Influence of variations in resting pressure applied by a transducer on Ultrasound shear wave elastography in the thyroid

Poster No.: C-1903
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Tissue characterisation, Technical aspects, Ultrasound, Thyroid / Parathyroids, Head and neck
DOI: 10.1594/ecr2014/C-1903

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Aims and objectives

Thyroid nodules are extremely common with prevalence over 50% in autopsy specimens, while only a small proportion are malignant (5-15%) [1]. Conventional ultrasound (US) is used widely as a first line imaging technique for thyroid evaluation [2, 3]. US is sensitive for detecting thyroid nodules and has utility for characterization as several conventional sonographic features are predictive of malignancy or benignity. However, its overall accuracy for malignancy is suboptimal as no single criterion is highly accurate, while combining criteria increases the specificity at the cost of lowered sensitivity, and vice versa [4].

In clinical practice, nodules that are suspicious or indeterminate for malignancy on conventional US usually undergo fine-needle aspiration for cytology (FNAC), which is minimally invasive and has a high specificity (>90%). However, FNAC is subject to interpretation errors, is suboptimal for discriminating follicular lesions, and up to 20% of FNACs are technically inadequate [5]. Even if FNAC were to be perfectly accurate, judicious selection of suspicious nodules based on sonographic criteria is still required as it not cost-effective or ethical to biopsy every nodule detected in routine clinical practice. Consequently, there is still a need for an accurate and non-invasive diagnostic tool to detect thyroid malignancy.

Elastography refers to imaging techniques that evaluate tissue elasticity, and can be performed using different imaging modalities including US. A relatively recent refinement of US elastography called shear wave elastography (SWE) can estimate tissue stiffness in real-time and produces quantitative stiffness output in units of shear wave velocity (m/s) or estimated tissue stiffness (kPa). Unlike an older and more extensively studied elastographic technique termed strain elastography, SWE uses acoustic radiation impulses to mechanically stimulate tissues, and does not require the operator to perform compression-decompression cycles for elastogram generation. As a consequence, SWE is reportedly relatively operator-independent, i.e. resistant to minor variations in operator practical technique.

Previous studies of SWE for thyroid nodules have documented generally optimistic accuracy results for detecting malignancy, however, the range of kPa values of benign and malignant nodules and optimum discriminatory cut-offs have varied considerably [6-9]. Unsurprisingly, some investigators have questioned the reproducibility of elasticity measurement using SWE in the thyroid [10-11]. In this regard, the amount of resting pressure, i.e. (pre)compression applied during SWE by the operator can influence SWE stiffness values, and this phenomenon has been systematically evaluated in the liver and breast [12-13]. Furthermore, there are sparse published biomechanical data from experiments on ex-vivo thyroidectomy specimens, which suggests that different types of thyroid nodule vary in their rate of change in stiffness according to the resting pressure applied [14].
However, to our best knowledge, the effect of compression on SWE on thyroid tissue has not been evaluated in vivo in a systematic study. The aim of this preliminary study was to evaluate the influence of variations in resting pressure applied by a transducer on SWE stiffness measurements of benign and malignant thyroid nodules and normal thyroid parenchyma.

**Methods and materials**

From January to December 2013, thyroid SWE was performed in 57 subjects using a 4-15 MHz linear transducer on commercially available clinical shear wave ultrasound system (Aixplorer, SuperSonic Imagine, Aix en Provence, France). SWE was performed on different thyroid tissue types as follows: 38 normal thyroid glands (Norm), 27 benign hyperplastic nodules (MNG) and 5 papillary carcinomas (PapCa).

Subjects were either normal volunteers or patients referred for thyroid US assessment, and the final diagnosis of thyroid nodules was based on sonographic, cytological ± histological results as per the patient's routine clinical work-up. Informed written consent was obtained from all subjects and local ethic committee approval had been obtained for this prospective study. This study was supported by a grant from the research grants council of the Hong Kong Special Administrative Region, China (grant Chinese University of Hong Kong. Project ID 2140771).

