

# Non-invasive assessment of hepatic fibrosis by tissue strain imaging in chronic hepatitis C patients

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Received 6 June 2013; revised 9 July 2013; accepted 23 July 2013

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## ABSTRACT

The development of fibrosis in hepatitis C patients is associated with increased rates of liver cancer. Assessing hepatic fibrosis during interferon treatment for chronic hepatitis C is thus an important factor in treatment planning. Complications such as bleeding may occur in association with liver biopsy and there are also some reports of sampling error [1,2]. In recent years, however, a number of studies looking at noninvasive means of assessing hepatic fibrosis have appeared in the literature [3-5]. The present study was conducted to determine whether it would be possible to apply an easily performed technique of myocardial examination to hepatic fibrosis. We have already documented our findings for strain rate imaging used to differentiate the normal condition, chronic hepatitis and cirrhosis of the liver identified by diagnostic imaging and haematology data [6]. In this study, patients identified by liver biopsy were investigated, and a comparative investigation with several fibrosis markers was carried out.

**Keywords:** Strain Rate Imaging; Chronic Hepatitis C  
Patirnts

## 1. INTRODUCTION

To examine the usefulness of tissue strain imaging for assessing the progression of hepatic fibrosis.

## 2. MATREIALS AND METHODS

The subjects of this study were fifty-one patients with chronic hepatitis C who underwent liver investigations prior to being put onto interferon at this hospital between November 2007 and January 2010. All the patients joined the study after being provided with [full] information and giving informed consent [in writing].

The liver biopsy findings could be broken down into F1: 22, F2: 14, F3: 4<sup>1</sup>, and F4: 11 patients.

7s collagen (latex agglutination reaction) and type III procollagen N-terminal peptide (P-III-P tube solid-phase technique) were measured as fibrosis markers.

## 3. HISTOLOGICAL MEASUREMENTS

The new Inuyama classification was used for histological staging of hepatic fibrosis, with F0 denoting no fibrosis, F1 periportal fibrotic enlargement, F2 bridging fibrosis, F3 bridging fibrosis accompanied by lobular distortion, and F4 liver cirrhosis [7].

## 4. METHOD

An Aplio XG diagnostic ultrasound system from Toshiba Medical Systems Corporation was used [in the study]. The ultrasound probe used with it was a PST-30BT cardiac transducer. Images obtained by tissue Doppler imaging (TDI) using this transducer were then analyzed. Strain values derived by tissue strain imaging [8-11] were used in the analysis. Strain is calculated by dividing the difference in length of an object before and after change by its length before change. Tissue strain imaging is analysis software developed as an applied analysis package for tissue Doppler imaging (TDI) capable of assessing local wall motility in ischaemic heart disease. It has attracted attention as a indicator capable of describing just the local expansion and contraction of cardiac muscle by eliminating the effects of global heart motion (translation) and the velocity of transmitted motion due to surrounding normal tissue (tethering) [12,13]. It is therefore a promising means of quantitatively assessing myocardial contraction in a stable fashion. In the present study, the technique was applied to the assessment of hepatic fibrosis. Video images were captured as raw data

<sup>1</sup>F: 34 Presumably a misprint. Corrected to F3: 4 to add up to 51 patients.

in the equipment, which had been set to harmonic TDI (Tissue Doppler Imaging) mode. The term “harmonic TDI” means that the harmonic components were used for transmission and reception in TDI mode. This is a new technique and, like the effect of tissue harmonics in B-mode imaging, it reduces artifacts in TDI velocity values and improves accuracy. The TDI-Q tissue Doppler analysis software installed in the Aplio system was used in the analysis. Measurements were taken five times from the epigastrum and the mean of these was taken to denote the strain value. Strain was measured setting the size of the region of interest (ROI) at 10 mm and derivative pitch at 3 mm (Figure 1).

## 5. STATISTICAL ANALYSIS

The statistical software Minitab, which performs hypothesis testing based on the P value, was used for statistical analysis. We use t-test. Statistically, significant difference was held to be present at  $P < 0.05$ .

## 6. RESULTS

The strain rate imaging data indicated a correlation be-

tween F1 and F2, F1 and F4, F2 and F4, and F3 and F4, but none was evident for F1 and F3, or for F2 and F3 (Figure 2).

A correlation was observed between strain rate imaging and platelets  $P = 0.0038$  (Figure 3).

A correlation was observed between strain rate imaging and P-3-P  $P = 0.0147$  (Figure 4).

