Biomedical Ultrasound: Fundamentals of Imaging and Micromachined Transducers

Prof. Karla P. Mercado-Shekhar, Prof. Himanshu Shekhar, Prof. Hardik Jeetendra Pandya

IIT Gandhinagar, IISc Bangalore

Lecture: 50

Recap of week 10

Okay welcome to this recap or revision lecture I hope you will find it useful so if you recall in the past few lectures we talked about the safety of Ultrasound. Ultrasound is a very safe modality relatively speaking but safety protocols are important because we want to avoid bio-effects now. We said that the exposure levels of ultrasound determine the safety. And the highest exposure you will find in ultrasound mediated surgery or high intensity focused ultrasound and histotripsy. These are not the focus of our present course. Then what's important for us is safety in diagnostic ultrasound, which involves modes such as B-mode, Doppler, M-mode, contrast enhanced ultrasound, et cetera.

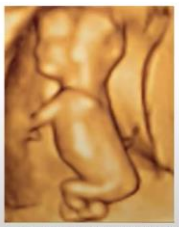
And then there's also applications in ultrasound therapy, again, which we are not going to discuss in detail here, but things such as hyperthermia, drug delivery, aided by the ultrasonic stimulus. So, bio-effects can be classified into two parts. One is thermal bio-effects, the other is mechanical bio-effects, because ultrasound interacts with tissue in this manner. There are thermal effects and there are a variety of mechanical effects.

Now when we use these bio-effects to our advantage, that is the field of therapeutic ultrasound. However, when we are talking about diagnostic ultrasound, we don't want any bio-effects. So, we would like to avoid these bio-effects. And that's where the ALARA principle or as low as reasonably achievable comes into play. So, we should always limit the dose of ultrasound.

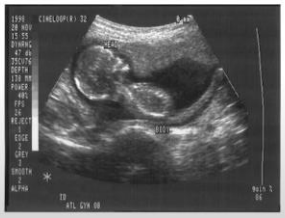
- The ALARA principle limits escalation of ultrasound exposure and scans that do not provide any additional diagnostic information

**Example:**

- A higher-pressure pulse improves the penetration depth, contrast, and signal-to-noise
- However, if no added significant value in the clinical context, this practice is discouraged



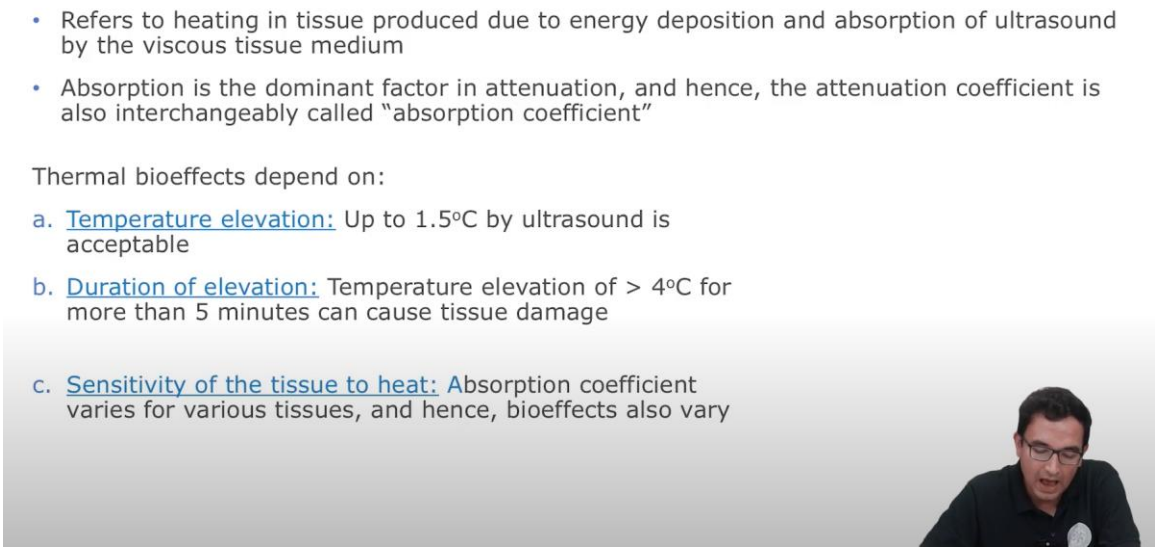
Biagio Azzarelli, CC BY-SA 2.0 <https://creativecommons.org/licenses/by-sa/2.0>, via Wikimedia Commons



Public domain, via Wikimedia Commons https://upload.wikimedia.org/wikipedia/commons/1/1e/Ultrasound_lores.jpg?20130804092500

So, the exposure in terms of intensities, duration, pressure amplitude should be reduced to the extent possible because if there is no advantage or no additional diagnostic information is coming because of higher exposures then better to go with lower exposures. So, one common example is that higher pressure pulse actually improves the penetration depth, contrast and signal to noise ratio, right. But you may not be interested in very deep targets anyways. So, in that sense we should not increase the pressure amplitude because it does not give you any advantage. Another example is if you have a three-dimensional ultrasound as opposed to two-dimensional ultrasound, then appearance-wise the three-dimensional ultrasound looks pretty, but unless there is a clinical reason where the two-dimensional ultrasound fails to provide adequate information and therefore the clinician switches to three-dimensional ultrasound one should stick to two-dimensional ultrasound because three-dimensional ultrasound involves longer exposure durations and more exposure so therefore it's favorable to go with two-dimensional ultrasound because of the ALARA principle and this is one of the reasons you will still see these kind of two-dimensional ultrasound images being very actively used even though 3D is available And the other variable of course is cost because 3D systems are more data intensive, more complex and more costly.

