A Software Tool for the Assessment of Salivary Gland Function

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***Abstract* — Salivary gland scintigraphy (SGS) is a noninvasive, simple and reproducible technique for the functional evaluation of salivary gland involvement in patients with Sjögren's syndrome. Using Labview environment (National Instruments, Austin, Texas) we have developed a software tool for the automatic calculation of most commonly investigated salivary and oral indices derived from salivary time-activity curves. We have shown examples that illustrate the application of the software. Our software enables the comparison of findings among several research centers with the aim of standardizing a processing protocol, defining the reference values of quantitative indices and introducing new salivary indices.**

***Keywords* — quantitative salivary gland scintigraphy, Sjögren's syndrome, time-activity-curve**

I. Introduction

SJÖGREN'S syndrome (SS) is a chronic, inflammatory, rheumatic disease in which immune cells attack and destroy moisture-producing glands (salivary and lacrimal glands) causing dry mouth (xerostomia) and dry eyes (xerophthalmia). Salivary gland scintigraphy (SGS) is a noninvasive, simple and reproducible technique for the functional evaluation of salivary gland involvement in SS patients. Classification criteria for SS established by the American-European Consensus Group [1] include the dynamic SGS (monitoring the distribution of radionuclide in time) as one of objective tests for the assessment of salivary gland function. Acquisition protocol for dynamic SGS includes intravenous ^{99m}Tc-sodium pertechnetate administration followed by visualizing and storing sequential images of the head (anterior projection) during a 20-40 min time interval (1 frame/min). During the acquisition, excretion of salivary glands is stimulated usually by vitamin C or lemon juice. Analysis of the dynamic SGS includes: 1) delineation of five regions (oral cavity and 4 salivary glands - left and right parotid, left and right submandibular) and 2) observing time activity curves (TACs) that are defined as changes in radioactivity over time in delineated regions. Over the past two decades, different quantitative indices obtained from salivary and oral TACs have been proposed [2]-[6]. The application of different acquisition and processing protocols has resulted in the wide dispersion of the reference values of indices [7]-[9]. At present, there is no gold standard for determining indices. For this reason, commercially available clinical software does not support the automatic quantitative analysis of salivary gland involvement.

We have developed a software tool for the automatic calculation of commonly investigated quantitative indices. Software specifications and user interface options are described in Section II. In Section III quantitative indices available in our software are defined. We show examples of the application of our software in Section IV. The conclusion is given in Section V.

II. Software Description

The software presented in this paper is developed in the Labview environment (National Instruments, Austin, Texas), version 2013. NI Vision Development Module 2013 and NI Labview Biomedical Toolkit 2013 are used for image processing and DICOM read support, respectively.

The software includes the following options:

a) Reading multi-frame DICOM files
b) Resampling of images to a 1024x1024 matrix by bilinear interpolation method for image quality enhancement [10]
c) Adjusting the background and brightness of all frames by two sliders that control the lower and upper threshold of the color map

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d) Image summarizing in the user-defined range of frames (optional)
e) Regions of interest (ROIs) selection within a currently observed frame or a summed image: drawing of "free" hand contours, rectangle or elliptic ROIs. Option for the ROI rotation is available.
f) Saving the ROI template
g) TACs manipulation: choosing the type of representation (counts or counts/pixel), smoothing (*N*-point median smoothing, N∈{3,5,7,9}), background correction (two backgrounds available), TAC preview window for the currently selected ROI, "free" cursor for getting single point coordinates
h) Automatic quantitative indices calculation: the only input parameter is the moment of stimulation, specified by the vertical cursor. Another vertical cursor corresponds to the TAC "shoulder" and is fixed at the first minute of TAC.
i) Saving and exporting the results of analysis in a *spreadsheet* format.

III. Quantitative Indices

We have implemented the automatic calculation of quantitative indices derived from TACs in dynamic SGS.

Fig. 1(a) shows standard delineations of the following ROIs: salivary glands (left and right parotid, left and right submandibular), oral cavity and two backgrounds (*background temporal* in the temporal region above the parotid gland and *background thyroid* in the area above the thyroid gland).

