

# ASSESSMENT OF THE EFFECTS OF AGING AND MEDICATION ON SALIVARY GLAND FUNCTION IN PATIENTS WITH XEROSTOMIA USING $^{99m}\text{Tc}$ -SCINTIGRAPHY

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## ABSTRACT

To examine the effect of aging and medication on xerostomia, the salivary gland function was evaluated in 20 patients with xerostomia using  $^{99m}\text{Tc}$ -scintigraphy and the measurement of unstimulated whole saliva (USWS). All of the patients showed USWS volume of less than 2ml/10min. The patients were divided into 2 subgroups based on age (under 65 and 65 and older) and medication status (patients who were on medication which reduced salivary secretion and patients who were not on such medication). The scintigraphic results, such as the maximum radioisotope (RI) count, RI secretion velocity and the volume of USWS, were compared between the subgroups. The maximum RI count and the RI secretory velocity in the submandibular gland and the volume of USWS revealed significantly different functional disturbances between relatively younger patients (under 65) and older patients (65 and older). There was no difference when the scintigraphic results and the volume of USWS measurements in medicated patients were compared with the results of similar tests performed on non-medicated patients. When the medicated and non-medicated groups were separated by age, an increase in age still diminished the volume of USWS in medicated patients. This result might be related to an organic change in the submandibular gland in older patients which was suggested by the scintigraphic results.

Key Words: Xerostomia,  $^{99m}\text{Tc}$ -scintigraphy, Unstimulated whole saliva, Aging, Medication.

## INTRODUCTION

Accurate evaluation of salivary gland function is important in patients with xerostomia because subjective symptoms can differ from the results of objective examination.<sup>1,2)</sup>  $^{99m}\text{Tc}$ -scintigraphy has been used to evaluate salivary gland function in a variety of diseases.<sup>3-7)</sup> Advantages of this technique are that it can be used for quantitative analysis and also for the evaluation of both salivary accumulation and release.<sup>4,8-10)</sup> Results from previous studies, where  $^{99m}\text{Tc}$ -scintigraphy was used, have demonstrated that  $^{99m}\text{Tc}$ -scintiscans accurately reflect the functional status of salivary glands.<sup>9,10)</sup>

The most frequent causes of xerostomia have been reported to be Sjögren's syndrome,<sup>11)</sup> irradiation,<sup>12,13)</sup> drugs,<sup>2,14-17)</sup> aging,<sup>17-20)</sup> and mental disturbances.<sup>21)</sup> Except for Sjögren's syndrome and radiation induced xerostomia, it is difficult to detect the etiology of xerostomia. There are few reports describing the differential diagnosis of xerostomia using methods other than saliva volume analysis.<sup>22-24)</sup> At present, the effect of aging on salivary dysfunction is still controversial. In this study, we tried to evaluate salivary gland function in patients with xerostomia using  $^{99m}\text{Tc}$ -scintigraphy to examine the influence of aging and certain medications (which reduce salivary secretion) on their condition.

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## MATERIALS AND METHODS

### Populations

Twenty patients (13 women and 7 men) with complaints of dryness of the mouth and USWS volume under 2ml/10min (flow rate 0.2ml/min) were investigated. Individuals who had a history of irradiation in the head and neck region were excluded from this study. After a detailed history was taken, all patients completed a course of blood analysis, USWS collection and <sup>99m</sup>Tc-scintigraphy. Sixteen patients who showed salivary gland dysfunction in scintigraphy underwent lip biopsy and sialography. As a result of these tests, no patients in this study were found to be suffering from Sjögren's syndrome.