A correlation was observed between strain rate imaging and 7s collagen  $P = 0.0318$  (Figure 5).

## 7. DISCUSSION

The development of fibrosis in hepatitis C patients is associated with increased rates of liver cancer. Assessing fibrosis in the liver during interferon treatment for hepatitis C is thus an important factor in treatment planning. Complications such as bleeding may occur in association with liver biopsy. The procedure may also present problems of sampling error, in which the findings differ depending on the site biopsied, or of differing assessments depending on the physician making the diagnosis. However, several studies looking at noninvasive means of assessing hepatic fibrosis have been appearing in the

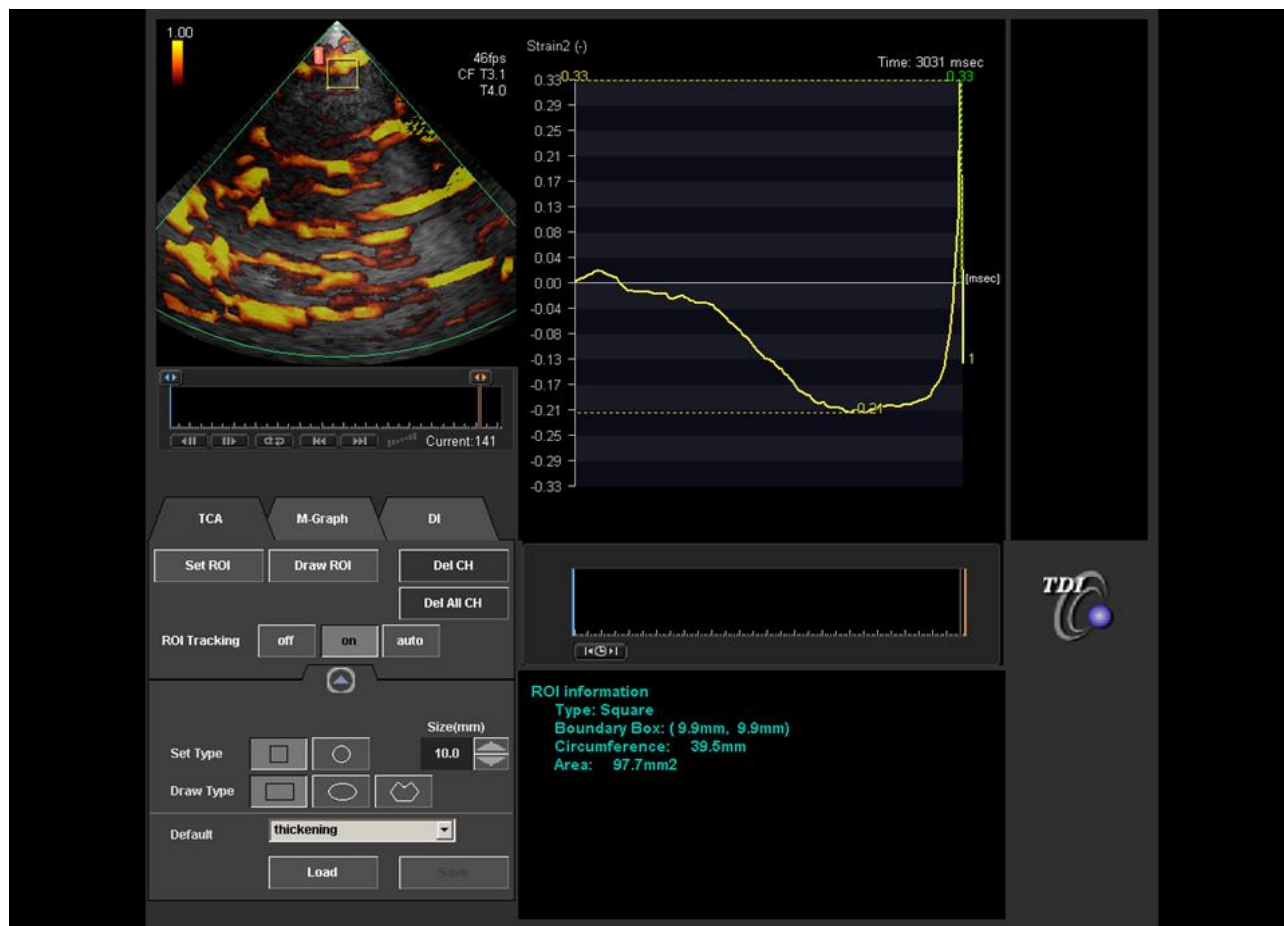
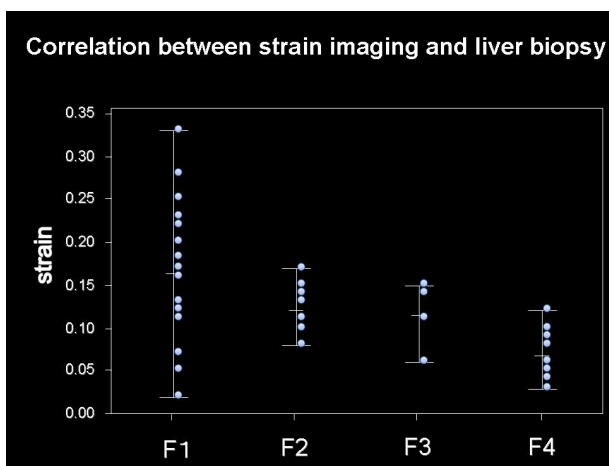
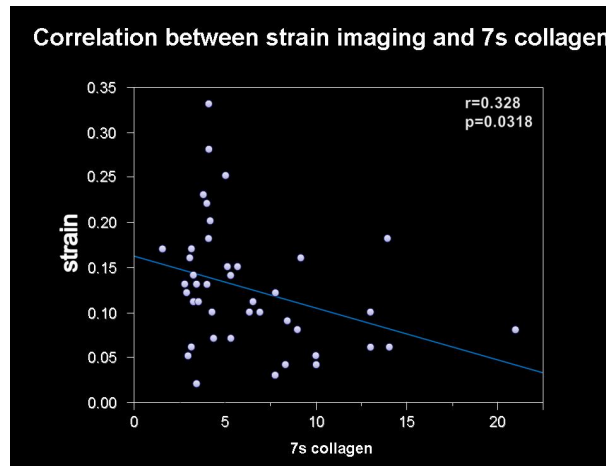


