Elastography in Chronic Liver Disease: Modalities, Techniques, Limitations, and Future Directions


Aparna Srinivasa Babu, MD • Michael L. Wells, MD • Oleg M. Teytelboym, MD • Justin E. Mackey, MD
Frank H. Miller, MD • Benjamin M. Yeh, MD • Richard L. Ehman, MD • Sudhakar K. Venkatesh, MD

Jeffrey Klein, MD  Hi, I’m Jeff Klein, editor of RadioGraphics and I welcome you to the second of our podcasts for the November 2016 issue of the journal which features an interview with the authors of one of our highlighted papers. I’m pleased to have Dr. Aparna Babu and Dr. Sudhakar Venkatesh join us for a discussion of their paper titled “Elastography in Chronic Liver Disease: Modalities, Techniques, Limitations, and Future Directions.” Dr. Babu is currently an Abdominal Imaging Fellow at the University of Pennsylvania. At the time that this paper was written, she was a part of the Department of Radiology at Mercy Fitzgerald Hospital in Darby, Pennsylvania. Dr. Venkatesh joins us from the Department of Radiology at the Mayo Clinic in Rochester, Minnesota. Let me begin by asking Dr. Babu the first question. Dr. Babu in the introduction to your paper I was struck by the instance of chronic liver disease both worldwide and in the United States. You make important points about the limitations of the pathologic assessment in serological tests in determining the extent of hepatic fibrosis in effected patients. You also briefly review the use of contrast-enhanced MR and CT to assess fibrosis, although it seems like these techniques are still relatively immature. Can you briefly describe to us the methods that are used to measure the elasticity of the liver which you can see in Figure 2?

Aparna Srinivasa Babu, MD  Sure Dr. Klein. Thank you for your question. It’s an excellent first question to help us introduce our readers to the concept of elastography. You’re right, you know the incidents of liver disease is indeed striking, and I was amazed that as many as 30 million people suffer with chronic liver disease in the U.S. alone. One of the first steps in management of these patients is assessment of the degree of hepatic fibrosis which is very important not only in treatment but also in prognostication of these patients. As we know, liver biopsy is a gold standard that all other modalities are measured by. While it’s a very good technique, it has its own limitations. One of the most important limitation is that it’s an invasive technique and that comes with small risk of morbidity and sometimes even mortality in some patients. And so there is ongoing focus on development of newer, non-invasive techniques for assessment of hepatic fibrosis. Serological testing has been found to beneficial in a small subset of patients, especially for confirming or refuting diagnosis, but it’s not very specific. Inflammation especially can mimic fibrosis in many patients and also grading of the severity of fibrosis is not possible in many patients. That’s where MR and ultrasound elastography comes into play. These modalities are useful not only in assessment of hepatic fibrosis for the presence or absence of fibrosis, but also they’re very useful in grading the degree of fibrosis and that’s helpful in management of these patients. The principle behind elastography is really quite simple. It relies on measurement of mechanical response of tissue to outside forces applied on that tissue. In many ways it can be considered a sophisticated out-patient technique that was used from several centuries ago. It can be divided into two main categories as we see from our figure, Figure 2, and these techniques are either static or dynamic techniques. In static techniques a series of compressions are used as mechanical forced and before mentioned within a specific lesion is measured with respect to the formation of surrounding tissues. It has been particularly useful in breast and thyroid lesions, but because the liver is a deep seated tissue, it’s less useful as an assessment of hepatic fibrosis. Amongst the dynamic techniques, the common principle is reduction of shear waves within tissues. So either vibration or acoustic radiation force impulse is used to produce shear waves in the tissues and the propagation of shear waves within the tissues is related to the elasticity of the tissues. The less elastic or more fibrotic a tissue is, the faster it propagates a shear wave and measurement of this velocity within the tissue can help grade the degree of fibrosis within these tissues. Shear wave imaging can be either dynamic or static. Examples of static shear wave imaging include the fibroscan which is a very popular device and that measures fibrosis by using vibration as its force to produce shear waves. It’s an out-patient technique that can be performed in many offices, simple, straightforward. There’s also use of ARFI which is Acoustic Radiation Force Impulse. For example in point of supersonic shear wave techniques. So what it does is uses sound waves to produce shear waves and measurement of these shear waves again helps rate the degree of fibrosis. The supersonic technique uses continuous acoustic radiation force impulses to produce a cone of shear waves and it’s a much more sophisticated technique. More of the liver tissue can be assessed, but it is still in main stages so it’s still in infancy not widely available in the market. Finally, MR elastography uses continuation vibration to produce shear waves. A special motion anchored at GRE sequence helps determine the degree of fibrosis in these patients. Going forward I think that will be the main modality used for assessment of elastography.
J.K. Great. Well thank you so much for that. Let me ask you, what would be the main clinical indications for the performance of liver elastography particularly in the setting of patients with hepatitis C?

