Viscosity Plane-wave UltraSound (ViPLUS) in the assessment of parotid and submandibular glands in healthy subjects – preliminary results

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Abstract

Aims: Viscosity is an important mechanical property directly linked to the shear wave dispersion within tissues. The purpose of this study was to establish the normal viscosity value of the parotid gland (PG) and submandibular gland (SMG) in a group of healthy subjects, using the novel Viscosity Plane-wave UltraSound (ViPLUS) technique, and to assess its potential dependence on gender and age. Material and methods: The study group included a total of 49 healthy volunteers (median age 31, 65% females) prospectively examined between February 2021 and March 2021. The viscosity of both PG and SMG was measured using the new Aixplorer MACH 30 ultrasound system (Supersonic Imagine, Aix-en-Provence, France) equipped with a curvilinear C6-1X transducer. The mean value of three valid measurements was considered (quantified in Pa.s). Results: The mean viscosity value for the PG was 2.13±0.23 Pa.s, significantly lower than the mean viscosity value of the SMG 2.44±0.35 Pa.s (p<0.0001). A negative low correlation between SMG viscosity and age was found (rho=-0.38, p=0.006). Viscosity values of the SMG were significantly lower in the age group between 35-77 years (2.12±0.35 Pa.s) than in the age groups 25-34 years (2.52±0.36 Pa.s), and 20-24 years (2.53±0.24 Pa.s), respectively (p<0.05). Viscosity values of both salivary glands did not differ significantly between gender groups. Conclusions: Supersonic ViPLUS represents an innovative and useful non-invasive method to assess the viscosity of the parotid and submandibular glands. Age is a potential confounding factor in the evaluation of normal SMG viscosity.

Keywords: viscosity; ultrasound; parotid gland; submandibular gland; healthy subjects

Introduction

Shear wave elastography (SWE) has been widely used recently for the quantitative assessment of parenchymal stiffness in different organs. So far, ultrasound SWE techniques presumed there is a linearly uniform, elastic and isotropic medium [1]. However, biological soft tissues are intrinsically rather viscoelastic, than entirely elastic [2]. Due to the presence of these two mechanical tissue properties, the link between the applied acoustic radiation force and strain is time dependent and not linear. The shear wave propagation process was proved to be influenced not only by elasticity, which correlated to the velocity of the shear wave, but also by viscosity, which is correlated to the shear wave dispersion [2,3].

To overcome this limitation of most current ultrasound SWE techniques, which do not consider the dispersion effect, two manufacturers (Supersonic Imagine and Canon) have developed new imaging methods that include tissue viscosity properties in their algorithm. Supersonic Imagine has developed Viscosity Plane-wave UltraSound (ViPLUS) 2D imaging mode, embedded in the new Aixplorer MACH 30 system that allows visualization and quantification of tissue viscosity over a region of interest, expressed in pascal seconds (Pa.s). Canon has developed shear wave dispersion imaging (SWD) available on Aplio i900 series diagnostic ultrasound System,
that provides quantitative assessment of the dispersion slope (expressed in m/s/kHz), a parameter directly linked to viscosity.

Dispersion is linked to the frequency dependency of speed and attenuation of the shear waves in the viscous component [4,5]. According to Sugimoto et al [6], an increase in necroinflammatory changes in tissues leads to an increase in dispersion, which is translated into higher values of tissue viscosity. Viscosity has the potential to make an important impact in clinical elastographic diagnosis in the future [7]. However, there are few studies focused on viscosity published so far and they are mainly concerning diffuse liver diseases. Viscosity values provided higher diagnostic performance than hepatic stiffness, in the detection of allograft damage after liver transplantation [8] and were also associated with the degree of lobular inflammation in patients with non-alcoholic fatty liver disease [9]. In a proof-of-concept study, viscosity analysis also provided additional information about focal liver lesions [10].

In the literature, major salivary glands have been studied with SWE but no viscosity assessment was performed so far. Therefore, this study aims to provide reference normal viscosity values of the parotid (PG) and submandibular glands (SMG), which could be further used as cut-off values in studies dealing with infectious or inflammatory conditions affecting salivary glands in the adult population.

