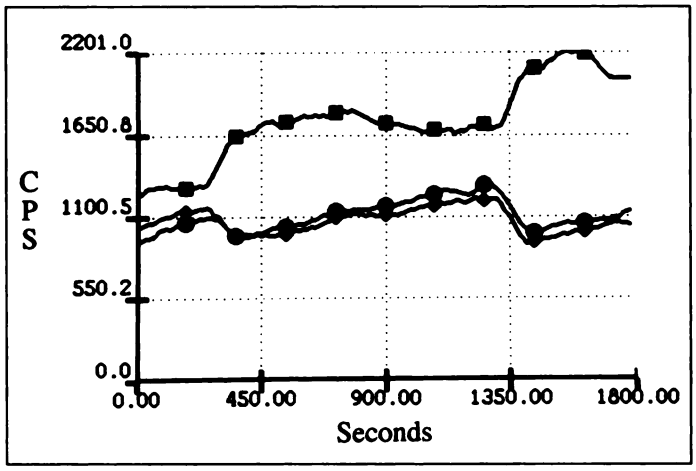


**FIGURE 2.** Prestimulatory time-activity curves of submandibular glands (lower) and mouth (upper) in a normal subject. Changes in glandular counts correlate inversely with those in the oral cavity, suggesting unstimulated gland-to-mouth transfer of saliva.

showed no unstimulated discharge, with resulting monotonic uptakes, delayed $T_{NUR}$s and high NURs. The remaining parotids showed discharge patterns indistinguishable from those of the submandibulars.

## DISCUSSION

Almost 30 yr of investigation have established that dysfunctional states of the salivary apparatus are accompanied by changes in scintigraphic patterns of trapping, uptake and discharge. Qualitative and quantitative diagnostic algorithms in the scintigraphic evaluation of xerostomia use a kinetic model of unstimulated salivary function that assumes early trapping and uptake followed by late secretion, each variably deranged by disease (*14–16*). Scintigraphic studies that document cyclically alternating unstimulated uptake and secretion are uncommon (*17*). This may be due to methodologic approach. We reviewed 32 scintigraphic salivary studies published between 1971 and 1997, 29 of which listed radionuclide dose and/or framing rates. The average dose was 178 MBq (4.8 mCi), and the mean frame time, a determinant of temporal resolution, was 231 sec (range 30–1200 sec). In general, framing frequency was a function of dose. As nonstimulated oral salivary transfer can occur several times per minute, the temporal resolution of most studies may have been too coarse-grained to detect wavelike fluctuations superimposed on increasing activity, instead presenting smooth, monotonic uptake, followed later by excretion. In radiosialographic studies, Mita et al. (*18*) linked increasing salivary pathology with decreasing DFs and progressively depressed (median → sloped → flat) TACs (*18*). Later, investigators reported that flattening of salivary TACs is highly correlated with sialographic changes and with histopathologic abnormalities of the minor salivary glands (*19*).

However, all of our normal subjects showed one or more resting median or sloped TACs and widely dispersed quantitative indices that implied substantial interindividual variability in the frequency and magnitude of salivary secretion. Every submandibular gland but two and half of the parotids showed multiple episodes of spontaneous nonstimulated excretion. The remaining parotids exhibited relentless uptake, with no significant oral transfer until gustatory stimulation. No gland during the time of observation showed smooth uptake followed by nonstimulated secretion. The interplay of simultaneous trapping, uptake, episodic discharge and possible vascular washout produced curves and index values that might extensively overlap those of the xerostomic population. This situation may disqualify certain uniglandular quantitative indices as decision variables, with implications for the detection of such abnormalities as Sjögren's syndrome, chronic sialadenitis and radiation- and drug-related effects. For example, acceptable false-positive rates might not be achieved unless individual submandibular PPs of <6%, NURs of <1.7, $T_{NUR}$s of <5 min or DFs of <32% were adopted as reference limits. Critical values this strictly set may erode test sensitivity and positive predictive value, but more lenient cutoffs risk the loss of specificity and negative predictive value. The additional information provided by higher temporal resolution and oral cavity monitoring could help differentiate truly dysfunctional TACs and indices from those resulting from active but normal cyclic secretion.

The finding that only half of normal parotids contributed significantly to the salivary pool before stimulation was unexpected and remains unexplained but is consistent with the well-recognized digestive function of their secretions versus the predominantly lubricative and mucosal protective role played by submandibular sialomucins. Thus, within the test duration, the submandibulars provided most of the average subject's resting oral pool activity even though the parotids accounted for two-thirds of the intraglandular activity.

It remains undecided whether incorporation of increased temporal resolution and oral TACs into xerostomia imaging protocols will materially improve their discriminatory performance, and low-resolution studies have provided their own insights into salivary behavior. Certainly, all TAC-derived scintigraphic parameters are modulated by uncontrolled physiologic variables, such as vascular washback, multicompartmental sites of uptake and thyrometabolic status. Swallowing of saliva occurs within 3–4 sec, making it as unapparent in our protocol's frequency domain as baseline oral secretion was to that of previous investigators. There is experimental evidence to suggest that quantitative salivary scintigraphy is sensitive only to histologic abnormalities exceeding 25% of glandular mass (*20*). These qualifications notwithstanding, the wide scatter of normal quantitative scintigraphic indices found in this study implies that diagnostic performance in xerostomic patients might be enhanced by invoking a broadened physiologic model that supposes cyclically active, unstimulated salivary glandular discharge as well as uptake.