A.S.B. The main indication is grading of fibrosis. As we talked about before, that’s useful in management and treatment of these patients. With respect to hepatitis C with the new polymerase inhibitive therapy which is excellent as compared to interferons with came with a lot of side effects, cure rates approach 100% with polymerase inhibitive therapy without the associated side effects. So the only downside to this is that it’s very expensive. You know a single treatment cycle costs about $90,000 and so insurance companies are quite stringent about who to provide these treatment to. They are particular that it has to be advanced fibrosis in order to approve this treatment. So measurement of fibrosis and grading of fibrosis is useful in these patients. Not only that, but in patients with hepatitis C, the five-year survival rate has been linked to the degree of fibrosis initially present and also it can help assess treatment response by using elastography. Also there are several novel indications for elastography, particularly in patients with hemachromatosis, serum transferring levels, along with elastography measurements can help assess the degree of fibrosis in these patients. One of the things that I particularly like, research is ongoing to actually determine pre-fibrotic stages. There information is present and that information is enough to cause alteration in the liver tissue and if we can somehow measure the alteration produced by inflammation and differentiate it from fibrosis, then we can perhaps pick up these patients earlier and help treat them earlier. So that is another exciting approach. Looking forward to what the future has in store for us.

J.K. Terrific, thank you so much Dr. Babu. Let me turn to Dr. Venkatesh. Dr. Venkatesh, focusing now on MR elastography, you indicate that MR elastography is currently regarded as the most accurate, non-invasive method for the detection and staging of liver fibrosis. In Table 5 you provide a list of patient-related factors that influence liver stiffness. Can you take us through these various conditions and how they impact liver stiffness as determined by ultrasound and MR elastography, focusing particular on those conditions where elastography is particularly helpful and those where it might be of more limited value?

