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● *Review*

ELASTOGRAPHY IN THE MANAGEMENT OF LIVER DISEASE

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Abstract—Normal liver tissue is soft and pliable. With inflammation, however, many of the cells die and are replaced by collagenous fibrils and the tissue gets stiffer. The progress is often slow—extending over decades in many cases. When liver stiffness increases by a factor of about five, the condition is called cirrhosis, a disease with serious medical implications. After the onset of cirrhosis, the probability of developing hepatic cancer increases at the rate of about 5% per year. Precise, noninvasive measurement of liver stiffness, a simple application of elastography, promises to be a safe, inexpensive method to monitor the progress of liver patients, improve outcome, save many lives and much suffering and reduce the cost of medical care. (E-mail: ecarsten@rochester.rr.com)

Key Words: **Liver stiffness, Shear waves, Elastography, Liver fibrosis.**

INTRODUCTION

The normal, healthy liver has very low shear stiffness (of the order of 1 kPa, comparable to a soft gelatin gel) (Catheline et al. 2003; Cohn et al. 2000). In response to inflammation, cells in the liver die and are replaced by scar tissue in the form of collagenous fibrils particularly in the tracts that contain branches of blood vessels and bile ducts. As fibrosis progresses, the fibrils interconnect between tracts, creating a progressively rigid structure and the shear stiffness of the tissue increases. During the early stages of fibrosis, the condition is potentially reversible if the cause of inflammation is eliminated. Severe fibrosis (cirrhosis), however, is likely to be irreversible and, in the extreme, results in liver failure. Furthermore, cirrhosis is associated with as much as a one hundred–fold increase in the incidence of primary liver cancer. Depending on the severity of the disease, the shear stiffness of cirrhotic liver can be an order of magnitude greater than normal liver.

Elastography creates images of the shear stiffness of tissues. Because most tumors have significantly higher shear stiffness than normal tissue, elastographic images give higher contrast for tumors than normal B-mode images. Monitoring the extent of damage to the liver as a whole is a somewhat different challenge. In that case, it is the absolute value of tissue stiffness not contrast between stiffness of tissue components that is used to characterize the liver.

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Among the many causes of the inflammation that lead to fibrosis are viral diseases (hepatitis), chemical toxins (ethanol) and autoimmune and inherited diseases. There are roughly five million hepatitis patients in the United States. Yet, the numbers of cirrhosis patients from all causes is only one tenth of that number. Approximately 95% of all hepatitis patients with liver cancer also have cirrhosis, and roughly 10% of patients with cirrhosis eventually develop primary liver cancer. There is evidence that the probability of hepatic cancer in hepatitis C patients is small until cirrhosis is well developed (Fig. 1), but then increases at the rate of approximately 5%/y (Degos et al. 2000). The relatively poor prognosis for liver cancer is related to the fact that the disease is asymptomatic and frequently is not discovered until it reaches an advanced stage. So there is a huge patient population (for hepatitis alone, more than 150 million patients worldwide) with a small, but slowly increasing, probability of developing cancer. If, after serologic detection of the disease, these patients were monitored frequently, it is highly likely that many cancer cases could be avoided or be detected early enough to be treated by resection rather than transplant. One can foresee the day when liver stiffness measurement will become so simple that it will become a part of primary care screening.

Today, fibrosis is monitored primarily by biopsy. The procedure is sufficiently expensive, unpleasant and potentially hazardous that its use is limited. A simple, noninvasive monitor of the progress of disease during the early stages of fibrosis could save many lives and reduce overall health care costs.

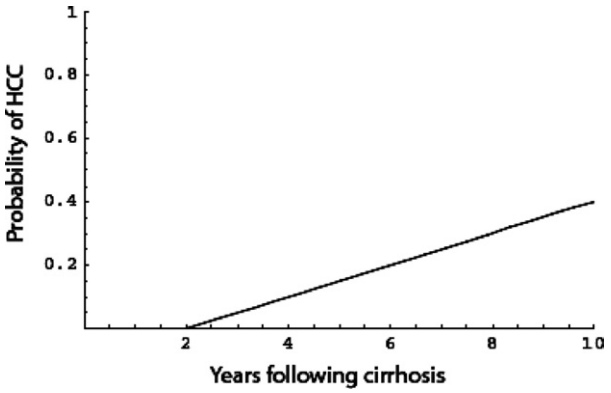

Fig. 1. Incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C. The figure is based on a study by Dagos et al. (2000), in which the subjects at the beginning of the study had cirrhosis but did not have an indication of cancer. Thus, the shear stiffnesses of the livers at the beginning of the study were at least twice that of normal liver. We may assume that there had been a prolonged period before the study began, during which there was a gradual increase in fibrotic stiffening of the tissue.

Management of patients with liver disease has two distinct phases: routine monitoring and tumor detection. Elastography promises to contribute to both phases. However, it is reasonable to expect that the equipment and the medical specialties involved in the two phases will be different.

Decades can pass between infection with hepatitis and the onset of cirrhosis for a patient with an otherwise healthy lifestyle. During that period, a quantitative measure of liver stiffness may provide the hepatologist with an indication of the progress of the disease, the need for treatment and a measure of the success of treatment. Relatively advanced stages of fibrosis would signal the need for patient referral to a specialized radiology facility for tumor screening. A serious weakness in hepatitis management today is the failure to detect tumors when they are small enough that they can be resected and the liver is healthy enough that it will regenerate.

In principle, elastographic determination of stiffness is much simpler than elastographic imaging. Shear wave velocity is simply and directly related to shear stiffness of the medium. Fibrosis increases the shear stiffness of the liver. High resolution is actually undesirable for stiffness measurement. Precise localization of the site of observation is of little concern. Thus, it should be possible to develop relatively inexpensive, dedicated, elastographic monitors of liver stiffness that can be used by unspecialized medical personnel.

Stiffness is in effect an integral of the damage caused by inflammation over very long periods of time. Traditionally, that assessment has been made qualitatively from biopsies. But the two approaches are quite different. Stiffness can be measured quantitatively over large regions of the liver, with accuracies of a few percent, noninvasively, and for very modest cost. It promises to serve as a fundamental parameter of liver health and pathology in its own right. With that understanding, it can become ubiquitous in medical practice and biopsies may become relegated to specific diagnostic tasks for which they are uniquely suited.

