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Application progress and prospect of ultrasound elastography in clinical staging of deep venous thrombosis

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Abstract: Ultrasound elastography techniques take advantage of the difference in elasticity values between pathological and normal tissues to produce qualitative and quantitative information for diagnosis. It is safety, real-time, low cost and has achieved good efficacy in the diagnosis of liver fibrosis, thyroid and breast nodules. In recent years, it has been found that ultrasound elastography can also be used for the differential diagnosis of clinical staging of lower extremity deep venous thrombosis by comparing the elasticity values of the thrombus with the surrounding normal tissues, but there are few clinical reports on this area. Therefore, this article systematically reviews the progress in the application of ultrasound elastography in various diseases in order to guide the clinical diagnosis and treatment of lower extremity deep venous thrombosis.

1. Introduction

Ultrasound Elastography (UE) proposed by Ophir et al [1], which uses the elasticity of pathological tissue to be different from the elasticity of surrounding normal tissue, measures the tissue stiffness in response to the applied mechanical force (compression or shear wave) under a special imaging mode, acquires the measured value, and generates qualitative and quantitative information that can be used for diagnostic purposes [2]. Commonly used measurement methods are elastic 5-point method and strain-rate ratio method [3], 5-point method is based on ultrasound image evaluation, green indicates normal tissue hardness, red indicates soft hardness, blue indicates hard hardness. The lesions were green as 1 point, blue-green as 2 points, blue-green as 3 points, blue-green as 4 points, and blue as 5 points [4]. The ratio rule is to determine the compliance ratio of the diseased tissue to the surrounding tissue and evaluate the softness and hardness of the diseased tissue by comparing the hardness of the two. To reduce the error, it is usually measured 10 times and averaged. A variety of UEs have been developed, and the commonly used quasistatic elasticity imaging, acoustic radiation force impulse (ARFI) and shearwave elasticity imaging (SWE) techniques [5] have been widely used in the fields of liver, breast, thyroid, and kidney. In recent years, a large number of studies have shown that UE can also compare the elasticity value of thrombus stiffness with the elasticity value of surrounding normal tissues for qualitative diagnosis of clinical staging of thrombus, but there are few reports on relevant clinical studies. The latest application progress of UE in various diseases is reviewed as follows in order to guide the clinical diagnosis and treatment of DVT.

2. Progress in the application of liver, breast, kidney, thyroid and other fields2.1 Background of the study area

UE is initially applied in the diagnosis of diseases of soft tissue organs, such as benign and malignant diagnosis of liver fibrosis, breast nodules, and thyroid nodules. Chen Xi [6] combined real-time elastography (RTE) and SWE to differentiate benign from malignant focal liver lesions (FLLs). RTE and SWE were used to diagnose benign and malignant FLLs, respectively, and the accuracy of the two was evaluated using the results of pathological examination as the standard. RTE uses an elastic 5-point method, with < 2 being diagnosed as benign and ≥ 3 as malignant. SWE focuses the ultrasound pulse to the region of interest (ROI) to obtain the shear wave velocity and calculates the Young's modulus value to diagnose benign and malignant FLLs. The results showed that the accuracy rates were 69.49% and 71.19%, respectively. Subsequently, RTE and SWE were scored in combination, bounded by the cutoff value measured by SWE, which was benign − 1 and malignant + 1. The combined score was subtracted by adding to the measured RTE value. The accuracy of the combined score was as high as 83.05%. Jing Zu fang [7] used US combined with RTE to diagnose benign and malignant plasma cell mastitis (PCM) patients. First, conventional ultrasound was used, followed by ultrasound classification of breast masses - BI-RADS classification. Then the ultrasound instrument was switched to RTE mode and diagnosed by 5-point method (4-5 points for diagnosis of malignancy). Results There were 29 and 10 cases with conventional ultrasound BI-RADS classification grade IV and above and elastography score > 4 points, respectively, accounting for 30.9% and 10.6% of the total cases. For the two groups assessed by BI-RADS alone and US combined with RTE, after analysis using the X2 test, (X2 = 17.05, P = 0.000), the difference was found to be statistically significant. The results showed that for patients with PCM, UE significantly improved the detection rate of benign breast lesions, and US combined with RTE could avoid unnecessary needle biopsy rate in patients with PCM. Xu Tao et al. [8] used US combined with UE to perform differential diagnosis of benign and malignant thyroid nodules in elderly patients with unenhanced thyroid findings. All 120 patients received US and UE examinations, and the surgical and pathological results were used as the diagnostic criteria. The results showed that the accuracy of US was 74.17% (89/120), UE was 84.17% (101/120), and combined diagnosis was 86.67% (104/120). It can be seen that the sensitivity of US combined with UE in the differential diagnosis of unenhanced thyroid nodules in the elderly is better than that of pathological findings. The above studies not only prove the feasibility of UE in the diagnosis of benign and malignant nodules, but also provide a new idea to improve the accuracy using combined diagnosis.