Background correction of the time activity curve corresponding to the salivary gland ROI ($R_{ROI}(t)$, R means radioactivity) is wide-spread according to the following equation:

$$R_{ROI}(t) = R_{ROI}^{non-corr}(t) - R_B(t)\frac{P_{ROI}}{P_B}, \quad (1)$$

where $R_{ROI}^{non-corr}(t)$, $R_B(t)$ are non-corrected TAC of the observed ROI and background TAC, respectively, and P_{ROI}, P_B are areas of observed ROI and background, respectively. Reference [11] shows that the most reliable regions for background corrections are *background temporal* for parotid glands (we have used the same background for the correction of oral cavity region) and *background thyroid* for submandibular glands.

The typical shapes of background TAC and background-corrected TACs for salivary gland and oral cavity are shown in Fig. 1(b). Starting time instance (t=0) is the moment of radiopharmaceutical administration. Two phases can be observed in normal salivary and oral TACs: the uptake phase corresponding to the radionuclide accumulation and the excretion phase initiated by the stimulation of salivary glands. Quantitative indices are derived from both phases of TACs.

Points in TACs enabling indices calculation are the following, Fig. 1(b):

a) points on the salivary TAC
A – initial shoulder representing a vascular perfusion radioactivity peak
B – maximum gland radioactivity point before stimulation
C – gland radioactivity one minute after stimulation
D – gland radioactivity two minutes after stimulation
E – minimum gland radioactivity after stimulation
b) points on the background TAC
F – background radioactivity at the moment of maximum gland activity
c) points on the oral radioactivity TAC
X – initial shoulder representing a vascular perfusion radioactivity peak
Y – maximum oral radioactivity before stimulation
Z – maximum radioactivity after stimulation
S – the point of stimulation

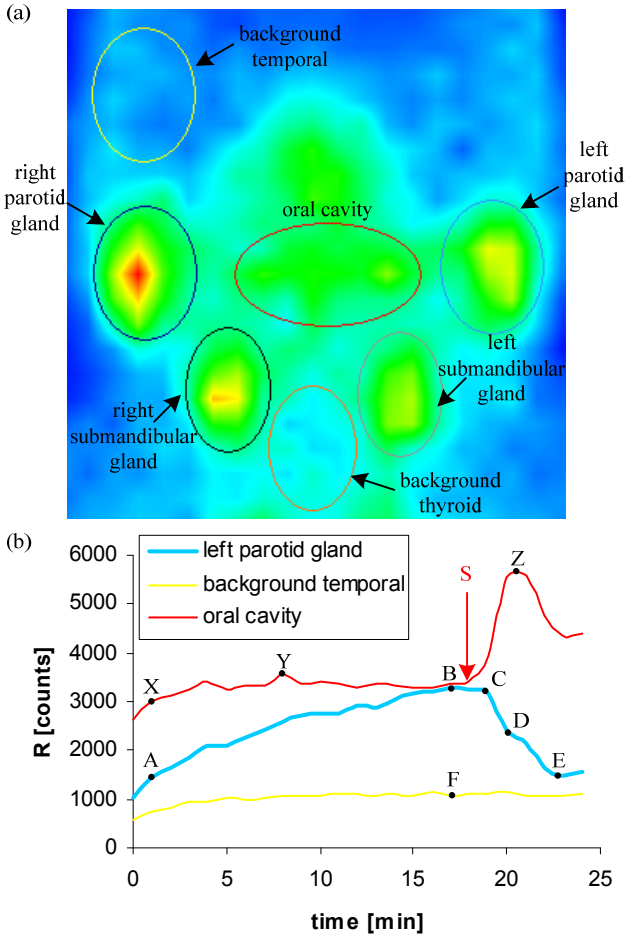

Fig. 1. (a) A single frame from a dynamic SGS image sequence, taken at the 20th minute, with delineation of salivary glands, oral cavity and two backgrounds. (b) Typical shapes of background-corrected TACs in dynamic SGS.

Quantitative parameters derived from the TACs are the following:

a) salivary indices

1) Maximum accumulation (*MA* [%]):

$$MA = \frac{B - A}{B} \cdot 100 \quad (2)$$

2) Time at maximum accumulation (T_B [min])
3) Maximum secretion (*MS* [%]):

$$MS = \frac{B - E}{B} \cdot 100 \quad (3)$$

4) Standard secretion velocity (*SV*) used in the literature [4], [6] is calculated from two points in the excretion phase of TAC (*SV* [%/min]):

$$SV = \frac{C - D}{C} \cdot 100 \quad (4)$$

We suggest a modification of the secretion velocity index by finding an exponential fit (Ae^{-kt}; A, k-constants, t-time variable) to the excretion phase of TAC, Fig. 2. A modified secretion velocity index *SVmod* [%/min] is equal to the damping factor k. For the example presented in Fig. 2, the coefficient of determination R^2 shows excellent goodness of fit for exponential fitting and poor goodness of fit for linearization through two points.