The technology for the second phase, screening for tumors and monitoring their progress, is already highly developed. Imaging with ultrasound, computed tomography and magnetic resonance imaging requires highly specialized personnel for equipment operation and image interpretation. The technical tools are sophisticated and expensive. Each modality relies on relatively subtle differences between relevant properties of malignant and normal tissue for tumor detection. Techniques and technology are continually improving. At the macroscopic level, the most striking difference between tumors and normal tissues is in their low-frequency shear stiffness (Manduca et al. 2001). Detecting that stiffness difference has been the motivation for the development of elastography from its inception (Lerner et al. 1987). The technical basis for elastography in general has been reviewed recently by Parker et al. (2005). Reconstructions of elastic constants in the liver and other tissues have been reported by Sumi et al. (2005). No further discussion of the imaging aspect of elastography will be given here.

There are two fundamentally different challenges to the stiffness application. One concerns the mechanistic relationship between stiffness and medically relevant tissue properties. The other aspect of the problem concerns the relationship between liver stiffness and the progress of and prognosis for liver disease.

Over the past 60 years, diagnostic ultrasound, which uses compressional waves, has provided the motivation for many studies of the biophysical basis for the acoustic properties of tissue. Nothing comparable has been done for shear waves. To maximize the clinically relevant information provided by shear waves, we need to relate both the molecular and structural properties of tissues to complex shear wave velocity. Normal liver, fatty tissue, fatty liver and fibrotic liver should be investigated. There is a high probability that the simplest “stiffness meters” will give the tissue shear viscosity as well. At the present time, the biophysical basis for tissue shear viscosity is essentially nonexistent.

The greater challenge is the creation of a comprehensive database that correlates stiffness and rate of change of stiffness to disease state and prognosis. This is a substantial undertaking. But, as the data accumulate, stiffness measurements will take their place as a fundamental parameter in the management of liver disease.

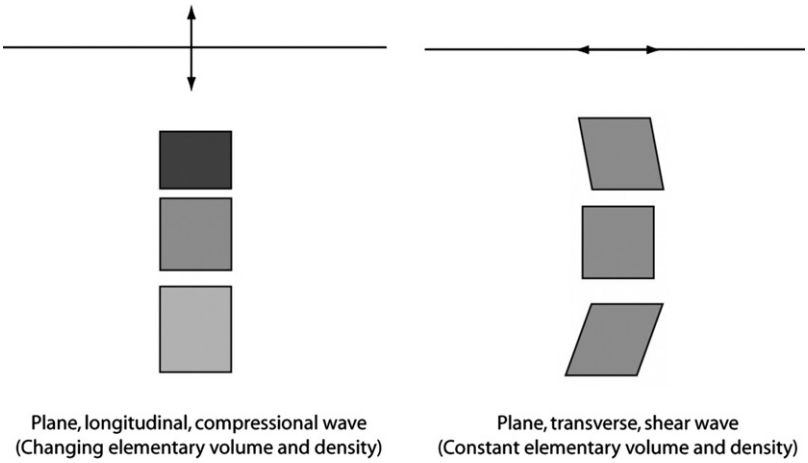

Fig. 2. Behavior of elements of the medium during propagation of idealized, plane, infinite, longitudinal, compressional and transverse shear waves.

Wave propagation

In much of ultrasound, the propagating medium is treated as though it were a fluid. Of course, tissues have shear stiffness. The simplifying assumption works, however, for most applications because shear waves, if generated, are highly attenuated and can be ignored. A notable exception, elastography, is based largely on the shear stiffness of tissues and the relatively large variations in shear stiffness with disease. This means that in elastographic applications, we must deal with the fact that tissue particle displacements (and velocities) have two parts: one associated with a simple rotation without change in volume and the other that involves compression of the tissue but is irrotational. In soft tissues, the stiffness that controls and transmits rotational displacement is orders of magnitude smaller than that involved in compression. For this reason, sound propagation in tissues is somewhat more complicated than it is in water. As elastography has evolved over the last two decades, several innovative techniques have been used successfully to deduce shear stiffness from observed particle displacements.

For the purposes of discussion, waves associated with the two parts of the particle displacement can be isolated in idealized, 1-D, infinite plane waves. In one case, the surface of the medium is excited by tangential stresses and in the other with normal stresses. Because the medium has mass as well as stiffness, an excitation applied at the surface of a medium requires time before it is experienced at a distance within the medium and so the displacement moves through the medium as a wave.

Under transverse excitation, the outer layer is displaced tangentially, dragging along a layer of tissue below it. The resulting wave has a speed of

$$c_s = \sqrt{\frac{\mu}{\rho}}, \tag{1}$$

where μ is the shear stiffness of the medium and ρ is its density (Graff 1975). During this process, individual particles in the medium move parallel to the surface of the medium or transverse to the direction of the propagation of the disturbance. An elementary cube in the medium is sheared and rotated without change in volume as the disturbance passes it (Fig. 2). The shape change *per se* involves no net transport of mass. The inertia that delays the propagation of the strain is in the rotation of the elements of the medium.

Applying a uniform, normal harmonic stress to the infinite surface of a medium, moves elementary particles perpendicular to the surface, and this disturbance is propagated into the medium at a speed of (Graff 1975)

$$c_L = \sqrt{\frac{\kappa + \frac{4}{3}\mu}{\rho}}, \tag{2}$$

where κ is the bulk stiffness of the medium (Fig. 2). An elementary cube of the medium changes volume in this case, the particles move closer and further apart in the direction of propagation as the disturbance passes—hence the involvement of the bulk stiffness. Because the model does not permit transverse particle movement, an elementary cube is flattened and stretched during passage of the disturbance. The change in shape of the cube explains the involvement of the shear modulus in the propagation of the compressional disturbance. For these compressional waves, the mass movement responsible for the delay of propagation of the disturbance is in the direction of propagation of the wave.

Terminology for these waves can be confusing because they are characterized more by what they are not than what they are. In the first example, the wave whose velocity depends only on the shear stiffness of the medium is primarily one in which the volume of the element of the medium does not change, *i.e.*, the divergence of the displacement is zero. It usually involves rotation and is frequently referred to as a "rotational" wave. But we can have a "rotational" wave with zero rotation. It is frequently transverse, as in the plane wave example (eqn (1)), but it can be longitudinal. It involves shear but so does the second example (eqn (2)), in which the propagation speed is much greater. For simplicity, but with all of these caveats, we shall refer here to waves of the first kind, which are controlled by the shear stiffness of the medium only, as *shear waves*.

