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Research Article

ARFI-Elastography: Clinical Applications in Diffuse or Nodular Thyroid Disease in Children and Adolescents

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Abstract

Elastography is a new step in diagnostic medicine. This technique makes it possible to measure stiffness of the thyroid gland.

Methods: In our study we conducted a cohort study of 141 children and adolescents aged 4-18 years with a suspected or known thyroid disease. Using a Siemens Acuson S3000 we examined thyroid glands both in longitudinal and cross-section.

Results: With increasing tissue changes in the B-Mode of the sonography, the ARFI Velocity increases. This resulted in the average speed of 1.61 +/- 0.36 m/s, however the results of the longitudinal measuring sections proved to be more reliable. It showed a difference between the left and the right lobe, which was particularly noticeable in the cross section measurement. With the increase of vascularization, the ARFI values were initially decreasing and ultimately increasing when vascularization was extreme. A reliable Assessment of clinical presentations using elastography is not possible. The volume of the thyroid gland, TSH, fT4 and sociodemographic factors such as gender, age, weight, height and BMI did not influence the ARFI values.

Conclusion: The ARFI elastography offers a wide range of gain in knowledge in the diagnostics of thyroid gland diseases in children and adolescents. Inflammation, dysfunction and structural diseases of the thyroid gland result in an increase of the ARFI values. During the examination, the examiner should pay attention the surrounding structures and its vascularization. Furthermore, the longitudinally position of the transductor should be carefully selected.

Keywords: Elastography; Thyroid; Children; Sonography

Abbreviations

BMI: Body Mass Index; Corr: Correlation; LQ: Cross-Sectional Sonography of the Left Lobe; LL: Longitudinal-Sectional Sonography of the Left Lobe; M: Mean Value; m/s: Meter Per Second; Max: Maximum; Min: Minimum; RQ: Cross-Sectional Sonography of the Right Lobe; RL: Longitudinal-Sectional Sonography of the Left Lobe; ROI: Region of Interest; SD: Standard Deviation; SF: Standard Error; Sig: Significance; SWE: Shear Wave Velocity; Var: Variance; Vs: Shear Wave Velocity

Introduction

The diagnosis and differentiation of thyroid parenchyma from diffuse or nodular thyroid disease can be challenging, especially in the early stages. Screening tools for thyroid dysfunction such as physical examination, laboratory tests and fine-needle aspiration do not provide accurate, specific and early diagnosis.

Thyroid ultrasound with gray-scale and color Doppler is the most helpful imaging modality to differentiate normal thyroid parenchyma from diffuse or nodular thyroid disease by evaluating glandular size, echogenicity, echotexture, margins, and vascularity.

However the lack of quantifiability made proper diagnostics and follow-ups difficult. Moreover an accurate assessment of tissue consistency was not possible.

Acoustic Radiation Force Impulse (ARFI) filled this gap. ARFI, as a virtual radiologist's hand, is an imaging technique to directly reveal the physical property of tissue with conventional ultrasound probes (Siemens AG, Erlangen, Germany with a 9L4 transducer). The probe is placed on the neck and no pressure is applied for measurement.

The tissue is mechanically stimulated using short-duration acoustic pulses.

The acoustic pulses generate localized tissue displacements within a defined region of excitation. The displacements induce a lateral shear-wave propagation which is tracked using multiple laterally positioned ultrasound "tracking" beams. By measurement of the time to peak displacement at each lateral location, the shear wave velocity (SWV) within the region of interest can be reconstructed [1].

The stiffer the tissue, the higher the shear wave velocity.

While this method is already being used to examine nodular changes in the thyroid gland, there have been few studies on the examination of diffuse thyroid disease.

This paper shows the results of imaging modality examinations on the thyroid glands of children and adolescents with suspected or already diagnosed diffuse thyroid disease.

Materials and Methods

This cohort study was initiated between February 2015 and June

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2016. Informed written consent was obtained from all patients and the study was performed in accordance with the ethical guidelines of the Helsinki Declaration and approved by the local ethics committee of the University of Halle an der Saale.

We examined 141 patients aged between 4 and 18 years (mean age = 12.6 years, 61.7% female and 38.3% male patients). We conducted a cohort study of children and adolescents with a suspected or known thyroid disease (Table 1).

