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Analyzing and modeling rheological behavior of liver fibrosis in rats using shear viscoelastic moduli*

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Abstract: The process of liver fibrosis changes the rheological properties of liver tissue. This study characterizes and compares liver fibrosis stages from F0 to F4 in rats in terms of shear viscoelastic moduli. Here two viscoelastic models, the Zener model and Voigt model, were applied to experimental data of rheometer tests and then values of elasticity and viscosity were estimated for each fibrosis stage. The results demonstrate that moderate fibrosis (≤F2) has a good correlation with liver viscoelasticity. The mean Zener elasticity E_1 increases from (0.452±0.094) kPa (F0) to (1.311±0.717) kPa (F2), while the mean Voigt elasticity E increases from (0.618±0.089) kPa (F0) to (1.701±0.844) kPa (F2). The mean Zener viscosity increases from (3.499±0.186) Pa·s (F0) to (4.947±1.811) Pa·s (F2) and the mean Voigt viscosity increases from (3.379±0.316) Pa·s (F0) to (4.625±1.296) Pa·s (F2). Compared with viscosity, the elasticity shows smaller variations at stages F1 and F2 no matter what viscoelastic model is used. Therefore, the estimated elasticity is more effective than viscosity for differentiating the fibrosis stages from F0 to F2.

Key words: Biological mechanics, Rheological properties, Liver fibrosis, Viscoelasticity, Shear modulus, Elasticity, Viscosity, Zener model, Voigt model

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1 Introduction

When a liver is invaded by various pathogens that damage and inflame the liver, the immune system of the liver tissue will be activated. Liver fibrosis is the result of a repairing process of the damaged tissue, which refers to the accumulation of extracellular matrix (ECM) proteins. The procession of liver fibrosis is an extremely complicated and gradual process. Currently a liver biospy is the only gold standard for the diagnosis of liver fibrosis. Fibrosis staging has been evaluated according to the METAVIR scoring system: F0 representing no fibrosis; F1 representing portal fibrosis without septa; F2 representing portal fibrosis and few septa; F3 representing numerous septa without cirrhosis; and, F4 representing cirrhosis (French METAVIR Cooperative Study Group, 1994).

The alterations of the tissue pathological state can be expressed by the changes of the biomechanical properties of the liver. Fung (1993) regarded viscoelasticity as the best indicator of soft tissue mechanical properties, which can be modeled by a combination of elastic and viscous components for characterizing the rheological behavior of the tissue (Joseph, 1990). However, determining viscoelastic parameters quantitatively requires an appropriate rheological model that describes soft tissue. Various viscoelastic models are proposed to describe normal tissues in literature. Bovine livers were investigated by oscillatory rheometry

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and the viscoelastic parameters were quantified by a fractional spring pot model (Klatt *et al.*, 2010). The Kelvin-Voigt fractional derivative model was applied to viscoelasticity characterization of canine livers (Kiss *et al.*, 2004), and the shear modulus of porcine livers was measured by a dynamic mechanical analysis (DMA) and modeled by a generalized Maxwell model with two modes of relaxation (Chatelin *et al.*, 2011). The speed of shear waves propogating in porcine livers was measured at multiple frequencies by shearwave dispersion ultrasound vibrometry (SDUV) and shear viscoelasticity parameters were estimated by fitting the shear wave speed dispersion curves according to the Voigt model (Chen *et al.*, 2009). The Voigt model was also applied to viscoelastic properties of bovine muscles using transient elastography (Catheline *et al.*, 2004) and *in vivo* human brachialis muscle using a noninvasive ultrasound-based technique by supersonic shear wave image (SSI) (Gennisson *et al.*, 2010). Among these models, the Voigt model is widely used to explain rheological behavior of normal tissue due to a simple formation of one spring and one dashpot.