In the second example, the wave whose velocity depends on both shear and bulk stiffness is irrotational, *i.e.*, the curl of the displacement is zero. It is usually longitudinal, but shear waves can also be longitudinal. It involves compression but it also involves shear strain. For simplicity, we shall call these waves, whose speed of propagation involves the bulk stiffness, *compressional waves*.

For much of acoustics, we can associate longitudinal waves with compressional waves having the speed of propagation given by eqn (2) and transverse waves with shear waves having a speed given by eqn (1). It is not difficult, however, to provide counter examples. For propagation of longitudinal waves in a beam or a rod, the wave speed is

$$c_{LS} \sim \sqrt{\frac{E}{\rho}}, \tag{3}$$

where E is Young's Modulus, the ratio of axial stress to longitudinal strain in the beam. (A more general discussion of this problem can be found in Benatar et al. (2003)). This specialized stiffness parameter is related to bulk and shear stiffness of the material,

$$E = \frac{3\mu}{1 + \mu/3\kappa}. \tag{4}$$

It is paired with Poisson's ratio ν, the ratio of radial to longitudinal strain in the rod.

$$\nu = -\frac{\varepsilon_{yy}}{\varepsilon_{zz}}.$$

For soft tissues, $\mu << \kappa$, $E \sim 3\mu$ and $\nu \sim 0.5$. With harmonic force applied normally to the end of the rod, the elements of the medium change shape but maintain approximately constant volume and density, giving a longitudinal shear wave (Fig. 3). Note, however, that the speed of this shear wave is greater by a factor of 1.7 than the transverse shear wave in Fig. 2. Direct, laboratory measurements (both static and dynamic) of Young's modulus have been made for excised tissues. There is probably no practical application of the specialized model of Fig. 3 *in vivo*. However, the use of Young's modulus to describe tissue properties has been carried over into much of the clinical elastography literature. The conversion from Young's modulus to the shear stiffness is simple enough. However, terminology in many cases is not precise and it is necessary to read carefully when authors use the term stiffness. They actually may mean Young's modulus rather than shear stiffness.

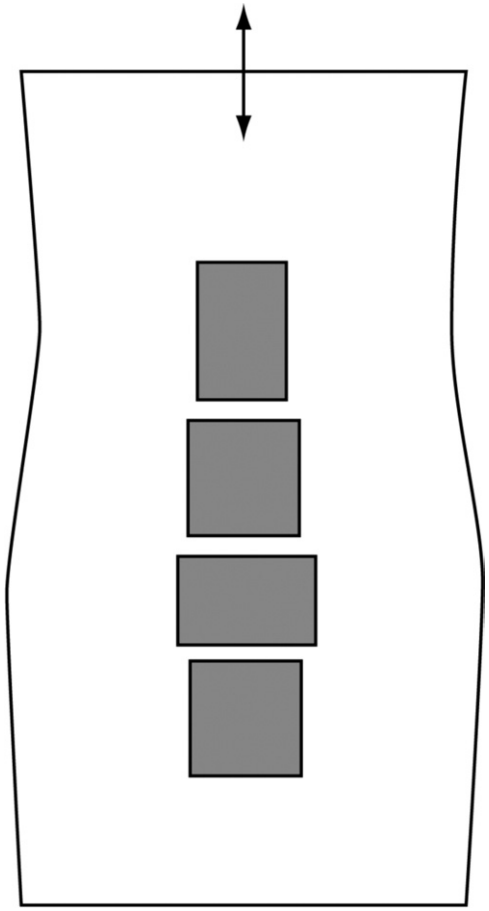

Fig. 3. Propagation of a longitudinal wave in a bar or rod. For soft tissues, the wave speed is dominated by the shear stiffness. The elements change shape but maintain constant volume and density.

With the finite sources used in real applications of elastography, the acoustic fields are not 1-D and particle displacements in general contain both high and low-speed components. When the excitation is a single cycle or a pulse, the two components of the displacement pulse are almost instantly separated in space. Only the slow

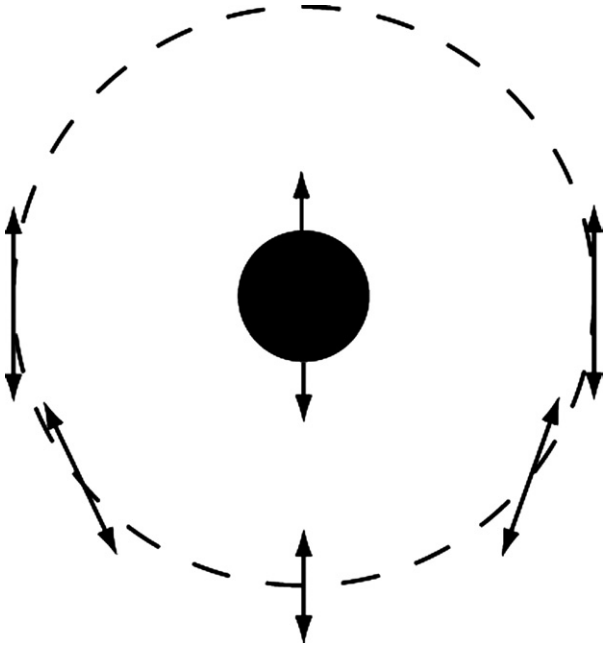

Fig. 4. Steady state shear wave generated by a vertically oscillating sphere. Arrows show direction and relative amplitudes of particle displacement along a wavefront at three wavelengths from the center of a one-wavelength diameter source, as predicted by eqn (1) (Oestreicher 1951).

component is used in elastography. When the source is continuous, both components are always present. However, the displacement field associated with the fast wave has essentially uniform phase throughout the field-of-view. Superimposed on this uniform field is the shear field traveling slowly enough that several full cycles may be observed within an organ the size of the human liver. As elastography developed over the last two decades, several techniques have evolved to detect the shear wave selectively in these complex fields.

The physical principles involved in most of elastography are demonstrated by Oestreicher's (1951) analytical solution for the displacement field of a transversely oscillating sphere in a viscoelastic medium. Oestreicher's model assumes the sphere is in an infinite medium. However, it demonstrates qualitatively the characteristics of the waves generated by normal excitation of a finite area of the surface of the medium.

Refinements and generalizations of Oestreicher's model include von Gierke et al. (1952), Miller and Pursey (1954, 1955), Royston et al. (1999), Zhang et al. (2001), Sandrin (2004) and Norris (2006). It is noteworthy that Sandrin (2004) identifies a phenomenon near the source (less than one shear wavelength) in which both shear and bulk moduli contribute to a wave that has a velocity as much as 50% greater than the shear wave velocity—a possible source of confusion for measurements near the surface of the body.