These included 27.6% patients with hypothyroidism, 3.6% with Graves' disease, 4.3% with Hashimoto's disease, 5.0% with cystoid changes, 2.1% with nodular changes, 12.8% with thyroiditis and 29.8% thyroiditis associated with diabetes mellitus. 4.9% of the patients were classified in the category "various clinical pictures". These include cystic fibrosis, MEN-1, and Turner's hypothyroidism. In a further 9.9%, the B-mode and color Doppler sonography showed suspect findings, which were classified as observable.

The diagnosis was made using conventional diagnostic tools for thyroid dysfunction such as symptoms, physical examination and laboratory tests. The ARFI-elastography was carried out with a Siemens Acuson S 3000 device. A 9MHz linear transducer was used, which has a freely positionable region of interest of 5x6 mm. The measurements were repeated five times and carried out on both sides, both in cross section and in longitudinal section. In case of hemithyroidectomy, the examination was only carried out on one side, which was the case in two patients. In order to avoid systematic errors, the sequence of the sides and the cutting plane was varied for each patient. Thyroid gland dimensions measured in length and width and the volume was calculated in the usual way. The thyroid structure based on echotexture was classified into subgroups as homogeneous, discret inhomogenous, moderate inhomogeneous, and markedly inhomogeneous (B1-4).

The vascularization of the thyroid gland was assessed morphologically and divided into four subgroups of normal vascularization (measuring scale at 8cm/s), slightly increased vascularization (19cm/s), moderately increased vascularization (30cm/s) and strongly increased vascularization (over 30cm/s).

The ARFI values were measured five times for both sides and in each case in longitudinal and transverse transducer positioning. A mean value was formed from the five measurements made in each case.

To evaluate the results, the means, standard deviations, standard errors and medians as well as minima and maxima were calculated. A paired T-test was performed to determine the influence of transducer positioning. The same procedure was followed when assessing the differences between the sides. According to the standard, the 95% confidence interval is specified for the significance value. The influences of gender, age, height, weight, BMI and thyroid volume were calculated using multivariate linear regression analysis. The relationship between laboratory values and ARFI values was also examined using correlation.

In order to work out differences in the ARFI values in certain diseases, box-whiskers-plots were created. The second and third quartiles are shown with a wide bar, while outliners are marked by dots.

The relationship between ARFI values and changes in structure and vascularization was examined by means of correlation and regression analysis.

The correlation of the ordinal and a metric scale was calculated using Spearman Rho. Fluctuations between the individual ARFI values at a measurement location were examined using an analysis of variance. A probability of error of 5% was determined for the analysis of significance. The statistical analysis and the creation of the graphics were carried out with the programs Microsoft Excel for MAC 2008 and SPSS Statistics for MAC Version 25 under the supervision of the Institute for Medical Epidemiology, Biometry and Computer Science of the University of Halle.

Results

Table 2 shows the changes in ARFI velocity with increasing structural changes in the thyroid tissue.

Table 3 shows the recorded ARFI velocity for each disease.

Overall, the measurement in transverse transducer position on the right side showed lower values and a higher range compared to the other positions. The measurement of the ARFI values in transverse transducer positioning showed a higher standard deviation than those in longitudinal positioning (SD 0.46 and 0.47 *vs.* 0.39 and 0.39).

Table 4 shows that there is also a difference between cross-section and longitudinal section.

The ARFI velocities are significantly lower in the cross-section than in the longitudinal section.

Table 5 shows in a side-by-side comparison that there is a significant difference between the measurements on the right and left

Table 1:

Characteristics (n=141)		Mean	SD	Minimum	Maximum
Age in years	Total	12.6	3.71	4	18
	Male	12.39	3.647	4	18
	Female	12.74	3.77	4	18
BMI in kg/m²	Total	20	4.34	13	33.53
	Male	19.4	4.35	13.78	32.08
	Female	20.37	4.33	13	33.53
Height in cm	Total	155.99	18.36	106	191
	Male	156.79	20.59	110	191
	Female	155.5	16.94	106	178
Body weight in kg	Total	50.44	18.3	17.8	104
	Male	49.8	20.17	18.7	104
	Female	50.84	17.14	17.8	88

Table 2: ARFI values (in m/s) with increasing structural changes in B-Mode Sonography.

	N	ARFI - M	SD	SF	Min	Max	Var
B1	43	1.496	0.284	0.043	0.98	2.28	0.08
B2	60	1.645	0.401	0.052	0.97	2.9	0.161
B3	25	1.608	0.303	0.061	1.08	2.27	0.092
B4	13	1.782	0.37	0.103	1.11	2.56	0.137

Table 3: Mean values of ARFI velocity (in m/s) broken down for individual disease categories.