5) Time interval from stimulation to minimum gland activity (T_{min} [min]):

$$T_{\min} = T_E - T_S \quad (5)$$

6) Gland-to-background uptake ratio (*UR*):

$$UR = \frac{B}{F} \quad (6)$$

7) Parotid-to-submandibular ratio (*P:S*):

$$P:S = \frac{UR_P}{UR_S}, \quad (7)$$

where UR_P and UR_S are uptake ratios for a parotid and submandibular gland, respectively, on the same body side.

8) Ejection fraction (*E* [%]):

$$E = \frac{S - E}{S} \cdot 100\,. \quad (8)$$

b) oral indices

1) Pre-stimulatory oral activity (*PRI* [%]):

$$PRI = \frac{Y - X}{Y} \cdot 100 \quad (9)$$

2) Post-stimulatory oral activity (*POI* [%])

$$POI = \frac{Z - X}{Z} \cdot 100 \quad (10)$$

3) Time interval between a perfusion peak and pre-stimulated maximum oral activity (T_l [min]):

$$T_l = T_Y - T_X\,. \quad (11)$$

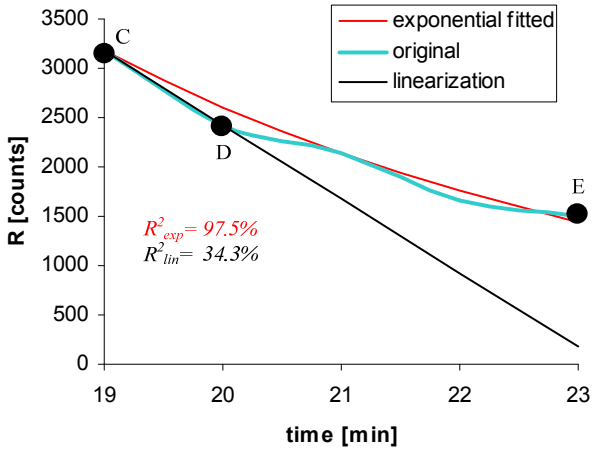

Fig. 2. Zoomed excretion phase in TAC for the left parotid gland selected in Fig. 1(a). The results of exponential fitting and "two points" linearization are presented.

IV. Examples

User interface with an example of the processing and quantification of dynamic salivary study is shown in Fig. 3.

Siemens e.cam camera and Siemens Syngo e.soft 2007 software (Siemens AG, Erlangen, Germany) have been used for image acquisition. After intravenous ^{99m}Tc-sodium pertechnetate administration (with the radioactivity of 160 MBq ≈ 4 mCi), 20 minutes of dynamic SGS (1 frame/min, dimension of image matrix: 64x64, anterior view) were performed.

The image presented in Fig. 3 is resampled to the 1024x1024 matrix by a standard bilinear interpolation method [10]. Three-point smoothing and background correction options from the left menu are selected. The box with all quantitative indices is located at the bottom right of the interface.

ROI delineation is usually performed in the frame of maximum salivary accumulation (*frame mode*). In the case of low salivary gland accumulation, better ROI selection is achieved in the summarized image including frames before the maximum accumulation (*sum mode*). Fig. 4 illustrates the advantage of the *sum mode* in relation to the *frame mode*. The same upper color threshold is adjusted (60%) in Fig. 4(a) and Fig. 4(b). Better ROI separation and the complete gland delineation could be observed in the summed image, Fig. 4(b).

Fig. 5 presents three examples of how *background* (*bcg*) ROI can be selected. Table 1 shows the influence of *background* selection on *UR* parameter in the patient presented in Fig. 5. ROI size has a large impact on these parameters, but it can be minimized by dividing the number of counts in ROI with ROI area (using *counts/pixels mode* instead of *counts mode*).

Fig. 6 shows an example of TACs in the secretion phase of salivary glands. The results of standard *SV* and modified *SV* are listed in Table 2. It can be observed that a standard approach did not recognize similar TAC trends unlike the suggested modification.