Material and methods

Between February 2021 and March 2021, a prospective monocentric study including 49 healthy subjects (32 women and 17 men, median age 31 years) was conducted.

The exclusion criteria were as follows: subjects with a medical history of infectious respiratory diseases in the last two months before the examination; subjects with autoimmune diseases or salivary gland pathology (history of sialolithiasis or tumoral masses); history of radiotherapy for head-and-neck neoplasia. All subjects had no solid or fluid food intake for at least 3 hours before the examination.

The real-time assessment of the parotid gland (PG) and submandibular gland (SMG) viscosity was performed in all subjects using the new Aixplorer MACH® 30 ultrasound system (Aixplorer, Supersonic Imagine, Aix-en-Provence, France). The ShearWave ViPLUS mode was employed, available on the C6-1X curvilinear transducer. All measurements were performed by a single researcher with 3 years of experience in ultrasonography. Both the parotid and submandibular glands of each subject were examined in a standardized approach. Viscosity measurements were performed on longitudinal views, choosing anatomical landmarks: PG was examined using a plane parallel to the posterior border of the vertical mandibular ramus, while SMG was assessed using a parallel plane to the inferior border of the horizontal mandibular ramus. Informed consent was obtained from all subjects in compliance with the World Medical Association Declaration of Helsinki (revised in 2000, Edinburgh).

ViPLUS mode provides information regarding shear wave dispersion within tissues by analysing shear wave propagation speed at various frequencies. The difference in shear wave velocity between frequencies is qualitatively displayed on a color-coded map inside a ViPLUS box and is also quantitatively expressed in Pa.s over a range of values. The ViPLUS box has adjustable sizes and can be placed anywhere within the tissue. The Q-box is placed inside the ViPLUS box and viscosity measurements are obtained displayed as the mean, median, minimum, maximum and standard deviation (SD). The depth and diameter of the Qbox are also shown, together with the Stability Index (SI).

**Viscosity Image Acquisition**

Before engaging the ViPLUS mode, an optimal US B-Mode image was obtained, with the best gain setting. When necessary, the AutoTGC function was selected. No pressure was applied on the probe which was perpen-

Fig 1. ViPLUS measurements performed in the parotid gland (a) and submandibular gland (b) of a healthy subject. A color-coded map is displayed in the ViPLUS box: high viscosity is represented by white-yellow colors, while low viscosity is depicted in red. Quantitative ViPLUS results from the Qbox are expressed in Pa.s. On the right side of the image the following parameters are displayed: the mean, median, and standard deviation (SD) of viscosity, along with the depth and diameter of the Qbox, and the Stability Index (SI).
icularly placed on the skin surface and an ample amount of gel was used. The patient was asked to hold his or her breath, while the ViPLUS mode was activated. After stabilizing the hand, the probe, and the image, the ViPLUS box was positioned over an area of uniform parenchyma, avoiding any large vessels or visible nodules (fig 1). Since the glands are superficially located, all ViPLUS boxes were placed 1 to 2 cm beneath the skin surface. ViPLUS box dimensions were set to be the lowest possible. Measurements with adjusted Q-Box diameter (10 mm and 5 mm) were obtained after the image had stabilized for 3 seconds. The Q-Box was placed at the centre of the ViPLUS box. The measurement was considered valid if the stability index (SI) was over 90% and the standard deviation was less than 10% of the obtained mean viscosity value. The acquisition was repeated three times to collect three valid measurements of viscosity expressed in Pa.s, as suggested by the manufacturer. The mean value of the three consecutive measurements was used to appreciate the gland viscosity. Two sessions of ViPLUS measurements were performed by one researcher to assess the intra-observer variability.

**Statistical analysis**

The statistical analysis was performed with dedicated software: MedCalc Version 20 (MedCalc Software Corp., Brunswick, ME, USA) and GraphPad Prism 8.0.1. Data distribution was evaluated with the Shapiro Wilk test. Normally distributed quantitative variables were presented as a means±standard deviation (SD), while variables with non-normal distribution were presented as median values and range. Categorical variables were presented as percentages and numbers. Parametric Student T-test and Welch test were applied to evaluate the differences of means for normally distributed data. Pearson’s correlation coefficient was calculated to assess the correlation between normally distributed data, while Spearman rank correlation (rho) was used if the distribution was non-normal. One-way analysis of variance (ANOVA) was used to assess the difference between the means of several subgroups, and the Student-Newman-Keuls test was used for pairwise comparisons. Statistical significance was conceded for p<0.05.