Then we discussed thermal bio-effects. So, we discussed that the sound gets absorbed in the tissue and because of absorption of this ultrasound the temperature is elevated. Now you can have some temperature elevation because of ultrasound and up to 1.5 degrees is considered acceptable. But if the temperature increases more than 4 degrees for more than 5 minutes, it can cause tissue damage and it can be particularly concerning for applications such as fetal imaging.



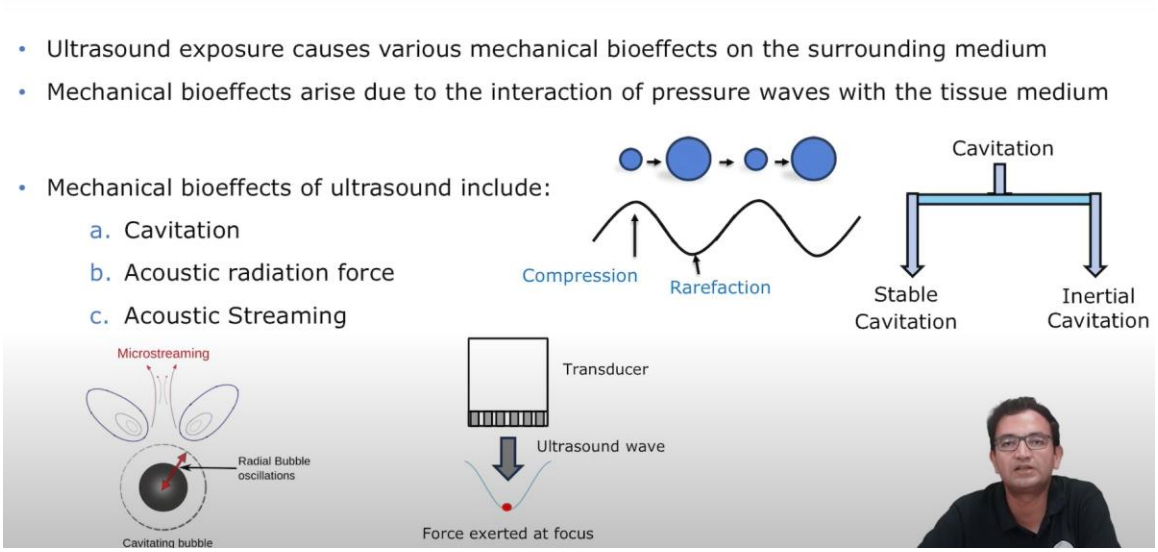

So, another point is the sensitivity of the tissue to heat. So, absorption coefficient of different tissues varies. You may have higher absorption coefficient for example in the region of interest if you have bone, you will have higher absorption coefficient and that will lead to higher temperature elevation. But certain tissues may have lower absorption. So apart from the exposure, the absorption is also of interest.

So, there is this formula by AIUM where for a given exposure time you are given a delta T max the temperature elevation that you should not exceed and that is determined by 6 minus log 10 of T where T is the exposure time in minutes divided by 0.6.

$$\Delta T_{max} \leq 6 - \frac{\log_{10}(t)}{0.6}$$

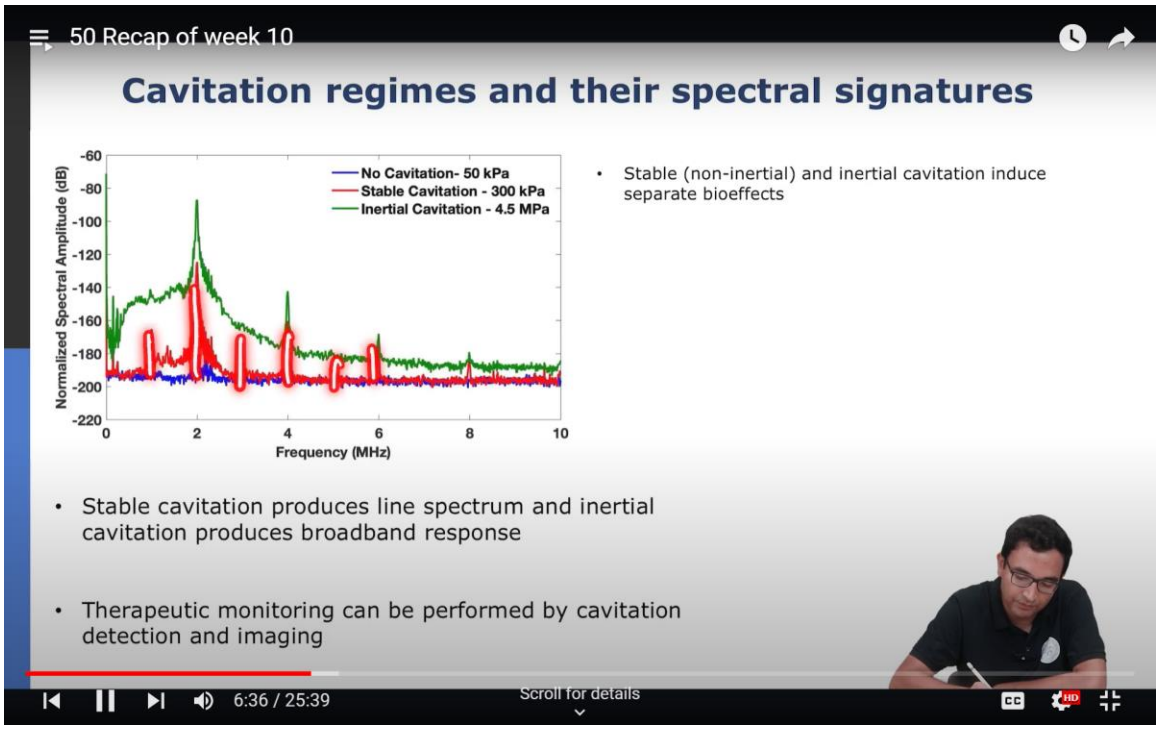
So, this is an empirical kind of rule which is important to keep safety in terms of thermal bio effects. So common therapeutic applications, if you remember, based on thermal effects are hyperthermia, which is also called diathermia, where you elevate the temperature of tissue by a few degrees to improve recovery, for example, wound healing, bone tendon healing, etc. And then is high intensity focused ultrasound therapy, where you kill the tissue by thermal necrosis by using this thermal bioeffect.