In this work, the shear viscoelasticity of liver fibrosis is studied and modeled by both Voigt and Zener models to answer the following questions: (1) If normal liver tissue is invaded by inflammation and tumor, due to the pathology state changing, does the Voigt model appropriately describe the rheological behavior of the liver tissue at different fibrosis stages? (2) Do both elasticity and viscosity have a good correlation with fibrosis stages, and/or which is more effective in staging? (3) Because there are no studies publicly reported in literature on rheological properties of liver fibrosis using other viscoelastic models, is the Voigt model a proper model for describing liver fibrosis? In this study, we report the findings of the rheological mechanical experiments for liver fibrosis in rats by comparing the Zener model and Voigt model.

2 Materials and methods

2.1 Methods

Rheological experiments measure the dynamic mechanical behavior of biological tissue. A sinusoidal shear strain $\varepsilon(t)=\varepsilon_0 e^{i\omega t}$ is imposed on the tissue, which induces a sinusoidal shear stress $\sigma(t)=\sigma_0 e^{i(\omega t+\delta)}$ at the same frequency. The ratio of sinusoidal stress to sinusoidal strain is represented by the complex shear modulus $G^*(\omega)$ (Macosko, 1994):

$$G^*(\omega)=\frac{\sigma_0 e^{i(\omega t+\delta)}}{\varepsilon_0 e^{i\omega t}}=\frac{\sigma_0}{\varepsilon_0}(\cos\delta+i\sin\delta)=G'(\omega)+iG''(\omega), \tag{1}$$

where ε_0 is the shear strain amplitude, σ_0 is the shear stress amplitude, ω is the angular frequency, t is the time, δ is the phase shift angle, $G'(\omega)$ is the storage modulus, and $G''(\omega)$ is the loss modulus. These complex moduli are related to the elasticity and viscosity by various rheological models.

The Zener and Voigt models are chosen to describe the complex shear modulus $G^*(\omega)$ in this study. As shown in Fig. 1a, the Zener model consists of two components in parallel. The first component is the Maxwell model, which includes a spring E_2 and a dashpot η, and the second component is a spring E_1. The Voigt model consists of a spring E and a dashpot η in parallel (Fig. 1b). The Zener model can describe both the creep and relaxation behaviors while the Voigt model only describes the creep behavior.

The complex shear moduli in Zener and Voigt models ($G_Z^*(\omega)$ and $G_V^*(\omega)$) can be respectively represented as (Chen *et al.*, 2012):

$$G_Z^*(\omega)=(E_1+\frac{\omega^2\eta^2E_2}{E_2^2+\omega^2\eta^2})+i\frac{\omega\eta E_2^2}{E_2^2+\omega^2\eta^2}, \tag{2}$$

$$G_V^*(\omega)=E+i\omega\eta. \tag{3}$$

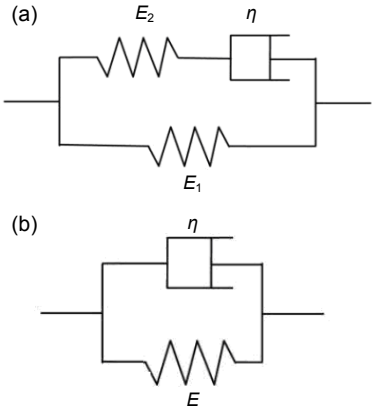

Fig. 1 Rheological models used in this study
(a) Zener model; (b) Voigt model

For the Zener model, the storage modulus $G'_Z = E_1 + \frac{\omega^2\eta^2 E_2}{E_2^2 + \omega^2\eta^2}$, the loss modulus $G''_Z = \frac{\omega\eta E_2^2}{E_2^2 + \omega^2\eta^2}$. Similarly, for the Voigt model, $G'_V = E$ and $G''_V = \omega\eta$. Here, E_1, E_2, and E are elasticities, η is the viscosity, and ω is the angular frequency in the two models.