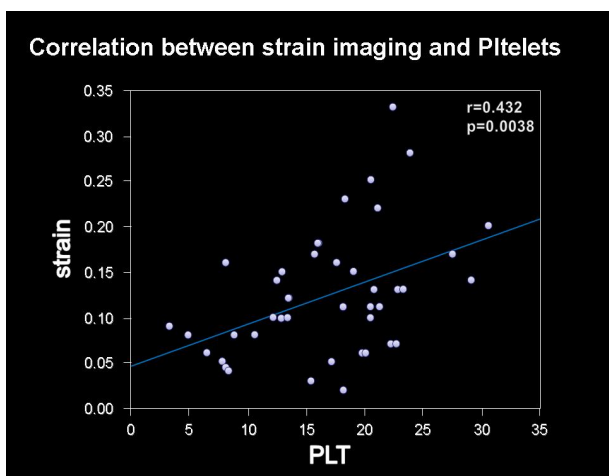
Figure 1. Method of measurement for strain imaging.



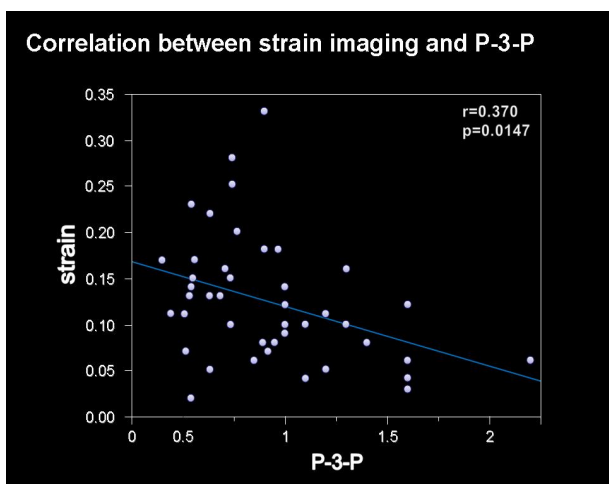
**Figure 2.** The strain rate imaging data indicated a correlation between F1 and F2, F1 and F4, F2 and F4, and F3 and F4, but none was evident for F1 and F3, or for F2 and F3.