Oestreicher's solution includes contributions to the particle displacement from both compressional and shear waves. As noted, only the shear component is of interest for quantitative stiffness measurements. It has the following form:

$$\xi_S \propto 2h_0(k_s r)\mathrm{e}_x - h_2(k_s r)(\mathrm{e}_x - 3\frac{x}{r}\mathrm{e}_r), \qquad (5)$$

where h_0 and h_2 are the zero and second-order spherical Hankel functions, $k_s = \dfrac{\omega}{c_s}$ is the shear wave propagation constant, x is the distance from the origin along the axis of oscillation of the sphere, r is the distance from the origin to the field point-of-interest and $\mathbf{e}_x$ and $\mathbf{e}_r$ are unit vectors in the x and r directions, respectively. It is immediately apparent that the particle displacement of the shear wave along the axis of oscillation of the sphere is entirely longitudinal. Regardless of whether the motion is longitudinal or transverse, the propagation speed c_s of the shear wave is controlled by the shear modulus of the medium (eqn (1)). As the direction of observation shifts off the axis of oscillation, the particle motion becomes increasingly transverse until it is entirely transverse at 90° to the axis of oscillation (Fig. 4). (Of course, in a clinical application where the source is applied to the skin, the free surface would make the wave somewhat more complicated than implied by Oestreicher's model (Zabolotskaya et al. 2007). For these waves, the medium is effectively incompressible. The propagated wave consists of shape changes in elemental volumes of the medium—stretched and flattened in the axial direction and

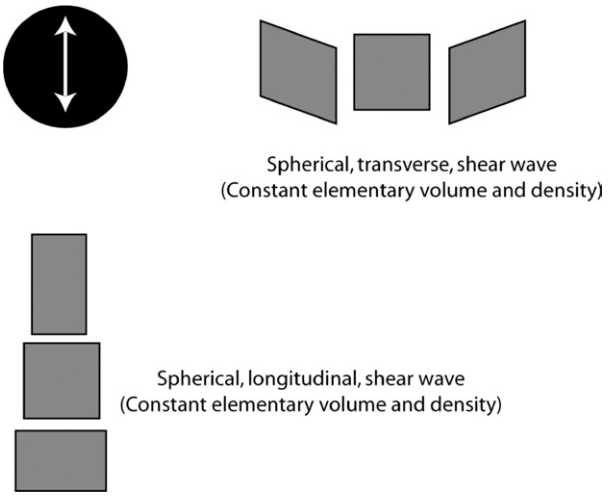

Fig. 5. Behavior of elements of the medium during propagation of longitudinal and transverse shear waves generated by translational oscillation of a spherical source.

sheared and rotated at 90° to that direction (Fig. 5). The rotation of the medium associated with passage of the shear wave is perpendicular to the plane containing the direction of propagation and the direction of particle displacement/velocity. The amplitude of the rotation varies as the sine of the angle between the axis of oscillation and the radial vector (the direction of propagation of the wave), vanishing on the axis of oscillation of the sphere. Thus, the translationally oscillating sphere in a viscoelastic medium produces a shear wave with a complete transition from a pure transverse wave with rotation when the direction of propagation is normal to the axis of oscillation to an irrotational, longitudinal wave when the direction of propagation is along the axis of oscillation.

If the tissue is anisotropic (*e.g.*, muscle), the stiffness in the direction normal to the axis of the source determines the speed of propagation of the longitudinal and transverse shear waves (Gennisson et al. 2003). We have no basis at present to conclude that the liver's stiffness is anisotropic.

Although the illustrations in this discussion all assume that the shear wave phenomena are linear, in principle, the elastic constants are functions of stress. Even modest stresses from palpation or from the force of application of the vibration source to the surface of the body cause rather large distortions in the tissue and alter the elastic constants, and may even produce anisotropy in an otherwise uniform medium (Catheline et al. 2003). As elastography takes its place among the tools of hepatology, it will be necessary to evaluate nonlinear effects in stiffness measurements. In most applications of elastography, however, it is reasonable to assume that the elastic constants of the tissue are independent of the amplitude of the shear wave (Liu and Bilston 2000).

Shear moduli of viscoelastic media

The above discussion has ignored absorption of the shear wave. In reality, however, the absorption coefficients of tissues for shear waves are so great that attenuation is a dominant factor that must be considered in any practical measurement of shear wave velocity. It is important to realize that the speed of propagation depends on both the real stiffness of the medium and its viscosity. For harmonic waves, this can be treated by the use of a complex wave speed c_s^+, which in turn depends on the complex shear modulus μ^+ of the medium,

$$c_s^+ = \sqrt{\frac{\mu^+}{\rho}}, \tag{6}$$

where ρ is the density of the medium and $\mu^+ = \mu_1 + j\omega\mu_2$ being the real shear stiffness, μ_2 being the shear viscosity of the medium and ω is the angular frequency. The complex propagation constant

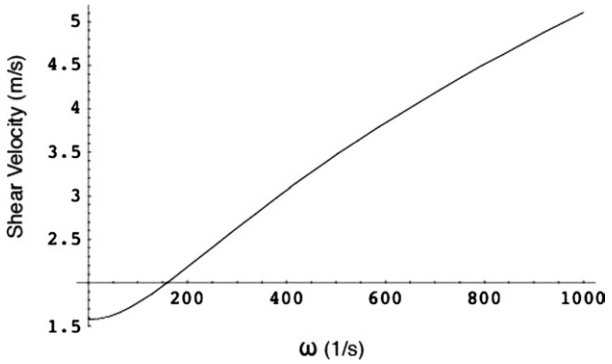

Fig. 6. Shear wave speed for tissue with shear stiffness 2.5 kPa and viscosity 15 Pa s (Oestreicher 1951).

$$k_s^+ = \beta - j\alpha = \frac{\omega}{c_s} - j\alpha = \frac{\omega}{c_s^+}, \tag{7}$$

If we define $\tau = \mu_2/\mu_1$, we can write the real (measured) shear wave speed

$$c_s(\omega) = c_{s0}\left[\frac{1}{2}\frac{1}{1+(\omega\tau)^2}\left(\sqrt{1+(\omega\tau)^2}+1\right)\right]^{-1/2}, \tag{8}$$

where c_{s0} is the low frequency, stiffness-dominated limit of the velocity

$$c_{s0} = \sqrt{\frac{\mu_1}{\rho}}. \tag{9}$$

In the absence of thorough studies of the viscoelastic properties of tissue, we can get an approximate quantitative picture of the frequency dependence of the sound speed in tissue from Oestreicher (1951), who for "human tissue" reported a stiffness of 2.5 kPa and a viscosity of 15 Pascal seconds, *i.e.*, $\tau \sim 0.006$. In other words, the transition from stiffness to viscosity-dominated velocity occurs at about 25 Hz (Fig. 6). Because the effective frequencies used in much of the practice of elastography are >25 Hz, it is apparent that measured wave speeds in general are functions of frequency and that it will be necessary to extrapolate these values to zero frequency to obtain unique, real, shear stiffness values. It is worth repeating that most of elastography deals with tissue displacement directly and that the propagation of shear waves is only peripherally considered as a tool for imaging.