## CONCLUSION

The application of salivary scintigraphy with 15-sec temporal resolution to a group of 31 well-characterized normal subjects disclosed a high degree of variability in four quantitative indices that have recently been proposed as objective and refined criteria in the classification of the xerostomic patient. This dispersion of values was largely due to the interplay of simultaneous trapping, uptake, cyclic discharge and possible vascular washout of resting, as well as poststimulated salivary activity. Diagnostic discrimination based solely on these indices may be suboptimal unless a physiologic model that includes both spontaneous and stimulated salivary behavior is adopted.

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# Differential Diagnosis of Atypically Located Single or Double Hot Spots in Whole Bone Scanning

Stefan Puig, Anton Staudenherz, Birgit Steiner, Edith Eisenhuber and Thomas Leitha
*University Clinics of Radiology, Nuclear Medicine and Internal Medicine, University of Vienna, Vienna, Austria*

Our study assessed the predictive value of atypically located hot spots in routine $^{99m}$Tc-DPD (3,3 diphosphono-1, 2-propane dicarboxylic acid tetrasodium salt) bone scanning for osseous tumor spread in patients with a history of malignant tumor. **Methods:** Of 1286 scans in consecutive patients with a history of malignant tumor, but with no current evidence of osseous tumor spread, 172 displayed one or two hot spots in the following locations: transverse process of a single vertebra, manubriosternal junction, unilateral process of L5/S1, unilateral shoulder, costal cartilage, single rib, and unilateral sternoclavicular joint. The final diagnosis could be established by a control bone scan after at least 6 mo, biopsy and/or postmortem, respectively, in 135 patients. **Results:** Of the atypical hot spots, 11.1% were the first indication for osseous tumor spread. This diagnosis was most probable for single hot spots in the rib (25%) and shoulder (21%). Conversely, hot spots in the sternoclavicular joint never indicated malignancy. **Conclusion:** The likelihood of atypically located isolated hot spots indicating osseous tumor spread is higher than expected during routine investigations in patients with a history of malignant tumor but no current evidence for malignant disease. Only hot spots in the sternoclavicular joint did not indicate metastatic disease in our study.

**Key Words:** bone scintigraphy; hot spots; metastases
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In 1942 Treadwell et al. (*1*) described the use of radiotracers for assessing bone metabolism and provided the basis for detecting metastatic disease by nuclear medicine imaging procedures. Bone scintigraphy with $^{99m}$Tc-labeled diphosphonates has been used for more than 30 yr to evaluate primary and metastatic bone lesions. Scintigraphic imaging identifies pathophysiological processes such as regional perfusion, permeability and bone metabolism. These processes precede morphological changes and account for the high sensitivity of nuclear medicine procedures for early detection of inflammatory, traumatic and neoplastic diseases (*2–6*) as well as for the low specificity for differential diagnosis of various diseases with similar pathophysiological characteristics. Such low specificity is a particularly problematic clinical dilemma in tumor patients who demonstrate isolated increased tracer uptake in locations such as the manubriosternal junction, ribs, lower neck or sacrum that may occur as a result of inflammatory or posttraumatic changes (*6–12*) but also may indicate incipient metastatic disease.

The purpose of our study was to assess the predictive value of isolated and atypically located hot spots in routine $^{99m}$Tc-DPD (3,3 diphosphono-1, 2-propane dicarboxylic acid tetrasodium salt) bone scanning for osseous tumor spread in patients with a history of malignant tumor but with no current evidence of metastatic disease.

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For correspondence or reprints contact: Stefan Puig, MD, University Clinic of Radiology, Waehringer Guertel 18-20, A-1090 Vienna, Austria.

## MATERIALS AND METHODS

### Patient Selection

Between October 1993 and May 1994, 1286 whole-body bone scans were performed on patients with a history of malignant tumor but with no current evidence of metastatic disease during routine follow-up. Patients with central hot spots in the vertebral column or skull but without signs of degenerative changes or trauma were assumed to have a higher likelihood for metastatic disease and were not included in our study.

In 172 patients (92 women, 80 men; age range 19–89 yr; mean age 59.62 yr ± 14.00 yr s.d.; median age 60.5 yr) there was normal tracer distribution with the exception of one or two areas of focally increased tracer uptake in the following locations: (a) transverse process of a cervical vertebra; (b) manubriosternal junction; (c) transverse process of the fifth lumbar vertebra and/or sacrum; (d) shoulder; (e) costal cartilages, up to four spots; (f) single rib; and (g) sternoclavicular joint.

In 135 patients (77 women, 58 men; age range 19–84 yr; mean age 57.93 yr ± 13.98 yr s.d.; median age 57 yr) of the above mentioned 172 patients (78.5%), a final diagnosis could be established by follow-up bone scintigraphy at least 6 mo later and/or by histological diagnosis after surgery or by postmortem examination. Restitution of a lesion without specific therapy was considered to confirm its benign nature. Persistence and the occurence of additional (typically located) hot spots with corresponding radiographs was considered to represent malignancy. All other patients were diagnosed by biopsy. The sites of their primary tumors are shown in Table 1. In stable lesions under therapy, the confirmation was based on biopsies in all patients.

### Bone Scintigraphy

Bone scintigraphy was performed in all patients 3 hr after the intravenous injection of 600 MBq $^{99m}$Tc-DPD (Teceos Behringwerke AG, Frankfurt, Germany) through an antecubital vein. Anterior and posterior whole-body images were obtained using a double-headed, large-field-of-view gamma camera (GCA 901A, Toshiba Corp., New York, NY) equipped with low-energy, parallel-hole, high-resolution collimators at a scan speed of 15 cm/min so that about 1000 kcounts were accumulated per image and stored in a 256 × 1024 matrix. The images were reviewed by three physicians in consensus.