V. Conclusion

In previous sections we have presented the new software for objective assessment of salivary glands function. The calculation of indices is not operator dependent thanks to the automatic algorithm. The only required input parameter is the moment of stimulation that usually has a fixed value for one type of study (has to be configured once, at the beginning of analysis). We have improved the quantification by modifying a secretion velocity index. Qualitative indices are sensitive to the choice of ROIs [7]-[9]. For this reason it is important that all studies are treated in the same way, with the same type of ROI selection. The proposed application enables the comparison of findings among several research nuclear medical centers with the aim of standardizing a processing protocol, defining the reference values of quantitative indices and introducing new salivary indices. A step forward is a multidisciplinary research that engages nuclear medical experts, rheumatologists, dentists and engineers for the evaluation of processing protocol.

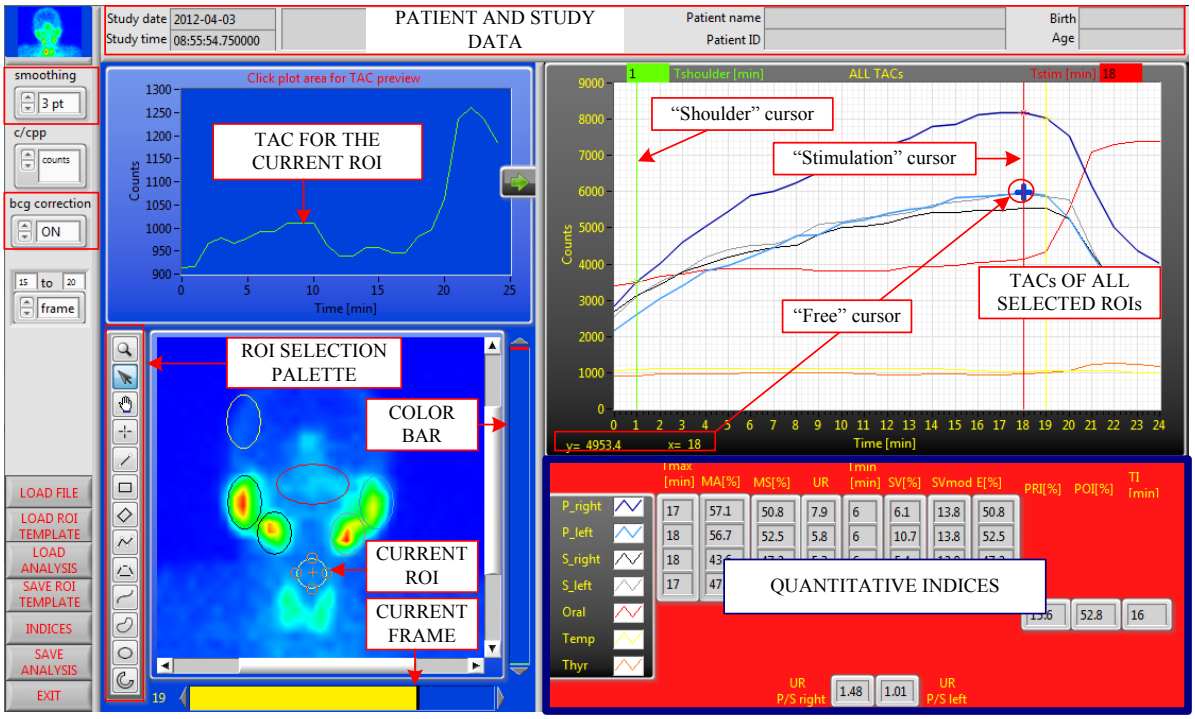

Fig. 3. The screenshot of an example of quantitative salivary analysis.