**Figure 5.** A correlation was observed between strain rate imaging and 7s collagen P = 0.0318.



**Figure 3.** A correlation was observed between strain rate imaging and platelets P = 0.0038.



**Figure 4.** A correlation was observed between strain rate imaging and P-3-P P = 0.0147.

literature in recent years [14-17]. The present study was conducted to determine whether it would be possible to apply an easily performed technique of myocardial examination to fibrosis of the liver. Strain imaging obtained by the tissue Doppler technique is a new and useful method for assessing the local contraction and expansion capacity of cardiac muscle that eliminates effects due to translational motion or tethering of the heart muscle. Strain is calculated by dividing the difference in length of an object before and after change by its length before the change. This technique has particular advantages in that it can be quickly carried out simply by switching from an abdominal to a cardiac transducer during a routine ultrasound examination, and that measurements can even be taken of patients with ascites. Another advantage is that the liver can be visualized while measurement is taking place. Disadvantages include the fact that data analysis takes some time<sup>2</sup> and the patient cannot be given the results on the spot, and that the technique can currently be carried out only with transducers designed for cardiac use. We look forward to the development of software that cuts analysis time and to the development of [dedicated] transducers. In recent years, a number of studies looking at the noninvasive assessment of hepatic fibrosis have appeared in the literature. For example, there has been the development of the FibroScan [18,19], which assesses liver stiffness by measuring elasticity, and some studies have contrasted the findings obtained using this system with those from liver biopsy in patients with hepatitis C or cirrhosis. However, the weaknesses of the FibroScan are that it cannot assess patients with ascites, that it is difficult to assess patients tending to obesity,

<sup>2</sup>“Tens of minutes” is not a natural expression in English, and so I have rendered it as “some time”. Perhaps something more concrete, like 10 - 30 minutes, or “up to half an hour” etc. could be used.

and that it does not provide direct visualization of the liver during operation. Assessment is therefore difficult, or measurement not possible at all, in liver cirrhosis patients with marked atrophy. However, the strain rate approach used in the present study could be employed even on such patients as these. Data from real-time elastography [20], ARFI [3] and so on are accepted as indices of fibrosis in modern echography practice. These methods are similar to the one described here in that the liver parenchyma is visualized while the examination is being carried out. A paper has also appeared describing the use of B-mode [21] while measuring hepatic fibrosis. As this method can be installed on the machine used in the present study, we are considering a comparative study of them for the future. There have also been reports of liver fibrosis using MRI, but the evident drawback from the paper by Laurent Huwart and others is that Magnetic resonance elastography could be performed in 133 of 144 patients (94%). The 8 failures were caused by claustrophobia in 3 patients, low hepatic signal related to hemochromatosis in 3 patients, and obesity in 2 patients [22]. Although there was no hemochromatosis in the present study, it would seem that our method could have been employed in the other patients. It should also be noted that it is quicker and cheaper than MRI. The FibroTest 1 [23] was developed in France as a laboratory data-based system that measures fibrosis in terms of a value computed using five parameters, namely  $\alpha$ 2-macroglobulin, hepatoglobulin<sup>3</sup>,  $\gamma$ -GTP, total bilirubin and apolipoprotein A1. However, it may prove difficult to use this approach in routine clinical practice as the analysis is expensive and, in Japan, only  $\gamma$ -GTP and total bilirubin are covered by health insurance and the other three items are not. The HALT-C trial [24,25] sought to estimate liver cirrhosis using platelet count, AST/ALT and INR data, but this provides no more than an estimate of liver cirrhosis and is not capable of identifying the F class. Strain rate imaging to measure liver fibrosis as used in the present study thus appears to be extremely useful. No correlation was identified between F1 and F3, and F2 and F3 in the study, but this may have been attributable to the small sample size of only 4 patients for F3. We hope to assemble more patients in future and search for any correlations. This study looked only at chronic hepatitis C, but for the future, we are considering examining its application to staging assessments in chronic hepatitis C and to differentiation of simple fatty liver and NASH.

## 8. CONCLUSION

It seems likely that this technique, which is noninvasive and can be carried out in the out-patient setting, will be

<sup>3</sup>The original text states "hepatogloburgain". Presumably a misprint.

increasingly useful in the assessment of hepatic fibrosis.

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<sup>4</sup>Corrected from the original: Naoki H, Minoru A, Akihiko O et al. Noninvasive assessment of Liver disease-measurment of hepatic fibrosis using tissue strain imaging *Clinical Imaging* 2007: 31 87-9. Other typographical errors in references corrected.

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