Then we discuss cavitation, which is the formation, growth, collapse of microbubbles in response to ultrasound. And if you have existing bubbles, for example, because of ultrasound contrast agent, their oscillations, their response to ultrasound is also termed as cavitation. And you will get compression and rarefaction of these pulses, which end up getting this kind of bubble response often. Now, apart from cavitation, there are other mechanical effects, which include radiation force, acoustic streaming. And when we talk about cavitation, there are two types of cavitation, broadly speaking, stable cavitation and inertial cavitation.




Radiation force refers to the momentum transfer caused by a propagating ultrasound beam. So, if you have the focal point here, the maximum force will be exerted at the focal point because that is where the intensity is the maximum.

Now in terms of stable and inertial cavitation, how do we differentiate between stable and inertial cavitation? If we are listening from the outside, essentially, we have a detector, and it is looking at the signal which is coming out from the bubbles that are oscillating. or collapsing for that matter there is a difference in their signatures for oscillating bubbles typically you will get this kind of line spectra where you have these lines present at some multiples of harmonics and sub harmonics and this is typically characteristic of stable cavitation and wherever you get this kind of broadband as you see in the green curve There is this broadband energy elevation. It typically is a signature of collapsing bubbles or inertial cavitation.




So, you can perform therapeutic monitoring by doing this. Now you hope that these kind of cavitation behaviors don't occur in diagnostic ultrasound. Stable cavitation is used for imaging like for example subharmonic imaging. But typically, when you are not interested in contrast enhanced ultrasound, you would prefer not to have any cavitation in your region of interest.

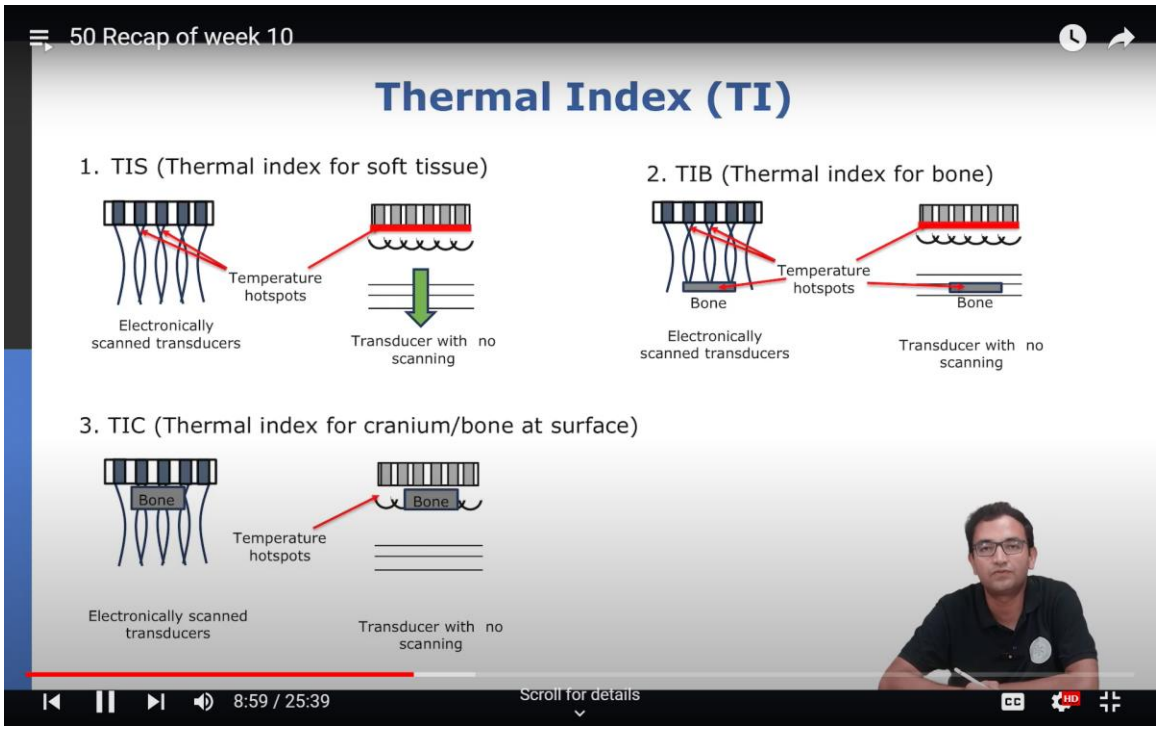
So there have been indices that have been defined, thermal and mechanical indices, as a marker or a metric for promoting safety.