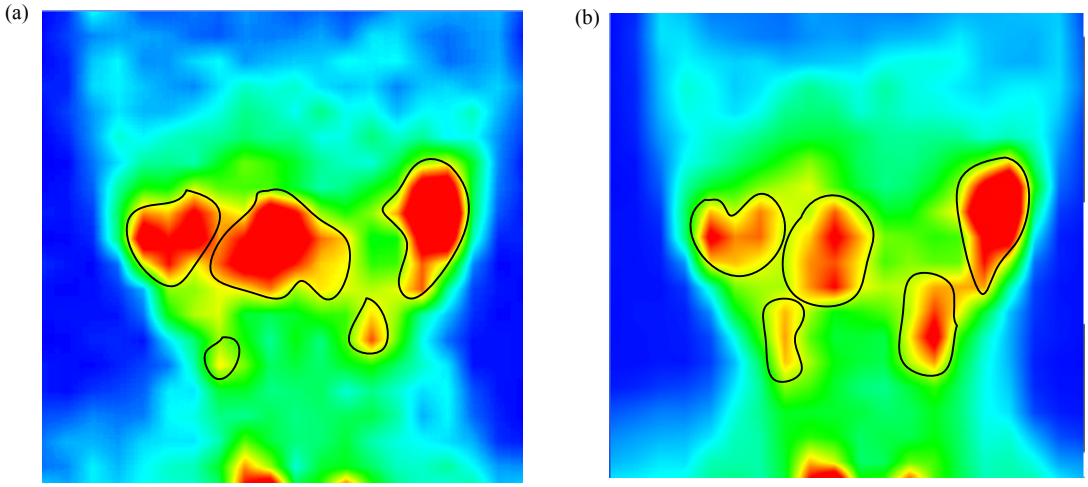

Fig. 4. (a) *Frame mode* (b) *Sum mode* – summed frames from the 1st to the 20th frame.

TABLE 1: VARIATIONS IN *UR* PARAMETER, DEPENDING ON BACKGROUND SELECTION.

TAC mode	***Background selection***	***Salivary gland UR values***			
		parotid		***submandibular***	
		left	***right***	***left***	***right***
counts mode	bcg1*	**5.4**	**6.4**	**5**	**5**
	bcg2	**11**	**13**	**7.7**	**8.7**
	bcg3	7.5	8.8	5.1	5.4
counts/pixels mode	bcg1	**4.2**	**4.9**	**3.6**	**4**
	bcg2	**3.7**	**4.3**	**3.2**	**3.6**
	bcg3	5.7	6.8	4.8	5.1

*bcg – *background* ROIs shown in Fig. 5.

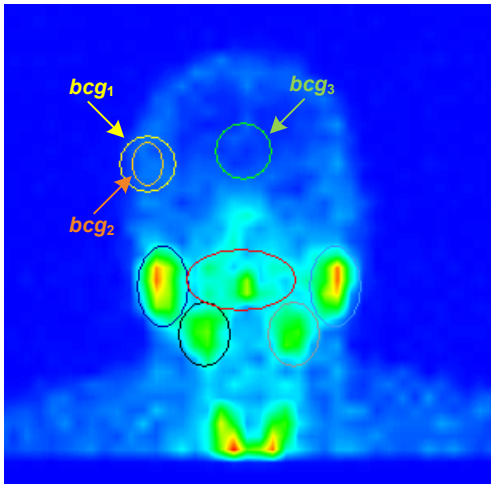

Fig. 5. Variations of *background* (*bcg*) ROI selection.

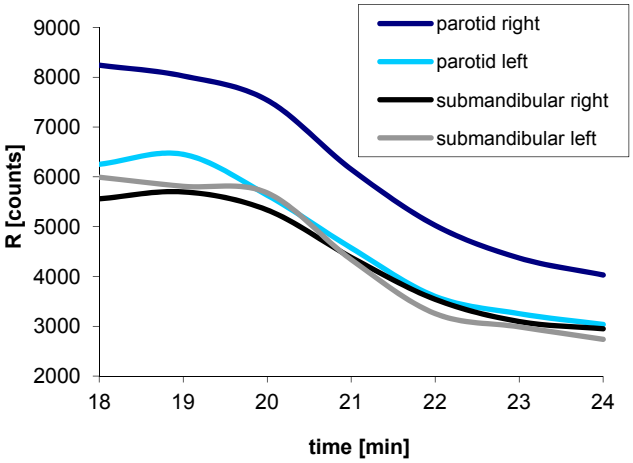

Fig. 6. An example of TACs in secretion phase of salivary glands.

TABLE 2: SECRETION VELOCITY VALUES OBTAINED WITH TWO METHODS (FOR TACS IN FIG. 6).

SV method	***Salivary gland selection velocity [%/min]***			
	parotid		***submandibular***	
	left	***right***	***left***	***right***
standard	10.7	6.1	1.7	5.4
modified	13.8	13.8	15	12.8

Future work will be focused on investigating the influence that the shape and position of selected regions have on the indices, with the aim of finding appropriate ROIs configurations. Normal subjects (without SS) will be examined to define reference values for quantitative indices. The difference between reference indices and indices in subjects with SS (biopsy proven) will be investigated. Eventually, an algorithm for the automatic recognition and classification of SS patients should be developed.

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