Zhang et al. (2007) reported measurements of the velocity of shear waves in liver tissue over the frequency range from 80–220 Hz. Using eqn (8) to extrapolate the data to their low frequency limit gives $c_{s0} = 1.5$ m/s and $\tau \sim 0.0009$ (giving a shear stiffness of 2.2 kPa and a viscosity of 2 Pa s). The transition from stiffness to viscosity dominance of the wave velocity occurs at

around 175 Hz. These data are in remarkably good agreement with recent values obtained for human liver by Klatt et al. (2006) using magnetic resonance elastography.

Kiss et al. (2004) directly determined the complex shear modulus of canine liver using a mechanical test system. The real part of the reported shear stiffness is 1–2 kPa, nearly independent of frequency from 0.1–100 Hz. The imaginary part of the stiffness in these data is less than the real component below ~120 Hz. These measurements are in reasonable agreement with those measured elastographically.

It is apparent that two parameters, the stiffness and the viscosity, are needed to describe the shear properties of tissues. Oestreicher and his colleagues at Wright Field concluded that each of these parameters was relatively independent of frequency in the range of frequencies that today are used by elastography. Whereas the real stiffness of liver appears to be relatively independent of frequency, values reported for the viscosity of liver are two orders of magnitude smaller at megahertz frequencies than at audible frequencies (Frizzell et al. 1976; Madsen et al. 1983). This suggests that, after further investigation, stiffness and viscosity will be found to contain qualitatively different kinds of diagnostic information.

Almost no attention has been given to the possible clinical information contained in the tissue viscosity, so we must proceed under the assumption that the imaginary part of the complex stiffness will be useful in its own right. But, there is a more basic reason for independent determination of stiffness and viscosity. Unfortunately, the term *stiffness* has been used rather loosely in the elastography literature. Frequently, when the term is used, the authors intentionally or otherwise mean the magnitude of the complex stiffness, which of course is a function of frequency, leaving us without a unique number to describe tissue stiffness. In principle, the underlying real parameters of the complex stiffness can be determined from the frequency dependence of the wave speed, as shown previously or from the measurement of the wave speed and its absorption coefficient at a single frequency.

From eqn (7), the shear wave absorption is (Fig. 7)

$$\alpha_s(\omega) = \frac{\omega}{c_{s0}}\left[\frac{1}{2}\frac{1}{1+(\omega\tau)^2}\left(\sqrt{1+(\omega\tau)^2}-1\right)\right]^{1/2}. \quad (10)$$

At high frequency, where viscosity dominates, the amplitudes of real and imaginary parts of the propagation constant are equal and proportional to the square root of frequency

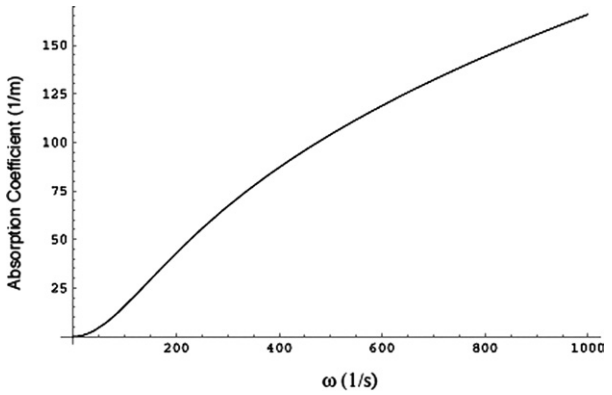

Fig. 7. Shear wave absorption for tissue with stiffness 2.5 kPa and viscosity 15 Pa s (Oestreicher 1951).

$$\beta(\omega) \to \alpha_s(\omega) \to \frac{1}{c_{s0}}\sqrt{\frac{\omega}{2\tau}}, \quad (11)$$

and the absorption per wavelength becomes independent of frequency—and very large,

$$\alpha(\omega)\lambda(\omega) \to 2\pi. \quad (12)$$

At very low frequencies when stiffness dominates the propagation of the shear wave, the wave speed approaches a limiting value c_{s0} and the absorption is a function of the square of the frequency

$$\alpha_s(\omega) \to \frac{\omega^2\tau}{2c_{s0}}. \quad (13)$$

Instrumentation

Most of the development effort in elastography has been motivated by the tumor detection problem. Elastography relies on the realistic assumption that tumors are stiffer than the host tissue. In principle, any of the several approaches that have been developed for tumor detection could be adapted for a measurement of tissue stiffness. However, the specifications for an instrument designed for imaging and one dedicated to stiffness measurements are somewhat different. In the former, high resolution is desirable. In the latter, it is an advantage to average over large volumes of tissue. Numerical precision is desirable for fibrosis staging. Imaging can be relatively qualitative. Imaging elastography will inevitably become more sophisticated and find its home in radiology facilities. Because of its relative simplicity, the use of elastography for fibrosis staging may be achieved eventually, with relatively inexpensive devices that can be used routinely in the primary care of liver patients.