And these indicators help to predict the possibility of bio effects in diagnostic ultrasound. Thermal index is a measure of the potential of the tissue to heat up during ultrasound imaging scans and mechanical index displays the probability of cavitation occurring in a medium or rather it is related to the probability of cavitation occurring in a medium for a specific frequency transducer and specific exposure regimes.

Now these indices have their own limitations, but they are still quite useful. They are not absolute; they are some relative metrics, and they also are displayed on the screen all the time. So, because of which you can even retrospectively go back and see what the exposure conditions were, if there are any bio-effects and then you can correlate those bio-effects with the exposure conditions.

We discussed that the thermal index is defined in three ways. There is thermal index for soft tissue, thermal index for bone, and thermal index for cranium or bone at surface. And depending on the type of orientation, like for example, for soft tissue, the highest

temperature elevation will be near the transducer surface where the beams overlap, because that's where the maximum exposure is happening. if you have bone then because of the high absorption typically the highest amount of temperature elevation will happen at the bone interface right and if you have the bone close to the surface then for sure because the highest  overlap of beams is at the surface and at the same time bone has a high absorption coefficient so you can be assured that the highest temperature elevation will happen at the transducer bone interface so these are some examples that are important for promoting safety but there are limitations to these indices. They are not absolute as I said earlier.




They are based on some simplified theoretical models. But they are useful. They don't fully capture the dynamics of thermal behavior wherein they assume a steady state behavior. They also consider some tissue types like bone, soft tissue, fat, etc. But human tissues are very diverse and heterogeneous.

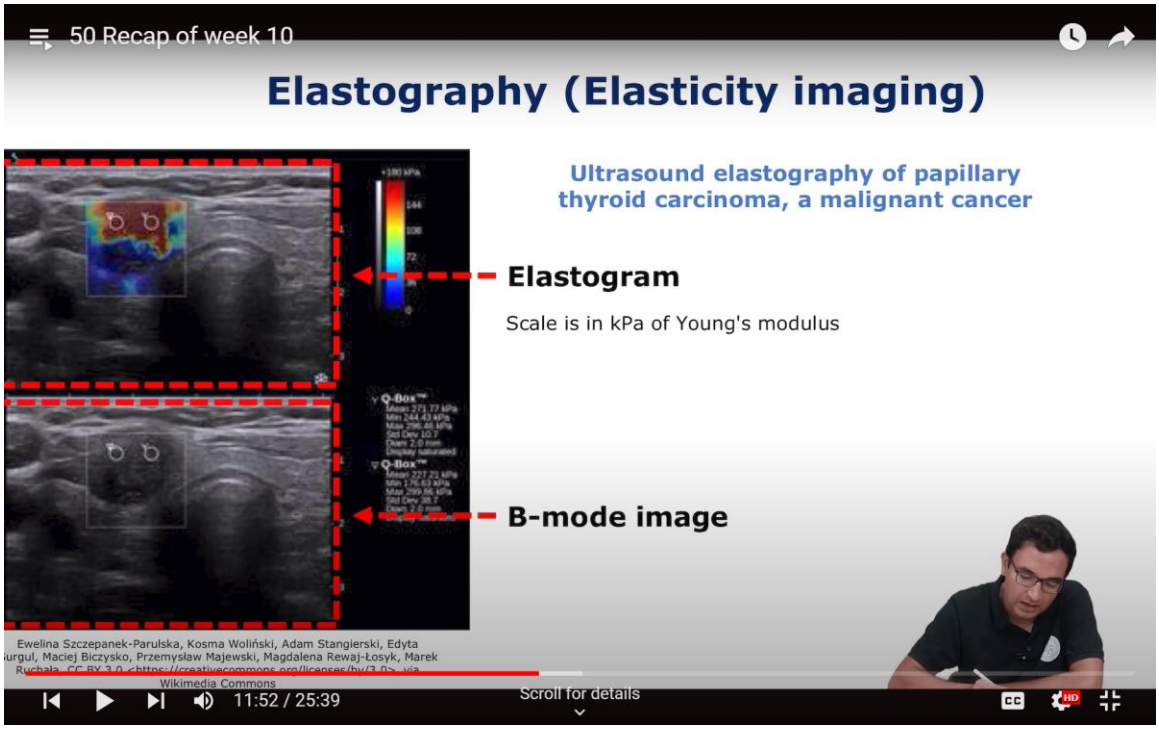
So that full complexity is not captured in this thermal index. Also, there is some modeling for perfusion or blood flow, but that is not very elaborate, and it also assumes uniform exposure of the region of interest, and it ignores any local hot spots. So, that is something which we should consider while interpreting the thermal index. then we discuss the mechanical index you calculate the mechanical index by taking the derated peak negative or peak rare factional pressure at the region of interest and this derating is performed by considering a theoretical attenuation of soft tissue and you divide by square root of frequency and the units of pressure have to be in mega pascal the units of

frequency have to be in mega hertz then this gives you a number So, this number tells you what is the likelihood of getting inertial cavitation in your imaging region. Now, there are certain limits that are set.