**Results**

A total number of 49 healthy volunteers with their characteristics summarised in Table I were included in our study.

The mean normal viscosity value for the parotid gland was 2.13±0.23 Pa.s, significantly lower than the mean normal viscosity value of the submandibular gland 2.44±0.35 Pa.s, p<0.05 (Table II, fig 2).

| Viscosity (Pa.s) | Parotid gland | Submandibular gland |
|-----------------|---------------|---------------------|
| Mean ± SD       | 2.13 ± 0.23   | 2.44 ± 0.35         |
| 95% CI          | 2.06 – 2.19   | 2.32 – 2.54         |
| Min             | 1.70          | 1.50                |
| Max             | 2.53          | 3.08                |

*SD = standard deviation, CI = confidence interval, Min = minimum, Max = maximum

Viscosity values recorded using a 10 mm sized Qbox highly correlated with the values obtained by using a 5 mm sized Qbox, for both PG (r=0.90, p<0.0001), and SMG (r=0.96, p<0.0001).

There was no statistically significant difference in PG and SMG viscosity between males and females (Table III).

A low negative statistical correlation between the age and viscosity values of the SMG parenchyma was found (rho=-0.385, p=0.006); however, there was no statistically significant correlation between age and PG viscosity. While making pairwise comparisons between different age groups, the viscosity values of the SMG were significantly lower in the age group between 35-77 years (2.12 ± 0.35 Pa.s), than in the age groups between 25-34 years (2.52 ± 0.36 Pa.s), and 20-24 years (2.53 ± 0.24 Pa.s).
Pa.s), p<0.05 (Table IV, fig 3). No statistically significant differences were observed between age groups regarding the viscosity of the PG.

The intraobserver variability was tested and the intraclass correlation coefficient revealed that viscosity assessment of PG and SMG is a highly reproducible technique: ICC=0.90 (95% 0.82-0.94).

### Discussions

Viscosity Plane-wave UltraSound (ViPLUS) provides information linked to the shear wave dispersion within a tissue, allowing viscosity measurements in a selected region of interest. Changes in tissue viscosity are being proved to correlate to the level of inflammation [6]; therefore, imaging methods that integrate shear wave dispersion modules might be used as complementary tools to assess diffuse diseases or focal lesions.

A first step in validating this new technique is to establish the normal viscosity value of soft tissues. To the best of our knowledge, there have been no studies performed so far to determine the normal viscosity values of the PG and SMG in healthy subjects.

In this study, normal PG viscosity significantly differs from the SMG viscosity. These differences might be explained in part by the structure of the glands. The PG is a predominantly serous gland, secreting watery saliva, while SMG is a mixed mucous-serous gland, producing more viscous saliva [11]. In terms of parenchymal elasticity, PG also presented lower values than SMG, assessed with 2D-SWE (5.39±1.45 kPa vs. 8.53±1.89 kPa) [12].
In our group of subjects, gender was not a confounding factor for PG and SMG viscosity and did not influence the elasticity modulus of the major salivary glands assessed with 2D-SWE on healthy subjects [13].

In this study, age did not correlate with PG viscosity but presented a negative low correlation with SMG viscosity. Age-related changes regarding saliva quality have been described. Low hydration and increased ionic concentration determine an increased saliva viscosity in the elderly population [14,15]. Surprisingly, in our study, the age group between 35-77 years presented a mean SMG viscosity value lower compared to younger age groups. This might be partly explained by the low number of subjects included in that group and the predominance of subjects under age 50.

Viscosity measurements performed with adjusted Q-Box diameters of 10 mm and 5 mm presented a very good correlation. Also, the intraobserver reproducibility was good, but results must be validated in larger studies. We strongly believe that following the manufacturer’s guidelines for the viscosity assessment is of paramount importance to obtain valid data.