Among all of the possible approaches to stiffness measurement, the propagation of shear waves is particularly attractive. Shear waves in liver, regardless of the way they

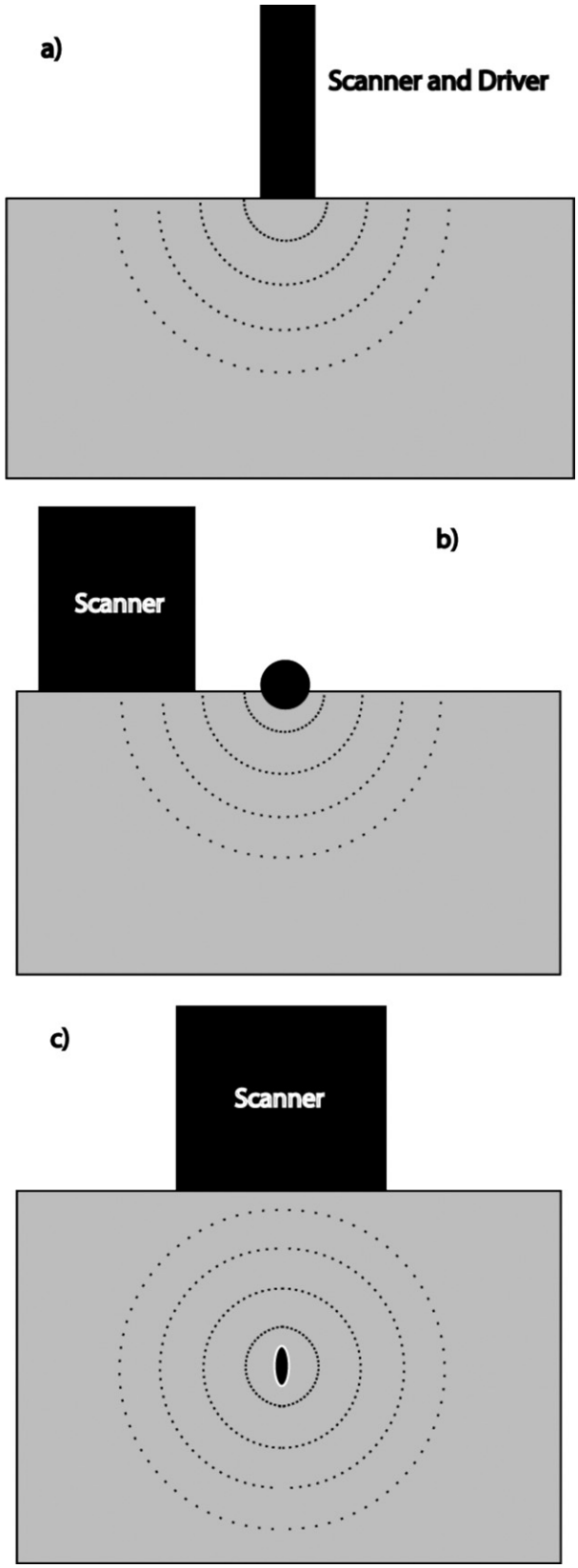

Fig. 8. Field configurations for elastographic stiffness measurements. (a) An M-mode ultrasound transducer follows the progress of the longitudinal shear wave along the axis of oscillation of the shear wave source. (b) An imaging scanner follows the progress of the shear wave, or a combination of shear waves generated by drivers on the surface of the body. (c) Radiation force produces a displacement that is qualitatively equivalent to the translational motion in Oestreicher's model. A scanner at the surface follows the movement of the transverse shear wave as it moves parallel to the surface of the tissue.

are generated, have propagation speeds that are simply and uniquely related to the complex shear stiffness of the propagating medium (eqns. (7), (8) and (10)). We need to know only that a shear wave can be generated and that its propagation speed can be measured. We need not know whether it is transverse or longitudinal, how it is generated or its absolute amplitude, as long as it is great enough to be detected. The limits in practice are set by the volume of liver tissue available at a given site and the design of the measurement system. Note again that, in contrast to imaging, averaging large volumes of liver tissue would be desirable in characterization of liver tissue.

Before elastography is adopted as a primary tool in hepatology, we will need a comprehensive database of correlations between stiffness and other indicators of liver pathology, the variance of those values and guidelines for action. Much of this information must come from direct clinical testing. However, important information can also be obtained in the laboratory with excised tissues, in which case the measurements can be more precise and detailed. Perhaps the simplest source for laboratory studies applies a sinusoidal, transverse excitation to one plane surface of a tissue sample and the propagation speed or wavelength of the resulting transverse, shear wave is observed as it propagates through the tissue.

Using that technique, Catheline et al. (2004) reported values of 25 and 50 kPa for the stiffness of beef muscle. The tissue is anisotropic. The lower value corresponds to propagation along the grain of the tissue (polarization of the particle motion perpendicular to the grain), and the higher value to propagation perpendicular to the grain (particle motion parallel to the grain). Measurements of the shear velocity were made over the frequency range 50–350 Hz. Reported accuracies for the computed stiffnesses were approximately $\pm$ 5%. The viscosities reported by Catheline were 3 and 15 P s, respectively, with accuracies of approximately $\pm$ 10%. The frequencies of transition from stiffness to viscosity dominance are 1300 and 530 Hz, respectively.

The generation and detection of shear waves in patients is somewhat more complex than described above for excised tissues. However, transverse and longitudinal shear waves in liver travel at the same speed, have the same absorption, and, in principle, provide the

same information about the viscoelastic properties of the medium. The engineering challenge as always is to find the optimum combination of precision, convenience and cost in a clinical device. In clinical measurements of liver stiffness, one is limited to exciting shear waves and observing them from the surface of the body.

From the point of view of wave propagation, three qualitatively different techniques have been considered for liver stiffness measurement *in vivo*. (i) In one of these, the wave is observed along the axis of oscillation of the driver, which is applied to the surface of the body. FibroScan (Sandrin et al. 2002, 2003, 2004), the first commercial system dedicated to the measurement of shear stiffness of liver, applies a single cycle of a 50-Hz indentation to the skin and observes the displacements in the tissue as the resulting shear wave propagates into the body. This device has been tested in several clinical trials and its value in monitoring liver disease has now been established. (ii) In a second approach (Hoyt et al. 2007), one or more drivers are applied to the surface of the body and shear waves are observed with a transducer on the surface lateral to the driver. (iii) A third method (Nightengale et al. 2007) uses radiation force to induce displacement of a focal region within the tissue (Fig. 8).