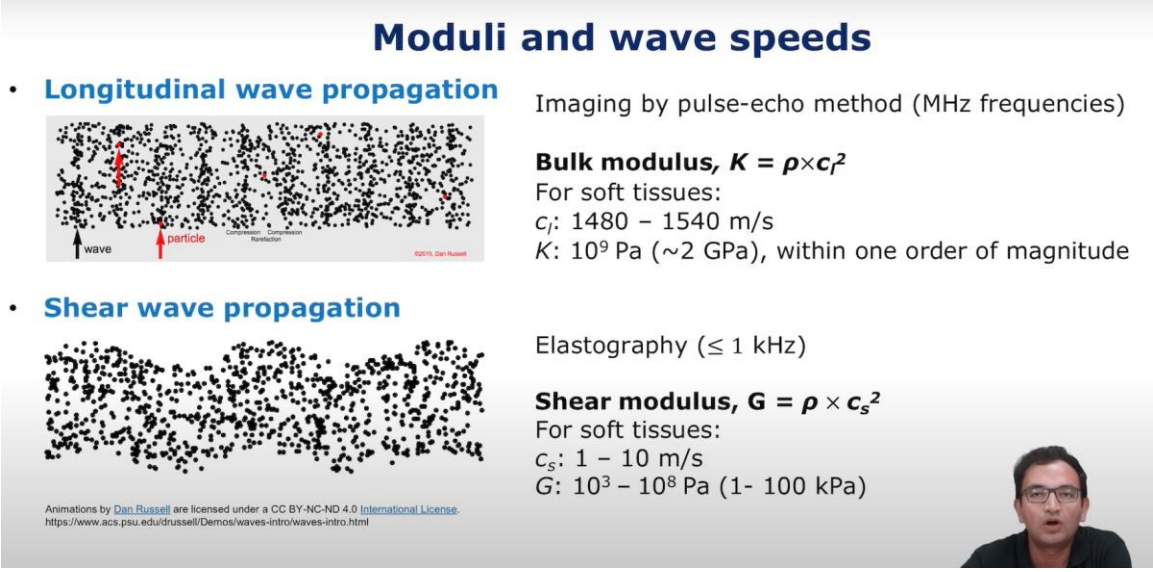
$$MI = \frac{Derated\ peak\ negative\ pressure\ [P\_](MPa)}{\sqrt{frequency\ [f](MHz)}}$$

So, for soft tissue, MI should be less than 1.9. For the eye, which is a very sensitive organ, the MI limit is even lower, 0.23. For lung, it is 0.7, because lung has air pockets, so there's high probability of cavitation-induced damage. And for contrast-enhanced imaging, also typically low MI is used. Then let's talk about tissue elastography imaging. In tissue elastography imaging, we try to non-invasively assess the tissue elastic parameters. It could be Young's modulus or shear modulus for example or in some cases surrogate matrix such as strain.

So here is an example of ultrasound elastography of papillary thyroid carcinoma, a malignant cancer where the elastogram shows you how this region, red actually shows higher stiffness in this color map. So how this region is stiffer relative to the background. But if you look in a simple B-mode image, you won't be able to really see whether this region is stiff or not. There is some contrast relative to the background. But it's very hard to differentiate that tumor, which you can do with tissue elastography imaging.

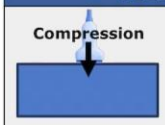
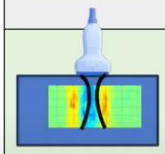


Let us discuss the types of wave propagation and how it is useful in elastography. If we look at the longitudinal wave propagation, then the speed of sound is similar for soft tissues. There is a certain range, but it does not vary much. Average of soft tissue propagation speeds is 1540 meters per second and the bulk modulus k which is determined as rho times longitudinal sound speed square is about 2 gigapascal for the soft tissues and it varies only within one order of magnitude. right so if you look at the differences within the soft tissue the variation is only within one order of magnitude therefore it may not be able to generate significant contrast you may have two different types of soft tissues but the elastic contrast may be limited when we perform imaging by exploiting the bulk modulus but it turns out if you look at shear wave propagation So, you can calculate the shear modulus as the density times the shear wave speed square.




So, if you remember longitudinal wave speed is high, but shear waves propagate in the human body with a range of speeds which ranges from 1 to 10 meter per second. And because of this the shear modulus can range from $10^3$ to $10^8$ Pascal which is almost 5 orders of magnitude. So, that is where you can get a lot of contrast because of shear wave elastography as opposed to using the longitudinal wave for elastic discrimination. So now if we assume certain simplifications, for example, we assume that the medium is isotropic, homogeneous, nearly incompressible, which amounts to a Poisson's ratio of 0.5. It is also an elastic medium. We ignore any viscoelasticity or hyperelasticity and those kind of constitutive relationships between stress and strain. Under this assumption we can relate the young's modulus E to the shear modulus. So, E is calculated as 3 times G. Now there are different elastography methods. There is a quasi-static method such as strain imaging where a very gentle deformation is applied, and the tissue is imaged, and the strain is calculated to assess the mechanical properties.

Then there are methods which require excitation where you may consider shear wave imaging where typically acoustic radiation force impulse is used to generate shear waves. or you may also have some mechanical shear wave generating devices or contraptions. Now, there are techniques which will just look at the shear wave speed at a point. They don't really calculate images. On the other hand, you also have techniques which lead to images.