The magnitudes of the complex shear moduli in the two models can be respectively defined as follows:

$$|G^*_Z(\omega)| = \sqrt{E_1^2 + \frac{(2E_1 + E_2)E_2\omega^2\eta^2}{E_2^2 + \omega^2\eta^2}}, \quad (4)$$

$$|G^*_V(\omega)| = \sqrt{E^2 + \omega^2\eta^2}. \quad (5)$$

In our study, a rheometer is used to measure the storage moduli and loss moduli of the rat livers at different fibrosis stages. The measurements are fitted by the Zener model and Voigt model, respectively. The fitting results are compared for evaluating the performances of the models and the quantitative viscoelastic parameters of each stage are given for analyzing the correlation with fibrosis staging.

2.2 Materials and experiments

Experiments were conducted by using medicated rats. Totally 24 male Sprague-Dawley rats (provided by Guangdong Medical Laboratory Animal Center, Foshan, Guangdong, China) weighing 180–270 g were randomly divided into two groups, including 6 rats in the control group and 18 rats in the model group inducing liver fibrosis. The control group was fed by normal water and food. The model group was fed by the mixture reagents of carbon tetrachloride (CCl_4) and olive oil at a volume ratio of 1:1. Meanwhile, the model group was also injected subcutaneously at a dose of 0.3 ml/100 g body weight (BW) twice a week during a 15-week period. The first injection dose was doubled (0.6 ml/100 g BW), and then was adjusted to 0.3 ml/100 g BW for the rest of the injections. After the 2nd, 5th, 9th, and 13th weeks, rats in different fibrosis stages were obtained. Fibrosis grading for each rat was identified by the pathological section and Masson's trichrome stain. Thus, 18 rats were differentiated by stages: 5 rats for F1, 8 rats for F2, 4 rats for F3, and 1 rat for F4. All the procedures used in the studies were approved by the Animal Care Committee of Shenzhen University, China.

To characterize the dynamic mechanical behavior of rat livers in fibrosis stages F0 to F4, rheological tests were performed on excised rat livers *in vitro*. The tests using small linear deformations were carried out at room temperature ((23±1) °C) by a strain-controlled rheometer (AR1000, TA Instruments, New Castle, DE, USA) with a 25-mm diameter parallel plate configuration. The livers were excised after euthanatizing the rats. Usually one or two liver specimens were extracted from one rat, thus rheological tests were performed on the 27 pieces, including 6 pieces for F0, 5 pieces for F1, 9 pieces for F2, 5 pieces for F3, and 2 pieces for F4. These specimens, which were (4±1) mm thickness, were placed between the parallel plates and the edges were carefully trimmed by a scalpel. Firstly, the tissue linear behavior between strain and stress was determined by performing strain sweeping oscillation, with strain amplitude range increasing from 0.01% to 2.00% at 1 and 40 Hz, respectively. Secondly, the strain and stress behaviors in the frequency domain were measured by frequency sweeping oscillations with a fixed strain of 0.5% from 1 to 40 Hz. Finally, the storage moduli and loss moduli were obtained for each specimen at different fibrosis stages.

3 Results

Five liver specimens for all fibrosis stages (one specimen for one stage, total five stages) are randomly selected. Because there is only one rat for stage F4, the measurement of stage F4 may not be representative. The measured storage moduli at different stages are shown in Fig. 2 (the loss moduli are not shown due to space constrains). Obviously, they are all frequency-dependent and the curvatures of the stages are different.

Model-dependent storage moduli G'_Z and G'_V are fitted with the measurements using the real parts of Eqs. (2) and (3) by the Levenberg-Marquardt method. The fitted value of the Voigt model is always a constant because of storage modulus $G'_V = E$, which does not correctly describe the frequency-dependent property of the measurements. However, G'_Z of the Zener model is frequency-dependent and it fits well with the measurements. Therefore, the Zener model shows better fitting results than the Voigt model.