Oestreicher's model should give a semiquantitative description of the shear fields measured at the depth of the liver in each of these procedures. Writing eqn (5) in spherical coordinates, r and θ, to separate the longitudinal and transverse components of the wave, using for the spherical Hankel functions,

$$h_0(z) = \frac{je^{-jz}}{z}; \; h_2(z) = -e^{-jz}\left(\frac{j}{z} + \frac{3}{z^2} - \frac{j}{z^3}\right), \qquad (14)$$

and letting $z = (\beta\text{-}j\alpha)r$ (eqn (7)),

$$\xi_s \sim -\frac{6e^{-\alpha r}}{r^2}\frac{(\beta^2-\alpha^2)Cos(\beta r) + 2\alpha\beta Sin(\beta r)}{(\beta^2-\alpha^2)^2 + (2\alpha\beta)^2}Cos\theta \mathbf{e}_r + \frac{3e^{-\alpha r}}{r}\frac{\alpha Cos(\beta r) - \beta Sin(\beta r)}{\beta^2+\alpha^2}Sin\theta \mathbf{e}_\theta, \qquad (15)$$

where $\mathbf{e}_r$ and $\mathbf{e}_\theta$ are unit vectors in the direction of increasing r and θ, θ being the angle between the axis of oscillation of the sphere and the position-of-interest in the field. Only first-order terms in r are given for the two components.

The low stiffness and high viscosity of liver present a measurement challenge. In a general sense, there are two competing requirements of a measuring system. Precision, either in wavelength determination or in measurement of time of flight, is improved by use of high frequency. Depth of penetration is improved by use of low frequencies. For liver measurements *in vivo*, we would only be interested in the behavior of the wave at distances greater than approximately two centimeters below the surface. The problem is illustrated in Fig. 9, which gives the magnitudes of the longitudinal (r) and transverse (θ) components of a 50-Hz shear sine wave in liver using data from Fig. 7. With the assumed properties of liver and a detection sensitivity of a few micrometers in displacement, it appears that a longitudinal wave of 50 Hz will interrogate a useful sample of liver tissue. At frequencies well above 50 Hz, the demands on sensitivity of the detector begin to be challenging. Much below 50 Hz, the liver may be too thin to obtain a good measurement of wave speed.

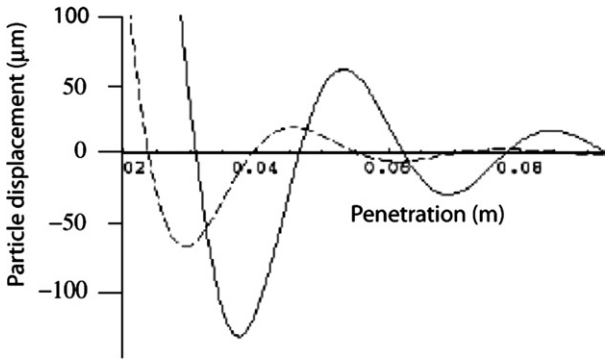

Fig. 9. Particle displacement *vs.* depth for 50-Hz longitudinal (dashed) and transverse (solid) sinusoidal shear waves in liver using parameters from Zhang et al. (2007). The net field at any point is the dashed curve multiplied by $Cos\theta \mathbf{e}_r$ plus the solid curve multiplied by $Sin\theta \mathbf{e}_\theta$. The displacements correspond approximately to a 1-mm amplitude oscillation of the spherical driver.

An important point to be considered in the design of any instrument is that measured shear wave speed is not uniquely related to tissue shear stiffness. In fact, at high frequencies, it is entirely dominated by viscosity. Therefore, to provide instrument independent stiffness, we must determine both real stiffness and real viscosity either through measurements of wave speed as a function of frequency or by measurement of wave speed and absorption at a single frequency. Furthermore, as noted earlier, it is likely that viscosity contains its own useful information about the condition of the tissue.

From the point of view of wave propagation, the measurement system described in Fig. 10a has the advantage of simplicity. For several reasons, it is desirable to operate at frequencies somewhat below the transition of the propagation constant from stiffness to viscosity domination. Topping the list of reasons is the need for the wave to penetrate well into the liver. In that case and if $\beta >> \alpha$, the wave along the axis of oscillation of the driver is of the form

$$\xi_s \sim \frac{e^{-\alpha r}Cos(\beta r)}{(\beta r)^2}. \qquad (16)$$

Comparing amplitude and position of scans as time

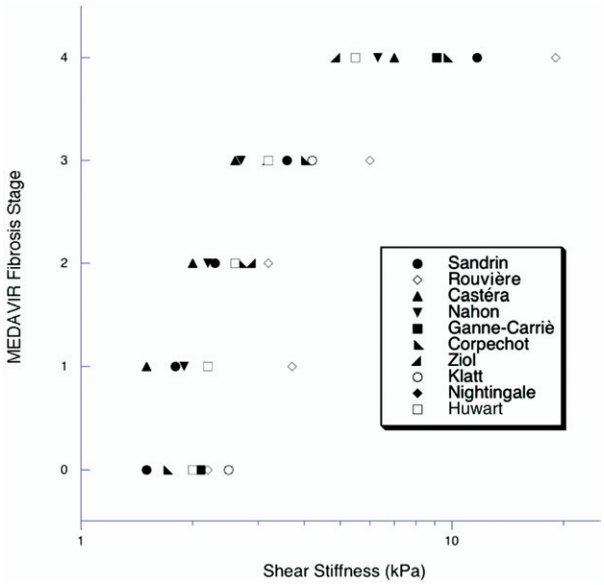

Fig. 10. The relationship between shear stiffness magnitudes measured *in vivo* and stage of fibrosis determined histologically. Each point represents the mean of values reported. Open symbols are magnetic resonance measurements. (Castéra et al 2005, Corpechot et al 2006, Ganne-Carrie et al 2006, Huwart et al 2007, Klatt et al 2006, Nahon et al 2006, Nightingale et al 2003, Rouvière et al 2006, Sandrin et al 2003, Ziol et al 2005).

progresses, taking into account the reciprocal distance-squared characteristic of the longitudinal wave, will give both the absorption and speed of the wave and thus unique values for real shear stiffness and viscosity.

Radiation force elastography (Fig. 10c) differs qualitatively from other techniques in several respects. Depth of penetration is determined by the high-intensity, high-frequency, compressional sound field rather than absorption of the shear wave itself. The amplitude of oscillation of the source tissue is limited by heat generation at the focus. Even so, displacement amplitudes induced by radiation force elastography at depths of interest in the liver are comparable to those used in other forms of elastography. The particle displacement and, hence, the amplitude of the "driver" of shear waves, depends on the stiffness of the medium. Hence, radiation-force, shear-wave generation is particularly effective in soft tissues such as liver.