UE technology has been continuously updated, and Garcovich et al. [9] identified the rate of patients who could safely avoid screening endoscopy with liver stiffness (LS) cut-off and platelet count measured with ElastPQ (a novel spot SWE technique) in patients with endoscopically confirmed compensated chronic liver disease. The results showed that 75/195 (38%) met the criteria for "BAVElastPQ" (LS < 12 kPa and platelet count > 150 000/μL). Potentially, surveillance endoscopy was avoided in 38% of the experimental population. Grossmann et al.10 applied multifrequency temporal harmonic elastography in 53 patients with glomerulonephritis and 30 healthy volunteers to assess its diagnostic efficacy for early glomerulonephritis. In this study, elastography of both kidneys was performed in all participants to generate a full-field view of renal shear wave velocity. Renal shear wave velocities were measured throughout the renal parenchyma, cortex, and medulla, respectively, and correlated with quantitative B-mode ultrasound results such as renal length and parenchymal thickness. Diagnostic performance of renal elastography was assessed with receiver operating characteristic curve analysis. The results indicate that multifrequency temporal harmonic sonoelastography can accurately describe abnormal renal stiffness in glomerulonephritis, especially in patients with early disease and preserved renal function.

3. Application in DVT

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is one of the common complications after total knee arthroplasty (TKA) and total hip arthroplasty (THA) (11).Studies have shown [12] that the incidence of postoperative DVT is as high as 41%~85% and 42%~57% in total knee and hip arthroplasty without thromboprophylaxis .The 2017 Chinese Guidelines for the Diagnosis and Treatment of Deep Vein Thrombosis [13] clinically divides DVT into acute, subacute, and chronic phases. It is specified that the onset of 14 is the acute phase, in which the thrombus is easy to fall off and may cause fatal pulmonary embolism (PE). 15-30 days into the subacute phase, more than 30 days into the chronic phase. Venography is the "gold standard" for the diagnosis of DVT [14], but it is a seminal examination and has a high cost, and is now gradually replaced by ultrasound (US) with non-seminal and high accuracy, becoming the method of choice for DVT examination [15], but US cannot determine the clinical stage of thrombosis, and popular UE in recent years can compensate for the defects of US.