The mean age of the group was 61 years (ranging from 16 to 81 years). Sixty percent of the subjects (n=12) were affected by systemic diseases such as digestive diseases (n=6) and circulatory disease (n=5) (Table 1). Sixty-five percent of the subjects (n=13) received general medication and 50% of the patients (n=10) received medication which reduced their salivary secretions; for example; anti-ulcerative drugs, vasodilators and tranquilizers, which were reported by Sreebny and Schwartz.<sup>15)</sup>

The patients were divided into subgroups based on age (under 65 and 65 and older) and medication status (patients on medication which reduced salivary secretion and patients who were not). The "under 65" group consisted of 12 patients, 6 of whom were on medication which reduced salivary secretion. The "65 and older" group consisted of 8 patients, 4 of whom were on medication which reduced salivary secretion. There were 10 patients in the medicated group (with an average age of 60) and 10 in the non-medicated group (with an average age of 63). Salivary gland function between the subgroups was compared using the following procedures.

### Saliva collection procedure

USWS was collected for 10 minutes (between 1 and 3 PM) at least 1 hour following a meal.

Table 1. Systemic diseases and medications of experimental subjects. There is repetition between each category in this table.

Systemic disease type	No. of subjects
Digestive disease	6
Circulatory disease	5
Bone and joint disorder	2
Respiratory disease	2
Ophthalmic disease	1
Endocrine disease	1
Intracranial vascular disorder	1
Systemic medications	No. of subjects
Antiulcerative drugs and digestives*	6
Antihypertensive agent*	4
Analgesics	1
Respiratory drugs	1
Tranquilizer*	1
Others	3

\*Medicines which reduce salivary secretion

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All subjects avoided stimulation and remained seated in a chair. First they were instructed to swallow all saliva contained inside their mouths. Subsequently, subjects avoided swallowing during the collection process and expectorated their saliva into a sampling tube.

#### $^{99m}\text{Tc}$ -Scintigraphic examination

$^{99m}\text{Tc}$ -scintigraphy was performed as described previously.<sup>4,9)</sup> Patients were placed in a supine position after the intravenous injection of 5 mCi ( $1.85 \times 10^8$  Bq) of  $^{99m}\text{Tc}$ -pertechnetate. A camera immediately began recording data which was fed to an on-line computer. Twenty minutes following the injection, lemon juice was placed on the dorsal surface of the tongue for salivary stimulation, and additional scanning was performed. Time-activity curves were constructed on the basis of RI counts. The scintigrams evaluated a given salivary gland's ability to accumulate the RI and release it in response to a stressor (lemon).

#### Accumulation and secretion velocity analysis

The maximum accumulation of isotope in each gland was calculated as the difference between maximum level of RI indicated as "c" and the background level (Fig. 1). The RI uptake of the temporal region, which has been regarded as blood RI radioactivity, was determined as the background. If the RI accumulation continued until the time of lemon stress (20 min), the RI level was thought to be equal to "c". The RI levels prior to and following the lemon stress (a and b, respectively) were determined at times  $T_a$  and  $T_b$  according to the method of Ishikawa.<sup>8)</sup> The RI secretion velocity in response to the lemon stress was determined from the slope of the graph ( $a-b/T_b-T_a$ ).