At frequencies where $\beta >> \alpha$, the laterally propagating, radiation force–induced transverse wave would have the form

$$\xi_s \sim \frac{e^{-\alpha r} Sin(\beta r)}{\beta r}. \qquad (17)$$

Thus, the transverse wave has the advantage of an inherent dependence on reciprocal distance instead of distance squared for the displacement along the axis of oscillation, which characterizes the longitudinal wave. As currently practiced, radiation force is applied to the tissue for a few hundred microseconds and the time dependence of the displacement is determined by the time constant of the tissue—for liver, of the order of 1 ms. In other words, the displacement pulse is not harmonic and extracting real stiffness and viscosity from measured wave speed and absorption is somewhat more complex than discussed previously for the harmonic, axial, longitudinal wave. Furthermore, with effective frequencies of several hundred Hz, viscosity rather than stiffness may dominate the wave speed. These problems are partially addressed by amplitude modulation of the radiation force (Chen et al. 2002).

Spatial modulation of the driving radiation force is a particularly attractive approach to the measurement of stiffness (McAleavey et al. 2007). In this method, the tissue is driven by a short pulse with known spatial harmonic variation. A shear wave is propagated away from the exposed region. A nearby detector measures the frequency of the passing wave. The wavelength and frequency give the wave speed. Note that the frequency observed is a function of tissue properties at the excitation site and is independent of the local tissue properties. Hence, the technique gives the wave speed of the tissue at the point of excitation. For homogeneous tissues, however, it should be possible in principle to measure both wave speed and attenuation, thus giving both stiffness and viscosity. Even greater simplicity and precision may be achieved through measurements of wave speed as a function of frequency.

The system suggested by Fig. 10b sees a varying combination of longitudinal and transverse waves depending on the angle of observation. Of course, wave speed is the same for both components so it is relatively straightforward to measure the wave speed at a given frequency. However, because of the different inherent distance dependences of the two waves, determining absorption would be a greater challenge with this system than for the one in Fig. 10a. Most modifications of existing elastography equipment will probably use the approach of 10b. It may be that, with these systems, dispersion measurements will be the simplest way to determine real stiffness and viscosity.

Stiffness and fibrosis

Liver stiffness is not a new measure of liver pathology. Hepatologists and surgeons have been aware of its relation to disease for many years. Elastography, however, holds promise for the determination of liver stiffness noninvasively, rapidly *and quantitatively*. Sandrin et al. (2003) report interoperator reproducibility of a few percent. Eventually, it will be desirable to separate the real and imaginary parts of the complex stiffness to arrive at a unique value for shear stiffness. In the process, we shall obtain, as a by-product, the viscosity of the

tissue. As discussed above, the viscosity may contain its own information about the condition of the liver.

In the current practice of hepatology, biopsy is the "gold standard" for diagnosis. A great deal of information about the condition of the liver can be learned from histologic examination of a small sample of the tissue. Included in the pathology report is a qualitative description of the extent of the development of fibrosis. By consensus, this is usually characterized by four stages, Stage 4 being an extreme condition called cirrhosis. Several recent clinical studies, comparing elastographically-measured stiffness to levels of fibrosis as determined by biopsy, are summarized in Fig. 10. Superficially, this comparison of a qualitative descriptor (fibrosis stage) with a quantitative measurement (shear stiffness) may appear to be inappropriate. However, there is a mechanistic basis to believe that, in a general way, stiffness will increase with the degree of fibrosis. Only the means of the stiffnesses in each study are shown. In each investigation, the range of values observed within any histologic category is large. Particle displacements in the studies by Klatt et al. (2006), Rouvière et al. (2006) and Huwart et al. (2007) were measured by magnetic resonance imaging. All of the other studies used M-mode ultrasound.

Because the staging of the pathology of fibrosis is subjective, only one of the categories arranged along the ordinate of Fig. 10 can be expected to be reasonably "the same" from one study to the next. That is F0, normal liver. There is consensus that normal liver has a stiffness of approximately 2 kPa. The range of values from all of these institutions is reassuringly small. (The literature contains one outlier: Sanada et al. (2000) report a shear wave speed of 6 m/s for normal liver, corresponding to a stiffness of approximately 35 kPa.)

As fibrosis progresses, shear stiffness measured elastographically increases. The point to remember in assessing that relationship is that the spread in the data at each stage reflects the uncertainty in sampling and interpretation of the biopsy specimen. The stiffness data are comparatively precise. Even with the very large spread in biopsy data, there is a clear separation between stiffness values for cirrhotic and normal liver.

Pathologists learn a great deal more from biopsies than the nature of fibril invasion of the tissue. However, the working hypothesis, which says that stiffness is a measure of the cumulative damage to the liver that has occurred over time, is consistent with the comparison between stiffness and fibrosis stage shown in Fig. 10. Stiffness should not be considered a replacement for any other test of liver health or pathology. Rather, as experience accumulates over time, this readily measured, precise quantity will very likely become an indicator of liver health and disease in its own right.

In the very short time after the availability of a commercial, dedicated liver stiffness monitor, clinical tests have validated the guiding hypothesis and demonstrated to some degree the efficacy of elastography as a monitor of the progress of liver disease. For the full potential of this technology, we need studies of the mechanistic basis for changes in real stiffness and viscosity of liver tissue and clinical data relating stiffness to the diagnosis and prognosis of liver disease.

SUMMARY

Cirrhosis of the liver is a major cause of morbidity and mortality. It ranks twelfth among causes of death in the United States and is associated with a significantly elevated risk for hepatic cancer. In this country, the major factors leading to cirrhosis are viral hepatitis and alcoholism, but there are many other causes. Once the liver becomes cirrhotic, there is little chance of reversal. However, cirrhosis is preceded, in many cases, by decades of slowly increasing fibrosis during which time the patient is largely asymptomatic. During that time, there are treatments that can slow or even reverse the course of the disease. A simple and reliable test that would detect and monitor the progress of liver disease in its early stages could greatly reduce human suffering, medical costs and lost productivity in the workforce.

Elastographically measured shear stiffness shows promise for that role. Figure 10 leaves little doubt that stiffness contains clinically useful information. There is reason to hope that stiffness data will eventually be as ubiquitous in management of liver disease as blood pressure is in cardiovascular disease.

Today we are at a transition in our approach to the use of elastography in monitoring liver disease. We no longer need to justify the technique through comparisons with biopsies. Instead, we should (i) investigate the biophysical mechanisms that lead to observed values of liver stiffness and viscosity and (ii) build a massive database relating the progress of liver disease and its treatment to the complex stiffness of its tissues. As the central role of elastography in hepatology develops, the engineering centers will respond through the addition of elastography to existing ultrasound (and possible MRI) equipment and through the development of ever simpler and less expensive, dedicated units for use in the routine practice of hepatology.

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