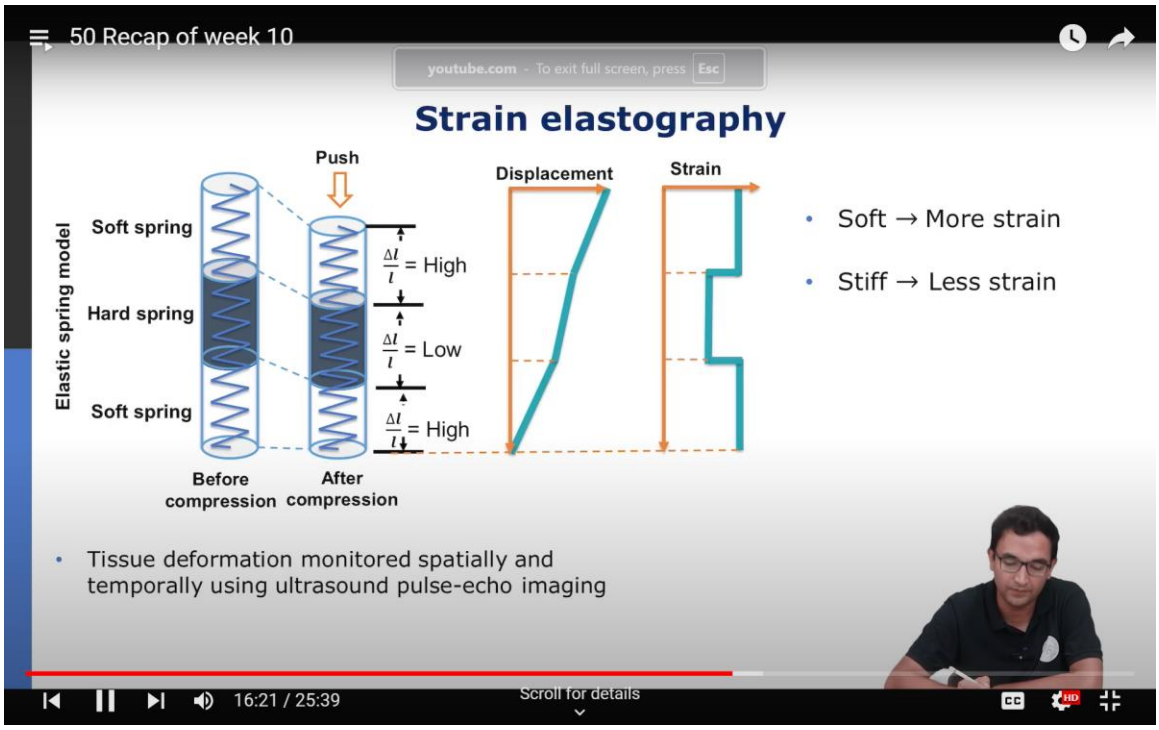
| Method | | Excitation Method | Technique | Measurements |
|---|---|---|---|---|
|   | Strain Imaging | - Manual compression<br>- Cardiovascular/ respiratory motion | Strain Elastography | ▪ Strain or Normalized Strain<br>▪ Geometric Measures<br>▪ Strain Ratio |
|  | Shear Wave Imaging | Acoustic Radiation Force Impulse (ARFI) | Point Shear Wave Speed Measurement<br>Shear Wave Speed Imaging | ▪ Shear Wave Speed (m/s)<br>▪ Young's Modulus (kPa) |

| Method | | Excitation Method | Technique | Measurements |
|---|---|---|---|---|
|   | Transient Elastography | External Mechanical Vibration (EMV) | Transient Elastography | ▪ Young's Modulus (kPa) |

So, they can provide parameters such as shear wave speed and Young's modulus which are related to tissue elasticity. Now there are other techniques such as transient elastography where there is a transient excitation, and the tissue response is measured. Typically, an external vibration system is used to generate that transient response and then the measurement that you can get is Young's modulus.

Now in strain elastography, we assume that tissue is composed of springs essentially, right. So, if you deform the tissue, it will provide resistance.

If you stretch the tissue, it will provide resistance. In that sense, the tissue is like a spring. So, if I have a spring, I have three springs here and I have a hard spring which is located between two soft springs. So now if I provide a deformation or a strain and I look at the displacement profile and I take the derivative you will have the same displacement for these top and bottom springs and you will have a different displacement in fact less displacement for this hard spring. So, if you take the derivative, you can see how you can clearly differentiate a change in the elastic modulus value between these locations.




So, this is called strain elastography. If a tissue is soft, it will undergo more strain. If a tissue is stiff, it will undergo lower strain. So, in strain elastography, tissue deformation is monitored spatially as well as temporally using ultrasound pulse echo imaging. So, here is an example of strain elastography. It is being used to evaluate invasive ductal carcinoma, which is a kind of breast cancer.

Now, the advantages of strain elastography are it's very simple and easy to use. High spatial resolution strain images can be created, and it also requires simpler hardware. It can give you single pixel deformations, very high sensitivity. But the challenge is, if you think about strain, strain is not a fundamental property of a material, right? Strain is something which will depend on the geometry, the boundary conditions etc. So, it's only under fixed stress that the strain is related to the stiffness properties.

But we cannot really calculate the stress distribution in vivo and therefore assuming that the stress distribution in vivo is known and is a constant is not always true which leads to artifacts. So, further strain imaging is qualitative, and it is difficult to perform quantitative comparison between different cases. Now there are some metrics which people have developed. It's not truly quantitative but there is something called normalized strain which is the strain divided by maximum amount of strain to compare at least do a first order comparison across days or across techniques. And here there are other geometric measures for example strain ratio which is the mean strain in the region of interest in the reference area divided by the mean strain in the lesion area or the region of interest.