The most important limitation in our study lies in the relatively small size of the analysed sample. Secondly, the curvilinear transducer was used given the fact that the ViPLUS module was only available on this type of transducer. However, the focus of this preliminary study was to obtain quantitative data regarding viscosity and not to assess parenchymal structural changes, where higher frequency transducers are mandatory. Moreover, the images acquired reached a stability index (SI) greater than 90%, which allowed optimal measurements. SI is a relatively new parameter designed by Supersonic Image, which derives from the stability in space and time of tissue rigidity within the circular Q-box. Additional studies with linear transducers are necessary to confirm the obtained normal viscosity values. Finally, the influence of food intake or last mastication upon the viscosity of salivary glands was not studied. Also, further studies need to be undertaken to assess interobserver reproducibility.

In conclusion, ViPLUS represents an innovative, non-invasive and effective technique in assessing parenchymal viscosity of PG and SMG, opening the perspectives for a new research domain and having the potential to become a promising imaging tool in the future. Larger studies on this current topic are therefore warranted to validate these preliminary results on different devices.

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References

1. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall Med 2017;38:e16-e47.
2. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. Ultraschall Med 2013;34:169–184.
3. Sugimoto K, Moriyasu F, Oshiro H, et al. Viscoelasticity Measurement in Rat Livers Using Shear-Wave US Elastography. Ultrasound Med Biol 2018;44:2018–2024.
4. Chen S, Sanchez W, Callstrom MR, et al. Assessment of liver viscoelasticity by using shear waves induced by ultrasound radiation force. Radiology 2013;266:964–970.
5. Chen S, Urban MW, Pislaru C, Kinnick R, Greenleaf JF. Liver elasticity and viscosity quantification using shear-wave dispersion ultrasound vibrometry (SDUV), Annu Int Conf IEEE Eng Med Biol Soc 2009;2009:2252–2255.
6. Sugimoto K, Moriyasu F, Oshiro H, et al. Clinical utilization of shear wave dispersion imaging in diffuse liver disease. Ultrasonography 2020;39:3–10.
7. Rus G, Faris IH, Torres J, Callejas A, Melchor J. Why Are Viscosity and Nonlinearity Bound to Make an Impact in Clinical Elastographic Diagnosis? Sensors (Basel) 2020;20:2379.
8. Lee DH, Lee JY, Bae JS, et al. Shear-Wave Dispersion Slope from US Shear-Wave Elastography: Detection of Allograft Damage after Liver Transplantation. Radiology 2019;293:327-333.
9. Sugimoto K, Moriyasu F, Oshiro H, et al. Value of viscosity and viscoelasticity measurement in patients with NAFLD using shear wave ultrasound elastography. Kanjo 2018;59:370-373.
10. Dong Y, Qiu Y, Zhang Q, et al. Preliminary Clinical Experience with Shear Wave Dispersion Imaging for Liver Viscoelasticity in Preoperative Diagnosis of Focal Liver Lesions. Z Gastroenterol 2020;58:847-854.
11. Holmberg KV, Hoffman MP. Anatomy, biogenesis and regeneration of salivary glands. Monogr Oral Sci 2014;24:1-13.
12. Bădarînză M, Serban O, Maghear L, et al. Shear wave elastography as a new method to identify parotid lymphoma in primary SJögren Syndrome patients: an observational study. Rheumatol Int 2020;40:1275–1281.
13. Badarina Z, Serban O, Maghear L, et al. Multimodal ultrasound investigation (grey scale, Doppler and 2D-SWE) of salivary and lacrimal glands in healthy people and patients with diabetes mellitus and/or obesity, with or without sialosis. Med Ultrason 2019;21:257-264.
14. Kazakov VN, Udod AA, Zinkovych II, Fainerman VB, Miller R. Dynamic surface tension of saliva: General relationships and application in medical diagnostics. Colloids Surf B Biointerfaces 2009;74:457-461.
15. Xu F, Laguna L, Sarkar A. Aging-related changes in quantity and quality of saliva: Where do we stand in our understanding? J Texture Stud 2019;50:27-35.