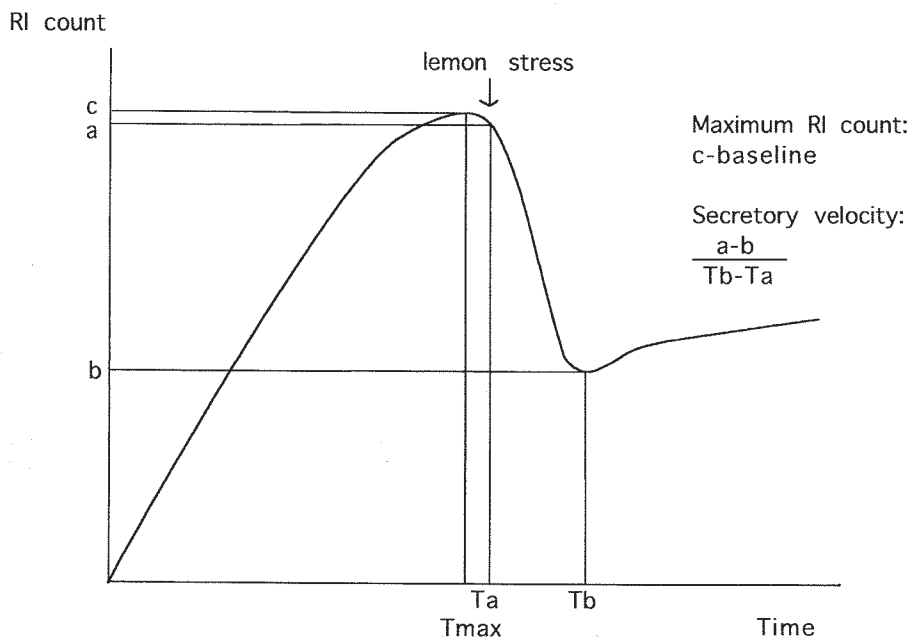


Fig. 1.  $^{99m}\text{Tc}$ -scintigraphy time activity curve.

a=RI count at the time of lemon stress, b=lowest RI count after lemon stress, c=maximum RI count,  $T_a$ =time of lemon stress,  $T_{max}$ =time of maximum RI count,  $T_b$ =time of lowest RI count, RI= radioisotope.

### Statistical method

The statistical method used in this study was the Mann-Whitney test.

## RESULTS

### Unstimulated whole saliva

The mean volume of the patients' USWS was  $0.44 \pm 0.34$  ml in 10 min (flow rate  $0.044 \pm 0.034$  ml/min). Furthermore, with regard to the USWS volume collected in 10 min, 89% of the patients had less than 1 ml (flow rate 0.1 ml/min), representing severe xerostomia. The volumes of USWS were compared between the "under 65" group and the "65 and older" group (Table 2). The mean USWS volume in the "65 and older" group ( $0.29 \pm 0.29$  ml in 10 min) was significantly smaller than that of the "under 65" group ( $0.60 \pm 0.31$  ml in 10 min) ( $p < 0.05$ ). As for medicated status, there was no significant difference between the medicated and non-medicated subgroups (Table 3).

When the effects of medication and aging were considered simultaneously, the volume of USWS still showed a reduction in the medicated "65 and older" patients (0.26 ml/min) when compared with the USWS levels of medicated "under 65" patients (0.64 ml/min).

Table 2. Salivary gland function with different age groups

SMG: submandiblar gland, PG: parotid gland, USWS: unstimulated whole saliva volume during 10 min

Age	Percentage of medicated patients	SMG		PG		USWS (ml/10min)
		Maximum RI count	Secretion velocity	Maximum RI count	Secretion velocity	
65 > (n=12)	50%	2243 ± 860	1189 ± 525	1993 ± 674	1958 ± 1078	0.60 ± 0.31
65, 65 < (n=8)	50%	1263 ± 725	611 ± 252	2519 ± 969	1624 ± 731	0.29 ± 0.29

(mean ± S.D.) \* $p < 0.05$

Table 3. Salivary gland function with or without medication

SMG: submandibular gland, PG: parotid gland, USWS: unstimulated whole saliva volume during 10 min

Medication	Average age	SMG		PG		USWS (ml/10min)
		Maximum RI count	Secretion velocity	Maximum RI count	Secretion velocity	
Not medicated (n=10)	60	1854 ± 710	980 ± 639	2212 ± 751	1863 ± 866	0.44 ± 0.38
Medicated (n=10)	63	1847 ± 463	1006 ± 810	2195 ± 910	1755 ± 955	0.45 ± 0.33

(mean ± S.D.)

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Table 4. Salivary gland function with different age group and with or without medication.