Classification of Thyroid diseases	N	Mean Shear-Wave Velocity in m/s	SD	Median	SF	Min in m/s	Max in m/s	V
Hypothyroidism	39	1.67	0.43	1.63	0.07	1.03	2.9	0.18
Graves'	5	1.69	0.2	1.62	0.09	1.48	1.95	0.04
Hashimoto's	6	1.78	0.34	1.76	0.14	1.41	2.27	0.11
Cystoid changes	7	1.47	0.26	1.49	0.1	0.98	1.74	0.07
Nodular changes	3	1.6	0.14	1.52	0.08	1.51	1.76	0.02
Thyroiditis	18	1.77	0.32	1.69	0.08	1.4	2.45	0.1
DM associated Thyroiditis	42	1.49	0.29	1.45	0.04	0.97	2.42	0.08
Other	7	1.66	0.53	1.34	0.2	1.22	2.57	0.28
Suspected Thyroid Disease	14	1.5	0.3	1.47	0.08	1.1	2.22	0.09

Table 4: ARFI values in longitudinal and cross-section.

	Mean Difference	SD	SF	95% CI	T	Sig.	Cor
RQ-RL	-0.132	0.386	0.033	-0.196, -0.067	-4.029	0.000092	0.591
LQ-LL	-0.045	0.431	0.036	-0.117, 0.027	-1.239	0.217	0.512

Table 5: ARFI values in a side comparison.

	MDiff	SD	SF	95% CI	T	Sig.	Cor
RQ- LQ	-0.143	0.36	0.031	-0.203, -0.082	-4.649	0.0000008	0.699
RL- LL	-0.057	0.29	0.025	-0.106, -0.008	-2.296	0.023	0.724

Table 6: ARFI values with increasing vascularization.

	N	Mean SWE in m/s	SD	SF	Min	Max	Var
1	50	1.709	0.406	0.057	1.03	2.9	0.165
2	65	1.556	0.331	0.041	0.97	2.56	0.109
3	18	1.49	0.261	0.062	1.2	2.28	0.068
4	8	1.618	0.278	0.098	1.18	1.95	0.077

Table 7: ARFI values (in m/s) with increasing structural changes in B-Mode Sonography.

	N	Mean Shear-Wave Velocity in m/s	SD	SF	Min	Max	Var
B1	43	1.496	0.284	0.043	0.98	2.28	0.08
B2	60	1.645	0.401	0.052	0.97	2.9	0.161
B3	25	1.608	0.303	0.061	1.08	2.27	0.092
B4	13	1.782	0.37	0.103	1.11	2.56	0.137

side.

In the present study, we also compared vascularization with ARFI velocity. Results are shown in Table 6.

In our study we found that there is no correlation between the level of laboratory test parameters (including TSH, fT3 and fT4, as well as thyroid antibodies) and ARFI values. The socio-demographic influencing variables of gender, age, body weight, height, BMI and age also showed no significant correlation with the ARFI values.

Discussion

The present prospectively conducted study shows the feasibility of elastography on childrens' thyroid glands. All children and adolescents suspected of having a thyroid disease were included in the study in order to examine its practicality in everyday clinical practice. Only subjects who were unable to remain under instruction for the examination were excluded. We performed the ARFI elastography five times per side and section, which is sufficient according to the recommendation of Sporea et al. to keep the examination time as reasonable as possible [2]. Both thyroid lobes were examined. ARFI measuring was performed in transverse and longitudinal transducer positioning on the left and the right lobe. Special attention was paid to place the region-of-interest in an area apart from interfering structures such as the trachea or carotid artery.

We propagate an additional gain in knowledge in the diagnosis and the follow-up through the additionally performed elastography.

Table 7 shows that the ARFI velocity increases with increasing structural change whereby an accurate differentiation in the area of moderate change are not possible.

When subdividing into disease categories, it becomes clear that thyroid diseases associated with structural changes, as in the case of Graves' disease and Hashimoto's disease, show a lower spread of values and the averaged ARFI velocity is increased if normal values for children are used as a basis. The research group led by Ceyhan Bilgici described the first normal values as 1.22m/s [3].

In a study of 26 children and adolescents with Hashimoto's thyroiditis Yucel et al. found that ARFI velocity increases up to 1.67m/s, which corresponds to the results of our study [4]. Changes such as cysts and nodules also show a low scatter with increased ARFI values.

Inflammatory tissue with increased perfusion also showed increased ARFI values, but with a greater scatter.

In order to avoid a selection bias, all patients who were presented for a thyroid ultrasound examination were included in the study.