Sudhakar K. Venkatesh, MD Thank you Dr. Klein for having us and for that nice question because you are right pointing out that MR elastography indeed has the highest accuracy both for detection and staging of fibrosis. And you might be wondering why MR elastography has (inaudible) This is basically because it samples a large volume of liver tissue. Now almost when we do it as standard GRE/MRE technique, we assess about one-third of the liver volume for the staging of fibrosis. This large volume of sampling overcomes the sampling error which is the common problem with other techniques including the ultrasound elastography technique and including the liver biopsy which also samples like 150,000th of the liver. The MR has very accurate because it samples of a large volume of tissue. In addition to that it has high rate of agreement, it has high repeatability and high reproducibility, and also it has very high technical success compared to the other ultrasound techniques as well as invasive techniques. All this makes ultrasound a very robust, MR elastography a very robust technique and it is very accurate. Let’s go to Table 5 where we have highlighted some of the patient conditions which can cause changes in liver status. Now liver fibrosis is the first one which is maybe the one which has the most effect on the liver stiffness and this causes increased stiffness which is detected by both ultrasound and MR elastography techniques and it is the reason why these elastography techniques are so successful and have been applied clinically. But in addition to that there are other conditions which can also increase the liver stiffness (inaudible) conditions for example heart failure, right heart failure or venous ultra-obstruction including Budd-Chiari syndrome. All these can cause condition of the liver tissue (inaudible.) The other condition which can cause increase in the stiffness is inflammation, acute inflammation particularly, like acute hepatitis, acute C hepatitis leads to edema interstitial pressure increase and that also can cause increase in the liver stiffness. Now chronic inflammation does cause an increase in the stiffness and that to a very lesser magnitude compared to the acute inflammation, but it does add on to the amount of stiffness we measure when we measure for stiffness. In this regard I would like to highlight that due to hepatitis which is going to be a very common chronic liver disorder in the US because (inaudible) is going to be the most common cause of chronic (inaudible) Simple steatosis does not cause increase in stiffness but (inaudible) hepatitis but inflammation along with hepatic change will cause increase in stiffness. This increase in stiffness can be helpful for different shading, NASH from simple steatosis which majority of the people have. As everyone is aware, NASH is important to be – is particularly need to be detected earlier because that’s the one which has high risk to progress to fibrosis, cirrhosis and more so forth. On the same line, acute alcoholic hepatitis like somebody goes for an acute binge of alcohol, that can also cause severe inflammation of the liver and at that time liver stiffness can be higher. We need to take into consideration that a patient has these co-existing confounding factors before using any of elastography techniques whether it’s MR or ultrasound because these are going to increase the stiffness and they are going to give you falsely elevated stiffness and you end up with cirrhosis. So you’d better be careful to rule out these conditions. Regarding the fasting stages, now this reads very interesting. Liver has dual blood supply from artery and portal vein. And the portal vein supply comes from the mesentery, is feed by the mesenteric circulation. When a person eats, is postprandial situation, particularly between 30 minutes or two hours especially a high carbohydrate meal, that increases the flow into the mesentery and increases the flow into the portal vein. When this increased blood flow comes from the portal vein, normally when it’s a very soft compliant organ like a sponge, so when this increased flow comes in it accommodates this without any increase in the stiffness. In a normal patient or a normal volunteer, the stiffness is not increased, but a fibrotic liver is less compliant. It cannot distend much. So when this increased flow comes it gets stretched, the capsule gets
stretched as a result of stiffness increases. So if you measure the stiffness in a patient postprandial who has fibrosis, the stiffness is going to be higher than what would be even in the fasting status. It is very important that patients should always be scanned in the fasting status. Fortunately, clinically we always scan patients in fasting status so this should not be a problem because fasting status at least minimum of three to four hours should be easy to follow. The other condition which might affect elastography techniques, particularly MR elastography, would be iron overload like patients having too much hemochromatosis. The standard MR elastography we use is the GRE technique which is very sensitive to the presence of high iron in the liver and this causes signal loss. Now mind you this does not prevent shear waves going through the liver, but the shear waves are just not visualized because there’s no signal coming from the liver and we cannot assess these shear waves going through the liver. If you have very severe iron overload and MR elastography can fail just because there’s no signal in the liver. So you might wonder what will you do in those conditions. In those conditions you might go for ultrasound elastography if need to be done. Or it so happens in our clinical setup, hemochromatosis patients become very good blood donors because they go for a lot of phlebotomies. And when they go for a lot of phlebotomies their iron will come down, and once their iron has come down and you’re worried about fibrosis, you can go and do and MR elastography. And lastly we go into the lower part of the thing as we already mentioned, hepatic steatosis or fatty change per se does not affect the stiffness evaluated by MR elastography that’s where a lot of studies were proven by. But there are some studies which are shown that ultrasound elastography may show an increased stiffness in these cases. So you have to be careful in those patients who have high BMI, a lot of fat, and you’re suspecting they may have a bit of hepatitis; they may have a higher increased stiffness. MRE can be easily performed even in high BMI patients and even with those who have a large amount of subcutaneous fat where ultrasound elastography techniques may fail. But I will say this, as long as a patient fits into the MR scanner, we can do MRI elastography. If he cannot, then you have to go for other techniques. But unfortunately these patients are those who when which ultrasound also fails. These are the patients who when which we have to go for other techniques like clinical tests or sometimes we might even have to use (inaudible). So far in all the publications in which we have seen over the last ten years, age and sex are not affected by stiffness although one might wonder whether men have more liver stiffness compared to women, and maybe it is related to alcohol intake which we don’t know. We cannot say anything about it. In summary I would say both ultrasound and MRE really are useful for the evaluation of liver fibrosis and you have to pay particular attention to confounding factors such as fasting condition, heart failure, acute inflammation, acute alcohol intake, these can falsely elevate the liver stiffness and always perform elastography in fasting status and follow-up the same in fasting conditions.

J.K.  Great, thank you so much for that. Let me ask you one other question, follow-up. Your paper provides a fairly detailed description of how to perform magnetic resonance elastography and in particular how to interpret the result in stiffness patterns and correlate these with the anatomic imaging. Can you take us through some clinical examples of patients as illustrated in Figure 15 in your paper?