SWE cineloops, each lasting 10 seconds to allow for SWE image stabilization, were acquired for normal parenchyma or nodules, which were exposed to four levels of static compression. Static compression was applied manually by an operator via the US linear transducer placed on the skin surface with an intervening US gel layer. The 4 levels were based on the operator's experience and by the following features on the corresponding grayscale images as follows:

1) MINIMAL, a thick US coupling gel layer between the transducer and skin surface

2) MILD, a thin US gel layer present

3) MODERATE, light compression of the skin over the thyroid gland

4) HIGH, substantial compression of the skin over the gland.

In addition, the level of compression was quantified in terms of percentage axial (vertical) strain of the thyroid gland relative to the minimal compression level by referencing to the
corresponding gray-scale images [Fig1]. All levels of compression were tolerated well by subjects. No dynamic or cyclical compressions were applied during SWE.

Following SWE acquisition, circular electronic regions-of-interest (ROIs) were placed on representative static SWE images; ROIs were placed either within the entire nodule or a 1cm diameter ROI was placed within normal parenchyma. SWE tissue stiffness data were displayed automatically and the mean value of the ROI was recorded [Fig.2]. Up to four SWE readings were obtained at each compression level and an averaged SWE value was used for subsequent analysis. SWE stiffness indices were compared between compression levels and between tissue types using Students t-tests, with a p<0.05 indicating statistical significance.

Images for this section:

Fig. 1: Longitudinal grayscale US and corresponding SWE image of a subject with normal thyroid parenchyma at minimal compression A) and moderate compression B) levels. Green arrows indicate vertical heights of thyroid tissue or nodule that were used to calculate % strain. Mean SWE of the ROIs were 15.3 kPa and 24.0 kPa at minimal and moderate compression respectively.
**Fig. 2:** Transverse grayscale US and corresponding SWE image of a benign hyperplastic nodule at minimal compression A) and moderate compression B) levels. Green arrows indicate the vertical heights of thyroid tissue or nodule that were used to calculate % strain. Mean SWE of the ROIs were 15.3 kPa and 24 kPa at minimal and moderate compression levels respectively.
Results

The mean SWE kPa values of each thyroid tissue type at different levels of compression are shown in Table 1 (Fig. 3). All tissue types had higher SWE stiffness at high compared to lower compression levels (P values <0.05). SWE values were higher for papillary carcinoma than benign hyperplastic nodules, and both tissues types were higher than normal parenchyma (P values <0.05).

Of importance, these differences were statistically significant at all compression levels except for hyperplastic nodule vs. papillary carcinoma at minimal compression level (Table 2 (Fig. 4)). Graphs showing the relative SWE (kPa) increment (%) versus % axial strain for different types of thyroid tissue are shown in Fig 5. Boxplots of absolute SWE (kPa) increment for different tissue types at different compression levels compared to minimal compression level are shown in Fig 6.

There was an increase in SWE stiffness (kPa) for each tissue type for successive increases in axial compression. Importantly, the rate of increase in SWE stiffness was different for each tissue type, evidenced by differences in the slopes of the SWE (kPa) versus strain graphs (Fig 5 d). In this respect, the SWE stiffness increment was higher for papillary carcinoma than MNG, i.e. steeper slope of the papillary Ca best-fit line, and both types of nodule were higher than normal parenchyma.

Images for this section:

<table>
<thead>
<tr>
<th>Compression level</th>
<th>Norm</th>
<th>MNG</th>
<th>PapCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal compression (0% strain)</td>
<td>13.7±5.2</td>
<td>19.7±8.5</td>
<td>31.2±18.2</td>
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<tr>
<td>Mild compression (7-12% strain)</td>
<td>15.4±7.4</td>
<td>26.2±11.7</td>
<td>54.1±26.1</td>
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<tr>
<td>Moderate compression (~14-20% strain)</td>
<td>17.7±6.5</td>
<td>28.4±11.6</td>
<td>87.5±24.4</td>
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<tr>
<td>High compression (~22-30% strain)</td>
<td>23.5±7.8</td>
<td>37.6±10.1</td>
<td>141.2±43.1</td>
</tr>
</tbody>
</table>

Fig. 3: Table 1. SWE stiffness (kPa) of different thyroid tissue types for different levels of compression.
**Fig. 4:** Table 2. P values of student t-test comparisons of SWE stiffness values between different tissue types at different compression levels. Note the statistically significant results for all comparisons except MNG vs PapCa at minimal compression.