This results in a high degree of heterogeneity, which is reflected

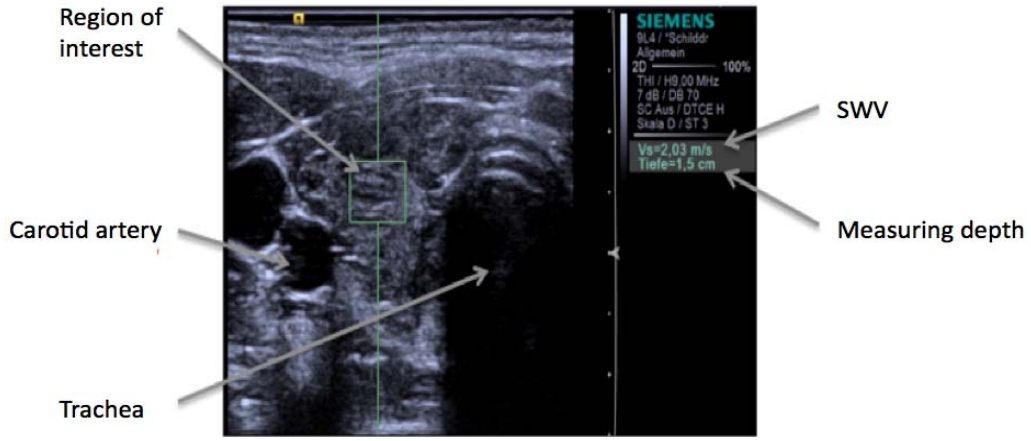

Figure 1: Application of ARFI elastography on a thyroid gland in transversal transducer positioning, with a measured shear wave velocity of Vs = 2.03m/s in a tissue depth of 1.5cm.

in the categories "Diabetes mellitus - associated thyroiditis" or "Suspected thyroid disease".

It can be clearly seen that the mean values are close together.

A reliable differentiation between the diseases is not possible based on the ARFI values alone. This corresponds to the results that Sporea et al. has already shown in the examination of adult thyroid diseases [2].

In addition, differences in transducer positioning as well as a side comparison were examined.

Since in the right thyroid lobe the beam sequences impinge in immediate surroundings to the blood-filled carotid artery and in the left thyroid lobe in surrounding of the air-filled trachea, we expected a difference of ARFI values in side comparison with no structural difference. This hypothesis is supported by the values collected, which are shown in Table 3. While studies such as that by Neuwirt et al. found no difference between left and right lobe [5], Cantisani pointed out a difference due to carotid pulsation [6].

Since there is more thyroid tissue in the longitudinal section and there are fewer surrounding structures in the immediate surroundings of the incoming beam sequence, the positioning of the transducer in longitudinal and transversal position was also compared. As the values in Table 5 show, there is a significant difference [7,8]. A higher standard deviation in the transversal positioning is particularly noticeable. Measurements in longitudinal positioning are therefore more reliable than those in cross-section [9].

This should be considered in particular with children and adolescents, because of their smaller thyroid glands, which means that the surrounding structures are closer to one another [10,11].

This is to be especial considered in examinations of children and adolescents since surrounding tissue is even closer in these smaller thyroid tissues (Figure 1).

Yucel et al. found a minimal positive correlation between vascularization and ARFI velocity which they didn't regard as noticible because of the small cohort in their study [4].

Our study shows a significant correlation between vascularization and ARFI velocity. The ARFI velocity initially decreases continuously with increasing vascularization and increases significantly with extremely high vascularization [12].

In our opinion, one explanation for the behavior of the ARFI velocity towards vascularization is that the tissue becomes softer with increasing blood flow, and consequently loses tissue stiffness.

This means that the shear wave speed cannot propagate as quickly. Accordingly, the ARFI speed decreases with degrees of vascularization 2 and 3.

On the other hand, if the vascularization is particularly high, the speed of propagation increases again, as the pressure in the tissue is presumably higher due to the extremely strong blood flow [13-17].

Based on the findings listed, we suggest performing an ARFI elastography in addition to the conventional ultrasound examination for examining the thyroid gland in children and adolescents [18]. The collection of 5 measured values per side and transducer positioning has proven itself. When evaluating the investigation, the values in the longitudinal section have a higher reliability [19,20].

It should be noted that the degree of tissue vascularization has an influence on the ARFI velocity.

Taking these aspects into consideration ARFI elastography offers a significant gain in knowledge and the possibility of quantifiable follow-up in thyroid diagnostics.

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