S.K.V.  Thank you again for that question. Yes MRE does provide a cross sectional view of the liver where we perform the elastography. MRE is typically performed with four slices. These four slices go through the largest cross section of the liver and it gives you a snapshot of a cross section of the liver and at the same time the stiffness map, with a wide view, the distribution of the stiffness. It’s very interesting, initially we didn’t think that the distribution of stiffness was something to do with the heterogeneity of fibrosis and may not be very important. But as we improve it or as we increase our experience we started noticing that particular diseases or particular conditions do have a hepatic pattern of stiffness. For example if you look at Figure 15, the first image, the top row images, the one on the left will show – I’m bringing up images on my hand over here, the top image A and B on the left shows the stiffness map and then the right is the contrast-enhanced CT. Now if you look at the contrast enhanced CT there is very full hypodensity where the arrowheads shows. This is an area of passive condition. This patient has constrictive pericarditis and you can see the IVC is kind of congested and this leads to passive condition. And this passive condition goes all the way to the sinusoid levels and stretches the capsule and ultimately affects the peripheral part of the liver. And when you do MRE in this condition you can see that the stiffness map actually shows the red and the yellow regions in the periphery of the liver corresponding to the areas of passive condition. This information goes along with what we see on the imaging which we didn’t probably knew what was happening, but we have evidence now that this is the area of condition and it relates to increase. This kind of an appearance can also be seen in primary sclerosing cholangitis in which peripheral ducts are involved and these ducts will lead to fibrosis and stiffness in the peripheral part of the liver and it can see a rim of increased stiffness where the central part may be going for just for hypertrophy and you may not see increased stiffness. You can look at the second image which is a case of primary sclerosing cholangitis and shows a focal area of increased stiffness as shown in the arrow on figure C. This is an area of biliary stricture along with biliary dilatation and you can see that on the correlate on the T2-weighted image in figure D in which it shows hyper intensity in that region and dilated ducts. These features were initially identified before. Everybody knew these things are happening and (inaudible) but we now have a correlate, and it corresponds exactly to the area of stiffness, and the area of signal intensity, and if we happen to do diffusion-weighted imaging in this patient it will show it as restricted diffusion in the same place and if we do arterial phase imaging to show arterial phase hyperperfusion in the same place. All these correlate exactly to the same area of stiffness. Now you might be wondering how is this useful because if you do an ERCP in this patient and do relieve the biliary stricture that particular area of stiffness will go and we are showing that there’s a response to what
(inaudible) and if you in future, right now primary sclerosing cholangitis does not have a treatment. In the future if there’s a treatment available we can show these changes are occurring with the treatment and this will be helpful. And these changes are very focal, they are globally in the early part of the disease and you can see these kind of changes also in autoimmune hepatitis wherein which you have rings of hyperplastic nodules surrounding by stiffness of fibrotic nodules. All these changes can occur and these changes can be very subtle and distributed throughout the liver. Let’s look at the third one, the third example, the Figures E and F showing the case of autoimmune hepatitis with confluent fibrosis. If you look at the MR elastography stiffness map the arrow points to an area of increased stiffness in one particular area. This corresponds exactly to a hyper intensity on the T2-weighted images which is a confluent fibrosis. Now this is exactly the region where there’s a lot of fibrosis and MR elastography exactly corresponds to that. This kind of information let’s say in a patient who comes in with an early autoimmune hepatitis of primary sclerosis cholangitis if you do an elastography you should see some areas of stiffness and some areas of normal areas of stiffness. So if you wanted to do a biopsy of particular or clinical indication or waiting for a trial or something, you can actually direct where to do the biopsy in order to get a positive result. MR stiffness maps can be useful for that to do a biopsy if at all is needed, but we are seeing more and more of these stiffness patterns, but these patterns can also change with treatment and we have to see furthermore a kind of an experience to see how this thickness pattern changes with any other (inaudible) But in general, MR elastography gives you a snapshot of what is happening, a cross-sectional view in the liver and which part of the liver is affected and which part of the liver is more affected than the others and this may be useful for evaluation of treatment or for response assessment.

J.K. That’s terrific. Thank you so much for that. I just want to thank Dr. Venkatesh from the Mayo Clinic, Dr. Babu currently at the University of Pennsylvania and from Mercy Fitzgerald Hospital in Pennsylvania for taking the time today to discuss their paper on liver elastography with me and with our readers.

S.K.V. Thank you.

A.S.B. Thank you.