3.1 Progress of elastography in animal thrombosis model

Emelianov [16] first applied UE to the determination of venous thrombosis time, they made different thrombi (2, 6 and 9 days) in the vena cava of rats and examined them by UE. They found that 6 clots were about twice as hard as 2 clots, and 9 clots were again twice as hard as 6 clots. Although elasticity was only recorded in a qualitative manner and no statistical analysis of the data was provided, the authors found the potential of UE in determining the age of venous thrombosis. Geier [17] created experimental venous thrombosis in a porcine model for 1, 3, 6, 9, 12, and 15 days. The thrombosed iliac veins were removed and embedded in gelatin and then examined by UE. Elastography showed that thrombus elasticity decreased on days 6 – 12, and 12 thrombi were about three times stiffer than 6 thrombi. This correlated with the histological findings, which showed a significant increase in fibroblast and collagen production in the clot during this period, and thrombi on days 12 and 15 showed signs of advanced tissue. The results of the analysis led to the conclusion that UE helps to determine the exact age of the venous thrombus in the experimental setting and that the difference in elasticity is most pronounced between days 6 and 12. Zhang Jing qiu [18] and others used SWE to study femoral vein thrombosis in rabbits and obtained similar experimental results to Geier. On the 6th and 7th day of thrombosis, fibrocytes and collagen in the thrombus components increased, thrombosis was organized, and SWE could effectively determine the exact age of thrombosis. Zhang Yan [19] and others subdivided patients in the acute phase of DVT according to the experimental results of Geier and divided them into four groups from the normal three groups according to the time of onset: group A (disease duration 1 to d), group B (disease duration 7 to d), group C (disease duration 14 to d), and group D (disease duration greater than 6 months) to assess the diagnostic efficacy of RTE for the clinical staging of DVT. The measured elasticity values were compared using ROC curves and the cutoff values were determined. The results showed that the difference was obvious and there was an accurate diagnostic cutoff point, and the longer the course of the disease, the greater the thromboelastic value. Conclusion RTE can accurately differentiate the clinical staging of DVT and may be a powerful basis for judging the course of thrombosis.

3.2 Progress in clinical research of elastography3.1 Occurrence regularities of the annual drought in Hunan

Hong Dengke [20] applied RTE in the diagnosis of clinical staging of common femoral vein thrombosis, divided the patients into acute phase group, subacute phase group and chronic phase group according to the onset time, used normal US and SWE techniques to diagnose the three groups of patients, respectively, and plotted ROC curves to compare the diagnostic efficacy of the two techniques. Results There were significant statistical differences in Young's modulus values among the three groups, demonstrating that SWE technique can be used to distinguish the clinical stage of common femoral vein thrombosis. Mumoli. [21] used UE to compare the E-Index values of patients with acute and chronic DVT to assess the diagnostic efficacy of UE for DVT. The mean E index of femoral and popliteal blood clots in the acute thrombosis group was 5.09 ± 0.38 and 4.96 ± 0.47 ($p = 0.15$), while the mean E index of femoral and popliteal blood clots in the chronic thrombosis group was 2.46 ± 0.66 and 2.48 ± 0.59 ($p = 0.81$).There was a significant difference between the acute and chronic groups ($p < 0.0001$), indicating that UE is diagnostic for acute and chronic clinical stages of DVT.YI [22] et al divided DVT patients into acute thrombosis group (within 14 days), subacute thrombosis group (2 weeks to 6 months) and chronic thrombosis group (greater than 6 months) according to the time of thrombosis. RTE imaging of thrombus formation was assessed using a 5-point scale by Itoh, and the strain ratio (reference/clot ratio: the strain rate of the clot divided by the strain rate of the reference material) was calculated. The results showed that 70.9% of the acute thrombosis group was red.62.8% in the subacute thrombus group were green.67.6% of the chronic thrombosis group showed blue color. The strain of subacute thrombosis group was higher than that of acute thrombosis group ($P < 0.001$). The strain ratio in the chronic thrombosis group was higher than that in the subacute thrombosis group ($P < 0.05$).Demonstrated that RTE can accurately assess DVT thrombus clinical staging and is a promising diagnostic method. Liu et al. [23] performed SWE measurements on a rabbit model of DVT for 2 weeks to measure head, body, and tail elasticity values, respectively, and performed quantitative pathologic image analysis (QPIA) to obtain the relative percentage of major clot components. The results showed an increasing trend in elasticity values with increasing days and a significant increase on individual days. And the number of days with significant increase was different in different sites: the head was significantly increased on days 4 and 6; the body was significantly increased on days 4 and 7; the tail was significantly increased on days 3 and 6, and QPIA showed that with the dynamic changes of thrombus mature thrombus composition, as fibrin and calcium salt deposition gradually increased, red blood cells (RBC) and platelets gradually decreased. Significant changes were observed on days 4 and 7, which may represent transition points for acute, subacute, and chronic thrombi.