<table>
<thead>
<tr>
<th>Compression level</th>
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<th>Mild</th>
<th>Moderate</th>
<th>High</th>
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<tbody>
<tr>
<td>MNG vs PapCa</td>
<td>0.13</td>
<td>0.029</td>
<td>0.0039</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PapCa vs Norm</td>
<td>0.029</td>
<td>0.013</td>
<td>0.0023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Norm vs MNG</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

**Fig. 5:** Graphs showing relative kPa increment (%) versus % axial strain for A) normal thyroid tissue (blue), B) hyperplastic nodules (green), C) papillary carcinomas (red), D) all tissue types pooled. Best fit-lines and goodness-of-fit results are shown.
Fig. 6: Boxplot of absolute kPa increment for different tissue types at different compression levels compared to minimal compression level. A) mild compression, B) moderate compression C) high compression.
Conclusion

Absolute SWE stiffness measurements (kPa) of normal thyroid tissue, hyperplastic nodules and papillary carcinoma vary depending on the resting pressure applied by the transducer. The differences in SWE stiffness results between papillary carcinoma and hyperplastic nodules are greater at higher levels of compression than at lower compression levels. In our study, there was no significant difference in mean SWE stiffness values between papillary carcinoma and hyperplastic nodules at minimal compression level, which refers to minimal contact of the transducer with the skin (evidenced by a thick US gel layer being maintained between the transducer and skin).

This finding is important as appears to contradict the advice that SWE should be performed with minimal compression of the skin in order to standardize the technique and prevent the operator from applying excessive precompression inadvertently. Indeed, this mechanism may also account for the discrepancy in published SWE stiffness values of benign and malignant nodules between different studies [13].

In this regard, in separate studies, Sebag et al. and Veyrieres et al. documented similar stiffness readings, 150 ± 95 kPa (mean ± SD) and 115 ± 60.4 kPa for malignant nodules, and 36 ± 30 kPa and 41 ± 25.8 kPa for benign nodules, respectively. However, in another study using identical SWE technology, Bhatia et al. documented a much lower median stiffness of 43.1 kPa, (range 12.2±187.5 kPa) for malignant nodules and 26.2 kPa (range 7.4±132.0 kPa) for benign nodules. Extrapolating the present study findings, it is possible that Bhatia et al. had performed SWE using minimal compression, whereas Sebag et al. and Veyrieres et al. had performed SWE using higher levels of compression.

There are several limitations of the present study:

First, the study sample is small, especially of papillary carcinomas, although the preliminary results are already informative and this study is ongoing.

Second, we did not measure actual compression force applied but instead measured a surrogate marker, axial strain. In practice, applying a fixed force and determining the precise stress applied to tissues in vivo is extremely challenging, partly due to many factors that can influence stress distribution such as stress decay and boundary conditions. Nevertheless, our study is the first step towards objective assessment the effects of different compression levels on stiffness measurements in the thyroid.
Third, SWE results for measurements acquired in the longitudinal and transverse planes through the thyroid were pooled, although it is theoretically possible that SWE plane may influence SWE measurements due to tissues displacing or behaving differently under different axes of compression, either due to intrinsic tissue anisotropy or due to differences in mobility/stiffness of the neighbouring tissues such as trachea and carotid vessels. We are currently collecting more data to allow subgroup analysis according to acquisition plane.

Finally, we acquired data at different SWE compression levels that were assigned arbitrarily by the operator, albeit with visual guidance from the corresponding image), which may or may not be comparable to the range of compression levels applied by most operators during elastography. Consequently, we do not know if the effect of different levels of pre-compression shown by our study is relevant to routine clinical practice. We are in the process of investigating this question in another related study.

To conclude, this preliminary study has shown that papillary carcinoma and hyperplastic nodules differ in their rate of increase of SWE stiffness for given increases in pre-compression, such that papillary carcinomas show a greater increase in stiffness. This variation may account for discrepancies in SWE stiffness values as well as accuracy results reported in different studies, and highlights the fact that thyroid SWE is potentially highly operator dependent. Further research is required to evaluate the influence of compression levels applied by operators on SWE in the thyroid, in order to standardize the technique before it can be considered for use in routine clinical practice.

Personal information

References