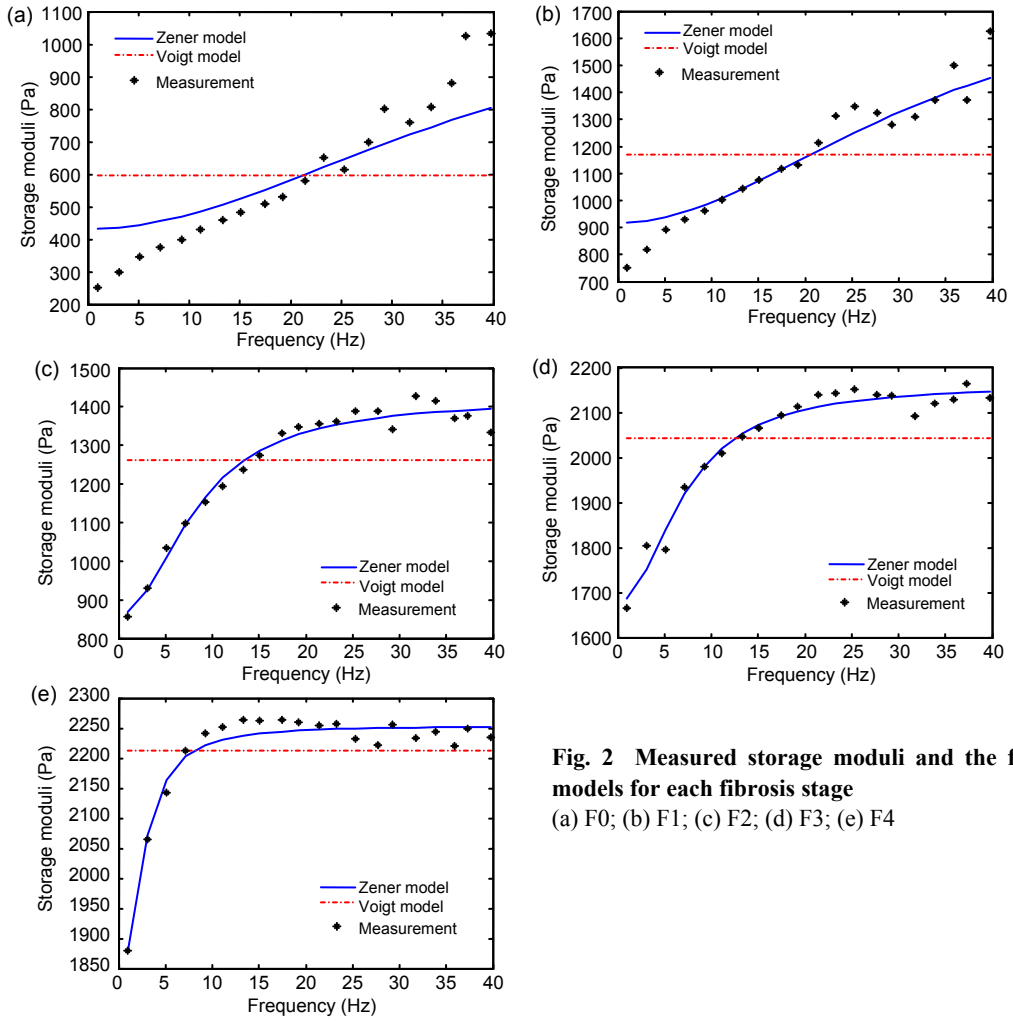

Fig. 2 Measured storage moduli and the fits of two models for each fibrosis stage
(a) F0; (b) F1; (c) F2; (d) F3; (e) F4

The mean values of the viscoelastic parameters for all fibrosis stages are calculated according to the two models, as shown in Table 1. The mean Zener elasticity E_1 increases from (0.452±0.094) kPa (F0) to (1.311±0.717) kPa (F2). The mean Voigt elasticity E increases from (0.618±0.089) kPa (F0) to (1.701±0.844) kPa (F2). The mean Zener viscosity increases from (3.499±0.186) Pa·s (F0) to (4.947±1.811) Pa·s (F2). The mean Voigt viscosity increases from (3.379±0.316) Pa·s (F0) to (4.625±1.296) Pa·s (F2).