Ho. WK [24] found that the possibility of venous thrombosis shedding in the lower extremities was negatively correlated with its formation period, with the extension of the thrombosis period, the degree of organization was small, while the possibility of complete organization of thrombosis shedding was very low, and emboli in the acute phase were more likely to shedding than those in the chronic phase. Animal experiments such as Geier, Zhang Jing qiu and Liu have all demonstrated that thrombi will be organized over time, with red blood cells and platelets predominating in the early stage and gradually developing to collagen and fibroblasts accounting for the main components. As this change occurs, the thrombus is more tightly bound to the wall and the thrombus is more stable. It is also due to the presence of such changes that it is possible to study the timing of thrombosis in UE.

4. Summary

Due to the serious aging of the population and prolonged average life expectancy, artificial knee and hip arthroplasty in China has entered a stage of rapid growth (25). Thrombus screening and clinical staging differentiation before and after surgery are very important. UE has the advantages of real-time, low cost and repeatability. UE detects the elasticity value of thrombus, reflects the "old and new degree" of thrombus from the side, and whether the thrombus is easy to fall off, so as to evaluate the stability. And a UE instrument can perform US and UE dual diagnosis by simply switching the channel, and some even allow the combined examination of multiple UE technologies, which not only saves time, but also improves the accuracy of diagnosis. There are a wide variety of UE and continuous innovation, which promotes the rapid development of UE. However, there are few reports on the clinical application of UE in DVT diseases, most of which stay in the animal experimental stage, and a large number of clinical studies can provide more reliable evidence for the differentiation of clinical stages of DVT. In summary, with the continuous development of UE technology, UE is bound to provide an important clinical diagnostic basis for the diagnosis and clinical staging of DVT and guide further treatment such as anticoagulation and thrombolysis in patients with DVT.

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References

[1] OPHIR J, CéSPEDES I, PONNEKANTI H, et al. Elastography: a quantitative method for imaging the elasticity of biological tissues [J]. Ultrason Imaging, 1991, 13(2): 111-34.

[2] SIGRIST R M S, LIAU J, KAFFAS A E, et al. Ultrasound Elastography: Review of Techniques and Clinical Applications [J]. Theranostics, 2017, 7(5): 1303-29.

[3] CHANG J M, MOON W K, CHO N, et al. Clinical application of shear wave elastography (SWE) in the diagnosis of benign and malignant breast diseases [J]. Breast Cancer Res Treat, 2011, 129(1): 89-97.

[4] Jinfang Yang, Yinli Li, Yuehua Yu. Research Progress of Ultrasound Elastography Evaluation of Liver Lesion [J]. Chinese Medical Innovations, 2016, 13(36): 137-40.

[5] Xiaona Li, Na Li, Chaoyang Wen. Progress in the application of sonoelastography in staging of deep venous thrombosis [J]. Chinese Journal of Medical Ultrasound Celectronic Edition, 2017, 14(01): 8-10.

[6] Xi Chen, Jiamei Niu,Peiqin Jiang, et al. The value of combined application of two sonoelastography techniques in the diagnosis of benign and malignant hepatic focal lesions [J]. Medical Review, 2021, 27(06): 1227-34.

[7] Fangru Jin, Tianjiao Zheng, Li Liang, et al. Diagnostic value of conventional ultrasound combined with real-time tissue elastography in plasma cell mastitis [J]. Chinese Journal of Ultrasound in Medicine, 2021, 37(03): 260-3.

[8] Tao Xu, Yiping Zhu, Li Yang, et al. Application of high-frequency ultrasound combined with sonoelastography in the differential diagnosis of thyroid nodules without thyroid enhancement in the elderly [J]. Chinese Journal of Gerontology, 2021, 41(07): 1451-4.