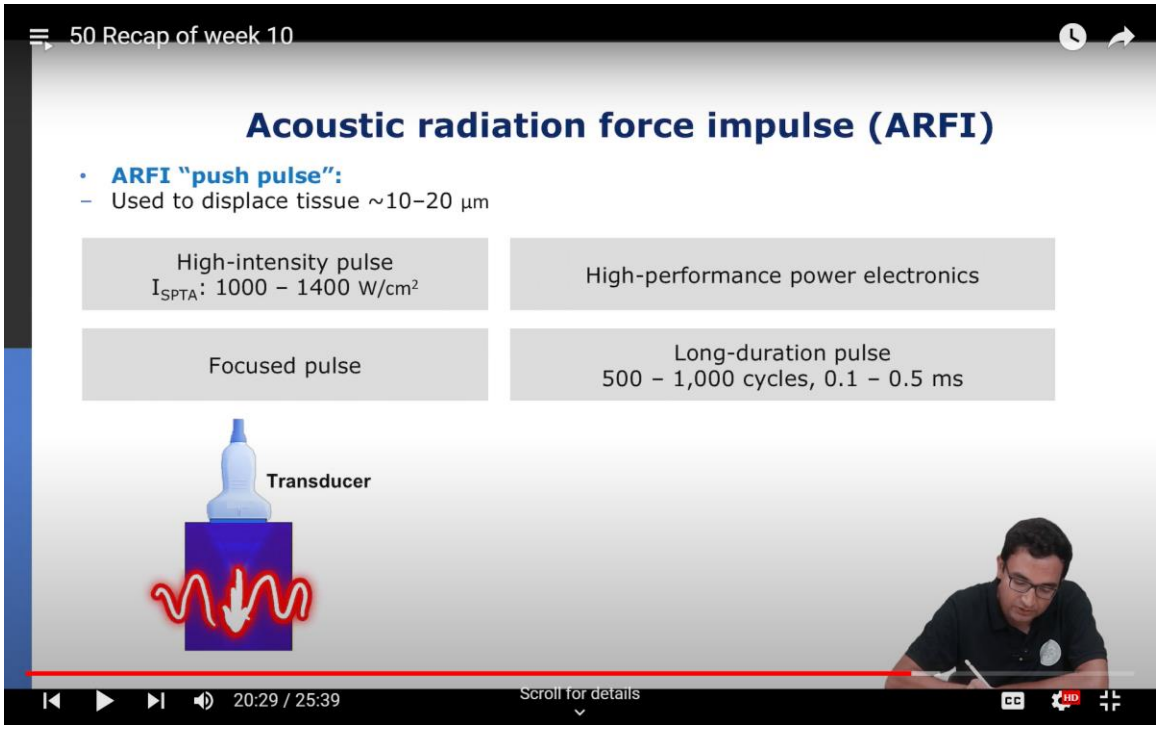
There is also E by B ratio which is the diameter of the lesion as visible in the strain image divided by the diameter of the lesion as visible in the B mode image. And it has been shown that there are some physical underpinnings of this because of which you are able to get diagnostic information from these metrics. But nonetheless, they have their own limitations.

$$SR = \frac{Mean\ strain\ B\ (reference\ area)}{Mean\ strain\ A\ (lesion\ area)}$$

Next, let's discuss shear wave elastography.

So, like I mentioned, this is the most exciting. Currently, it's being researched the most, and it's most in use, where you look at the shear modulus. And as I mentioned, the shear modulus can vary over five orders of magnitude in soft tissue. So, because of this variation, you take two different soft tissues, and you will have very different shear modulus. You can get good elastic contrast in the images. And the shear wave speed in the body varies from 1 to 10 meters per second.

Now, under certain assumptions which I defined earlier; you are able to get the Young's modulus also from the shear modulus. And typically, many scanners just show you the shear wave speed, which is a parameter which is related to the elastic properties of the tissues. So now for shear wave imaging, there are two ways of generating excitation. One is the acoustic radiation force impulse. You can send a slightly long duration ultrasound push pulse.