Boxplots of viscoelastic parameters estimated by the two models for each fibrosis stage are shown in Fig. 3. Both the Zener elasticity E_1 and Voigt elasticity E increase from stages F0 to F2 (Figs. 3a and 3d), both the Zener viscosity and Voigt viscosity also increase from stages F0 to F2 (Figs. 3c and 3e). However, the Zener elasticity E_2 shows no similar phenomenon with fibrosis grading (Fig. 3b). There is no significant difference for the elasticity values of the two models between stages F2 and F3 (Figs. 3a and 3d). It is difficult to compare F4 with the other stages due to having insufficient specimens.

4 Discussion

In our study, rheological experiments were performed to quantify the mechanical behavior of rat livers at different fibrosis stages. The storage and loss moduli for all specimens were obtained.

The fitting between the measurements and the Voigt and Zener models were done by using the storage moduli and loss moduli, respectively, for each stage. We found that directly fitting viscoelastic parameters with the measurement by the magnitudes of the complex shear moduli (Eqs. (4) and (5)) will produce larger fitting errors. According to the viscoelastic theory, tissue viscosity contributes to energy

Table 1 Mean viscoelastic parameters of each fibrosis stage according to two rheological models

Stage	n	Zener model			Voigt model	
		E_1 (kPa)	E_2 (kPa)	η (Pa·s)	E (kPa)	η (Pa·s)
F0	6	0.452±0.094	1.507±1.446	3.499±0.186	0.618±0.089	3.379±0.316
F1	5	0.688±0.264	0.921±0.906	4.212±1.468	0.991±0.555	4.023±1.165
F2	9	1.311±0.717	0.561±0.221	4.947±1.811	1.701±0.844	4.625±1.296
F3	5	1.284±0.674	0.962±1.105	4.829±0.922	1.616±0.587	4.443±0.329
F4	2	1.605±0.809	3.404±1.475	4.972±1.757	1.644±0.824	4.060±0.813

Data are expressed as mean±standard deviation (SD)