[9] GARCOVICH M, DI STASIO E, ZOCCO M A, et al. Assessing Baveno VI criteria with liver stiffness measured using a new point-shear wave elastography technique (BAVElastPQ study) [J]. Liver Int, 2020, 40(8): 1952-60.

[10] GROSSMANN M, TZSCHäTZSCH H, LANG S T, et al. US Time-Harmonic Elastography for the Early Detection of Glomerulonephritis [J]. Radiology, 2019, 292(3): 676-84.

[11] Chinese Society of Orthopaedics. Chinese Guidelines for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery [J]. Chinese Journal of Orthopaedics, 2016, 2): 65-71.

[12] Zili Liao, Haibo Si, Bin Shen. Risk factors and prevention of lower extremity deep venous thrombosis in joint replacement [J]. Chinese Journal of Orthopaedic Surgery, 2020, 28(14): 1293-6.

[13] Xiaoqiang Li, Fuxian Zhang, Shenming Wang. Guidelines for the Diagnosis and Treatment of Deep Venous Thrombosis (Third Edition) [J]. Chinese Journal of Vascular Surgery (Electronic Version), 2017, 9(04): 250-7.

[14] KOCAKOC E. Detection of deep vein thrombosis with Doppler sonography [J]. J Thromb Thrombolysis, 2008, 26(2): 159-60.

[15] LANDEFELD C S. Noninvasive diagnosis of deep vein thrombosis [J]. Jama, 2008, 300(14): 1696-7.

[16] EMELIANOV S Y, CHEN X, O'DONNELL M, et al. Triplex ultrasound: elasticity imaging to age deep venous thrombosis [J]. Ultrasound Med Biol, 2002, 28(6): 757-67.

[17] GEIER B, BARBERA L, MUTH-WERTHMANN D, et al. Ultrasound elastography for the age determination of venous thrombi. Evaluation in an animal model of venous thrombosis [J]. Thromb Haemost, 2005, 93(2): 368-74.
[18] Jingqiu Zhang, Yongping Lu, Tingting Liang, et al. Elasticity study of femoral vein thrombosis in rabbits by real-time shear wave elastography [J]. Chinese Journal of Ultrasound in Medicine, 2017, 33(03): 267-70.
[19] Yan Zhang, Feng Liu, Yang Chen, et al. Real-time Shear Wave Elastography in Evaluating the Course of Deep Venous Thrombosis [J]. Journal of Zhengzhou University (Medical Science), 2014, 49(04): 585-7.
[20] Dengke Hong, Jiajia Yang, Ensheng Xue, et al. Application of real-time shear wave elastography in clinical staging of common femoral vein thrombosis [J]. China Medical Imaging Technology, 2019, 35(08): 1200-4.
[21] MUMOLI N, MASTROIACOVO D, GIORGI-PIERFRANCESCHI M, et al. Ultrasound elastography is useful to distinguish acute and chronic deep vein thrombosis [J]. J Thromb Haemost, 2018, 16(12): 2482-91.
[22] YI X, WEI X, WANG Y, et al. Role of real-time elastography in assessing the stage of thrombus [J]. Int Angiol, 2017, 36(1): 59-63.
[23] LIU X, LI N, WEN C. Effect of pathological heterogeneity on shear wave elasticity imaging in the staging of deep venous thrombosis [J]. PLoS One, 2017, 12(6): e0179103.
[24] HO W K. Deep vein thrombosis--risks and diagnosis [J]. Aust Fam Physician, 2010, 39(7): 468-74.
[25] Niaoniao Bian, Kaiyuan Cheng, Xiao Chang, et al. Preliminary Statistics and Analysis of Total Hip and Knee Arthroplasty in China from 2011 to 2019 [J]. Chinese Journal of Orthopaedics, 2020, 40(21): 1453-60.