SMG: submandibular gland, PG: parotid gland, USWS: unstimulated whole saliva volume during 10 min

	Not medicated			Medicated		
	SMG	PG	USWS (ml/10min)	SMG	PG	USWS (ml/10min)
65 >	Maximum RI count	2264	2274	2221	1712	0.64 (n=6)
	Secretion velocity	1085	2280	1292	1637	
65, 65 <	Maximum RI count	1239	2119	1287	2919	0.26 (n=4)*
	Secretion velocity	642	1237*	579	2011	

\*p &lt; 0.05

<sup>99m</sup>Tc-scintiscan analysis: Accumulation and secretion velocity analysis

Mean values of maximum RI count based on the estimations of the difference between “c” and background levels were determined for the submandibular gland and parotid glands. The maximum RI count was significantly different between the “under 65” patients and the “65 and older” patients only in the case of the submandibular gland ( $p < 0.05$ ) (Table 2). The mean secretory velocity of the saliva, in response to the lemon stress (the slope of the graph), was determined for both the parotid and the submandibular glands. A significant difference existed in the mean secretory velocities of the submandibular gland between the “under 65” patients and the “65 and older” patients ( $p < 0.05$ ), while the difference in the mean secretory velocities of the parotid gland was not significant. As for medication status, no apparent reduction was observed in maximum RI count and secretion velocity between the patients who were taking saliva reducing medication and non-medicated patients (Table 3).

When both age and medication status were considered, maximum RI count and secretion velocity in the submandibular gland showed a tendency to be lower in “65 and older” patients without reference to their medication status (Table 4). However, the differences were not statistically significant in the groups we studied.

## DISCUSSION

It is difficult to detect the etiology of xerostomia except for Sjögren’s syndrome and radiation-induced xerostomia. Common causes of xerostomia, (other than Sjögren’s syndrome and radiation-induced xerostomia), have been thought to be systemic disease, medication and aging, because most older patients suffer from systemic disease and also because the population of the medicated patients apparently increases with advancing age. Recent investigations have shown that the secretory capacity of salivary glands was maintained in healthy older individuals,<sup>20,21,22</sup> and that age itself is not considered the primary factor causing xerostomia in this population-based study. It has been reported that the reduction of saliva accompanying advancing age might reflect an increase in systemic disease and associated saliva reducing medications.<sup>20,21</sup>

However, some authors insist that aging might reduce the salivary flow in extremely old individuals (over 81 years old).<sup>17)</sup> Thus, the effects of aging and medication are still ambiguous.

Our previous investigation on this topic presented an interesting result.<sup>25)</sup> From USWS volume analysis, the effect of medication was different in the "under 65" group when compared to the "65 and older" group. In the former group, systemic medication did not affect salivary secretion. On the other hand, in the latter group, the medicated patients apparently showed a reduction in USWS volume.

From scintigraphic analysis, it is clear that medication could not affect salivary gland function by itself. It is natural that the drugs could not affect the gland morphologically, and only induce hyposalivation functionally. In another words, the effect of medication on the salivary glands is considered reversible.

On the other hand, aging may induce an organic change in the glands. In this study, aging was shown to impair the uptake and release of RI in the submandibular gland. This finding was consistent with a previous histological study that salivary glands exhibit a decreased number of acini with concomitant increases of fatty tissue in older patients.<sup>26)</sup> As indicated in Table 4, the effects of aging on salivary gland function was not detectable when medication status was adjusted. A possible explanation for this fact is that the number of subjects in this study might be too small to evaluate any difference statistically.

Furthermore, in older patients, it has been reported that renal excretion and liver function decreased.<sup>27)</sup> This phenomenon should affect the pharmacokinetics and make the effects of medication more severe in elderly patients. In our study, medication seems to easily affect salivary secretion in the elderly due to a decline of renal and liver functions and degenerative change of the gland. On the other hand, in the "under 65" patients, the effect of medication might be slight because of the normal renal and liver functions and less histological change of the gland. Therefore, the medicated "65 and older" patients in this study, should have, and in fact did have, the most largest reduction in USWS volume.

This scintigraphic study proved the existence and contents of salivary gland functional disturbances. Many factors may be related to the etiology of xerostomia. <sup>99m</sup>Tc-scintigraphy provides a useful method for evaluating salivary gland function, in addition to other procedures such as sialography and the collection of USWS.

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