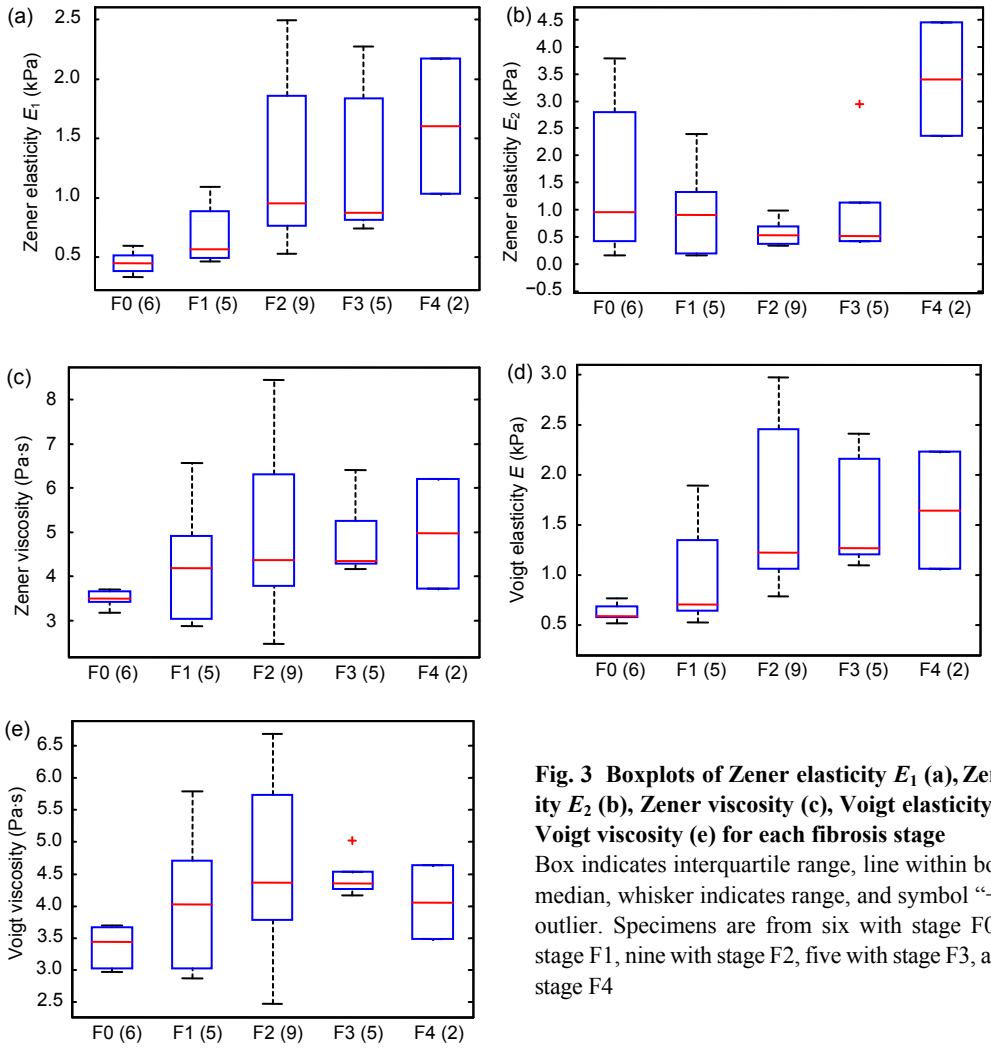

Fig. 3 Boxplots of Zener elasticity E_1 (a), Zener elasticity E_2 (b), Zener viscosity (c), Voigt elasticity E (d), and Voigt viscosity (e) for each fibrosis stage

Box indicates interquartile range, line within box indicates median, whisker indicates range, and symbol "+" indicates outlier. Specimens are from six with stage F0, five with stage F1, nine with stage F2, five with stage F3, and two with stage F4

dissipation, so the viscosity should be inferred from loss moduli. Similarly, tissue elasticity contributes to energy storage, so the elasticity should be inferred from storage moduli. Thus, in this study, Voigt elasticity E and viscosity were solved by fitting measured storage moduli and loss moduli with the Voigt model, respectively, while the Zener viscosity was solved by fitting measured loss moduli, then it was used as an initial value to solve elasticity values E_1 and E_2 from the measured storage moduli with the Zener model.

The Zener model performs well for the curve fitting as its storage modulus is frequency-dependent. For the Voigt model, the elasticity E is a constant in the frequency domain. As the Zener model describes creep and relaxation, while the Voigt model describes creep, the Zener model is equal to the Voigt model if

its elasticity E_2 is infinite (Chen *et al.*, 2012). Therefore, the Zener model should be preferred to the Voigt model for describing rheological properties of liver fibrosis in rats.

Our results indicated that moderate fibrosis (≤F2) had a good correlation with liver viscoelasticity. For these two models, there are larger variations of standard deviation in their mean viscosity values from stages F1 to F2 (from (4.212±1.468) to (4.947±1.811) Pa·s for the Zener, from (4.023±1.165) to (4.625±1.296) Pa·s for the Voigt). Nevertheless, normal liver (F0) shows smaller variations of standard deviation ((3.499± 0.186) Pa·s for the Zener, (3.379±0.316) Pa·s for the Voigt). It demonstrated that the pathological states of stages F1 and F2 changed more greatly than that of stage F0.

Our results are in agreement with the studies reported in the past. Asbach *et al.* (2008) studied eight healthy volunteers and eight patients with biopsy-proven liver fibrosis (grades 3–4) by magnetic resonance (MR) elastography. In this paper, the Zener model was applied to analyze MR elastography data. Fibrotic liver had a significant higher (P<0.01) elastic moduli (E_1 (2.91±0.84) kPa, E_2 (4.83±1.77) kPa) and viscosity ((14.4±6.6) Pa·s) than the elastic moduli (E_1 (1.16±0.28) kPa, E_2 (1.97±0.30) kPa) and viscosity ((7.3±2.3) Pa·s) of normal livers. Chen S. *et al.* (2013) reported that elasticity measurements from SDUV and time-to-peak (TTP) methods were closely related with liver fibrosis staging. Yeh *et al.* (2002) studied 20 human liver samples using the cyclic compression-relaxation method. He found that the correlation between the fibrosis score and the elastic modulus was significant. Huwart *et al*. (2007) studied 88 patients by MR elastography and concluded that the elasticity appeared to be a more discriminant marker for liver fibrosis staging. Barry *et al.* (2012) showed that viscosity may be associated more closely with another tissue pathological state-liver steatosis, which is an accumulation of fat in the liver. In this study, Barry concluded that increasing the amounts of fat evidently increased the liver viscosity, which resulted in increased dispersion of shear wave speed and attenuation. The elasticity or viscosity, which is closely related to the change of tissue pathological state, needs further investigations in the future.