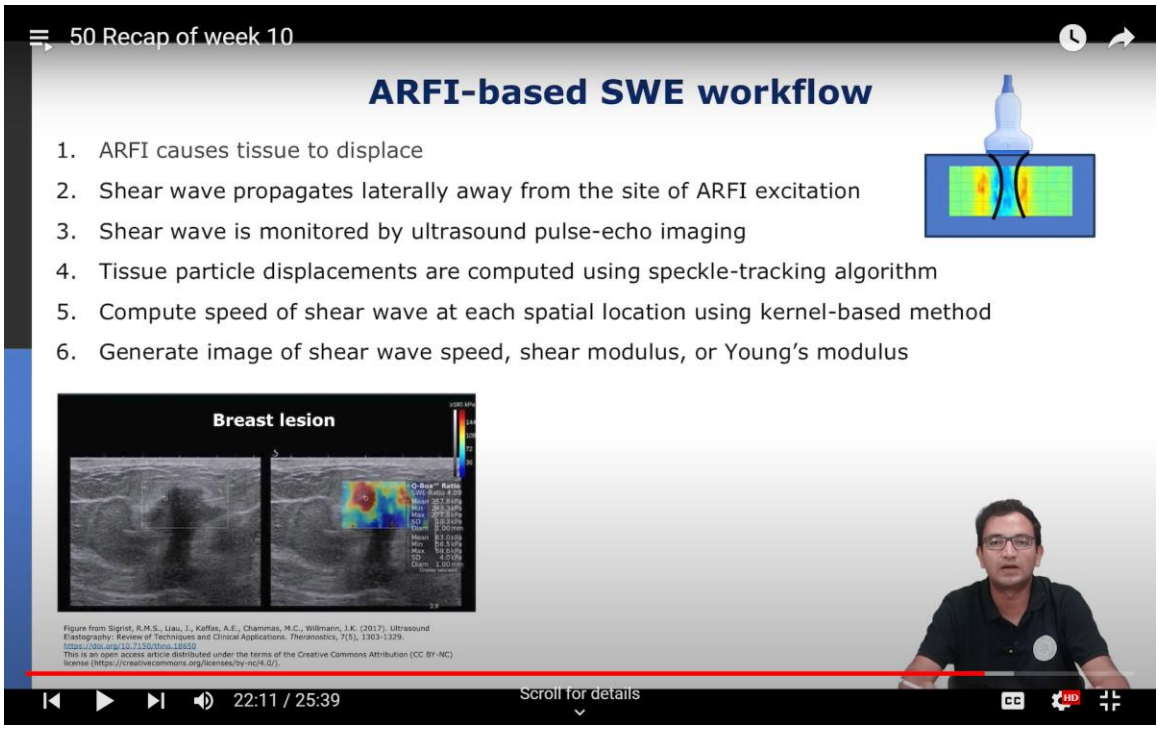


This pulse will cause absorption, and this absorption at the target of interest will displace the tissue. There is an impulsive displacement because this is a short pulse. and this pulse will generate displacements in tissue of the order of 10 to 20 micrometers in this direction right. Now this sudden displacement and then the relaxation will actually lead to shear wave generation in the perpendicular directions. Now, this pulse that is being used is of relatively high intensity 1000 to 1400 watt per centimeter square, but very low duty cycle is used.

So, you will not expect much temperature elevation because of this push pulse. Because this push pulse needs thousands of watts per centimeter square. So, your power electronic should be able to deliver this kind of intensity and therefore should be high performance. The beam is focused because when you focus the beam, your ability to cause the displacement increases. And here are the pulse parameters, 500 to 1000 cycles, which is 0.1 to 0.5 milliseconds. So even though there are large number of cycles, it's a short millisecond burst, which leads to this displacement. And it can be approximated as an impulse. So that's why we say acoustic radiation force impulse imaging. Now how do we get information from this shear wave imaging? First you cause the tissue to displace by applying the acoustic radiation force impulse.

Then laterally the shear wave flows. Then it is monitored. We tried to take snapshots of the propagating shear waves at different locations. And from that we try to figure out the speed of the shear wave propagation. and that you can do by computing tissue particle displacements using a speckle tracking algorithm in ultrasound. Speckle displacement is actually taken as a surrogate for the actual tissue’s displacement, and this is a good approximation.

From that you get the speed of the shear wave at each spatial location at each pixel essentially using kernel-based methods. And then you can generate an image of either the shear wave speed or the shear modulus or the Young's modulus under these approximations.




So here is a shear wave elastography image of a breast lesion and you see this hot spot that is related to a region of high stiffness which is actually a tumor. So, there are certain advantages and limitations of shear wave elastography.

The first thing is it is relatively speaking it's quantitative. It can give you parameters which have some quantitative significance. For example, the shear wave speeds, the shear modulus, Young's modulus, etc. It can also be used for imaging at several centimeters of depth. Depending on the frequency of choice, you can imagine up to a certain several centimeters in depth. Now there are some assumptions, this is obviously the first generation elastography had a lot of assumptions, you are assuming elastic medium, but the tissue is typically viscoelastic and there are other interesting behaviors also such as poroelasticity which we will not discuss in detail here, but again this is a simplifying assumption, we are assuming uniform properties in all directions, we are assuming incompressibility. So, by incompressible I mean if you deform it in one dimension, it will expand in the other dimension, the total volume remains unchanged. Then we are assuming homogeneity of the medium and also the system used for ARFI will require high end power electronics. Now this is still an active area of research. Researchers are looking at estimating parameters such as viscoelasticity and other elasticity parameters.

They also are looking at what happens when there is heterogeneity, right? There may be some boundary effects, etc., and how that influences the targets. Professor Karla Mercado-Shekhar's group has also done some work in this regard. And then how to evaluate anisotropic and heterogeneous tissues.

So, let's summarize what we discussed in this recap lecture. We discussed ultrasound bio-effects and safety, particularly the thermal index as well as the mechanical index. We discussed the different ultrasound elastography techniques, quasi-static techniques such as strain imaging, which give you information about the mechanical properties but is also affected by artifacts because of the assumptions. We discussed shear wave imaging wherein you get information such as shear wave speeds or shear modulus of tissue and it helps you generate good elastic contrast between soft tissues. We also discussed acoustic radiation force impulse and in the prior lecture we had discussed EMV or this is a mechanical way of generating the shear wave excitation.

You can go back to Professor Karla's lecture and recall this. And lastly, we discussed a few clinical applications and some examples. I hope this was useful for you to revise the material. I will end the lecture here now. See you in the next lecture.