Our experiments were limited by the small sample size. Two specimens taken at stage F4 from one rat had no statistical significance and therefore no impact for the above discussion.

The original motivation for this work was to investigate the mechanical property of livers for the research on the noninvasive ultrasound method to assess a rat's liver fibrosis. Generally, the Voigt model is a classic rheological model used in ultrasound methods (Zheng *et al.*, 2007; Chen S. *et al.*, 2009; Chen X. *et al*., 2013), but its application was not extensively compared with other models for liver study (Chen *et al*., 2004; 2009; 2013; Catheline *et al*., 2004; Gennisson *et al*., 2010; Orescanin and Insana, 2010; Mitri *et al*., 2011). Our next work will assess the feasibility of the Zener model in the estimation of viscoelastic parameters for liver fibrosis staging in ultrasonic elastography methods.

5 Conclusions

A rat's liver fibrosis in stages F0 and F2 can be differentiated by a rheometer that measures the shear moduli of the tissue, which supports the method of the ultrasound vibrometry. The study found that both elasticity and viscosity are correlated with the various stages of liver fibrosis. The study also found that the Zener model is a preferred model to fit the measurements due to the dispersion of the storage moduli in the frequency domain.

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Compliance with ethics guidelines

Ying ZHU, Yi ZHENG, Yuan-yuan SHEN, Xin CHEN, Xin-yu Zhang, Hao-ming LIN, Yan-rong GUO, Tian-fu WANG, and Si-ping CHEN declare that they have no conflict of interest.

All institutional and national guidelines for the care and use of laboratory animals were followed.

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中文概要：

本文题目：利用剪切黏弹性模量对大鼠肝纤维化流变特性进行分析和建模

Analyzing and modeling rheological behavior of liver fibrosis in rats using shear viscoelastic moduli

研究目的：肝脏的纤维化进程改变肝脏组织的流变属性。

创新要点：本文利用剪切黏弹性模量描绘并比较了大鼠肝脏 F0 期到 F4 期的纤维化过程。

研究方法：两个黏弹性模型，即 Zener 模型和 Voigt 模型用于解释流变力学测试得到的实验数据，由此得到每个纤维化分期的肝脏弹性和黏性值。

重要结论：肝脏中度纤维化（≤F2 期）与黏弹性值密切相关。Zener 模型的弹性均值 E_1 从 F0 期的(0.452±0.094) kPa 增加到 F2 期的(1.311±0.717) kPa，而 Voigt 模型的弹性均值 E 从 F0 期的(0.618±0.089) kPa 增加到 F2 期的(1.701±0.844) kPa。Zener 模型的黏性均值从 F0 期的(3.499±0.186) Pa·s 增加到 F2 期的(4.947±1.811) Pa·s，而 Voigt 模型的黏性均值从 F0 期的(3.379±0.316) Pa·s 增加到 F2 期的(4.625±1.296) Pa·s。无论选用哪个黏弹性模型，在 F1 期和 F2 期，肝脏弹性值的标准差比黏性值的标准差变化要小。因此，测得的弹性比黏性更有效地区分肝纤维化 F0 期到 F2 期。

关键词组：生物力学；流变属性；肝纤维化；黏弹性；剪切模量；弹性；黏性；Zener 模型；Voigt 模型