Introduction to Liver Ultrasound Elastography

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## Conflict of Interest Disclosure

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<th>Company</th>
<th>Relationship</th>
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<tr>
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<td>Toshiba of America</td>
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“Any sufficiently advanced technology is indistinguishable from magic.”

Arthur C. Clarke
• **Elasticity**: a physical property which indicates tissue's ability to change shape in response to a force and recover its original form.

• **What’s a kPa?**
  - KiloPascal (1000 Pascals)
  - Pascal is a measure of pressure/stress defined as force (F) per unit area (A)
  - 1 Pascal = 1 Newton (N) per m²
  - We will be seeing “kPa” a lot in this talk 😊

Blaise Pascal (1623-1662)
French mathematician/physicist
Young’s Modulus

- Describes an object’s response to **linear stress** (compressive or tensile)
  - i.e. Weight on top of a column or pulling the ends of a wire
- Defined as ratio of stress to strain (in kPa)
- **US elastography**

\[
E = \frac{\text{Stress}}{\text{Strain}} = \frac{F/A}{\Delta L/L}
\]
One Last Formula . . . I Promise!

- Young’s modulus (kPa) = 
  
  \[ 3 \times \rho \times (\text{shear wave velocity})^2 \]

- For our purposes, \( \rho \) (density) of soft tissue equals that of water, which is 1

- So, Young’s modulus = 3 x SWV\(^2\)
Definitions

- So how can we image elasticity?!
- **Elastography**: a non-invasive measurement of tissue elasticity
  - US elastography
  - MR elastography
- Both use essentially same basic principles
  - Mechanical stress of targeted tissue by either external or internal forces
  - Measure tissue movement/wave propagation speed induced
  - Qualitative or quantitative evaluation of tissue elastic properties from the measured displacement of tissues
  - Faster wave propagation = stiffer tissue
Q: Why all the fuss about elastography in Children?

A: For the most part, it’s all about obesity and predicting/surveilling liver fibrosis without biopsy.
Wide spectrum of disorders

- Biliary atresia
- Familial intrahepatic cholestasis syndromes
- Alagille syndrome
- Metabolic syndromes (e.g., glycogen storage)
- Veno-occlusive disease
- Cardiac causes
- Hemochromatosis
- Autoimmune hepatitis
- α1-antitrypsin
- PSC
- Wilson disease
- Drug-induced hepatitis
- Viral hepatitis
- Cystic fibrosis
- NAFLD/NASH
Pediatric Chronic Liver Disease/Fibrosis

- Non-alcoholic fatty liver disease/Nonalcoholic steatohepatitis (NAFLD/NASH)
  - ~6 million children in U.S. and rising \(^1\)
  - 2.6 – 9.8% prevalence in children/adolescents, with increased risk in presence of obesity \(^2\)
  - NASH affects ~25% of NAFLD patients, of which ~20% progress to severe fibrosis/cirrhosis (sometimes rapidly)
  - Simple steatosis has a relatively benign prognosis, NASH with or without fibrosis does not
  - Therefore, differentiation important for prognosis and management

### Pediatric Obesity (USA)

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI Cut-off</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Overweight</td>
<td>BMI &gt; 85%</td>
<td>&gt;25 kg/m²</td>
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<tr>
<td>Obese</td>
<td>BMI &gt; 95%</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>Severely Obese</td>
<td>BMI &gt; 120%</td>
<td>&gt;35 kg/m²</td>
</tr>
<tr>
<td>Extremely Obese</td>
<td>BMI &gt; 140%</td>
<td>&gt;40 kg/m²</td>
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Prevalence

Skinner AC, Skelton JA. *JAMA Pediatr* 2014;168(5):561-6
NAFLD Spectrum

Simple steatosis: up to 10% of children

Steatohepatitis (NASH): 2-3% of children

1 in 5 may progress to severe fibrosis / cirrhosis

HCC & Portal Hypertension

ELASTOGRAPHY

Adapted from an AGA educational slide
Liver Fibrosis Pathophysiology

- Excess deposition of extracellular matrix macromolecules
- Response to repetitive liver injury (“wound healing”)
- Activation of hepatic stellate cells, the central event in fibrogenesis
- Fibrosis a dynamic process with potential for regression
- Fibrosis is very heterogeneously distributed throughout the liver
- **Fibrotic tissue is stiffer**
  - Stiffness can be imaged and quantified

Diagnosis of Liver Fibrosis

- Diagnosis, surveillance and therapeutic monitoring of fibrogenesis important
- Presence of fibrosis the most important prognostic factor determining disease progression and complications
- Early identification may allow treatment of causative underlying disease and potential regression of fibrosis
- Novel antifibrotic agents in development
  - Noninvasive techniques for assessment and quantification of liver fibrosis are critical for clinical surveillance and validation

Diagnosis of Liver Fibrosis

• Currently, liver biopsy the “gold” standard
  – However, it’s an imperfect “gold” standard

• Painful
• High cost
• Complications in up to 6% (up to 0.1% life threatening) ¹
• Sampling error ~15-25% (only ~1/50,000th of liver mass obtained)
• Sedation/general anesthesia
• Typically 24° inpatient observation

• Variability between pathologists depending on biopsy length, fibrosis stage, and experience ²
• Substantial variability in staging of fibrosis (discordance in up to 33% of cases) ³
• ~20% of specimens understaged ⁴
• No validated histological scoring systems for liver fibrosis in children

US Elastography
US Elastography

Static/Manual/Strain Elastography

- Siemens
- GE
- Philips
- Toshiba
- Hitachi

Transient Elastography

- Echosens (FibroScan)

Acoustic Radiation Force Impulse

- Siemens
- Philips
- Toshiba
- GE

Shear Wave Imaging/Supersonic Shear Imaging

- SuperSonic Imagine

“Real Time Elastography”

- Hitachi

Fibroscan
In 2002, Yeh et al found that using ultrasound elastography, liver stiffness positively correlated with liver fibrosis.\(^1\)

Healthy livers less stiff and allow greater internal displacement with increased pressure compared with cirrhotic, stiffer livers.

Technology first used by the cheese industry to evaluate internal stiffness of different cheeses!

FibroScan (Echosens) first to apply ultrasound elastography technology clinically.
FDA approved for use in adults, but not in children

50 Hz wave generated by small vibrator applied to chest wall at level of right hepatic lobe through intercostal space

Needs at least 6 cm thick tissue and no large vascular structures
  ~1 x 4 cm cylinder of tissue interrogated

Pulse-echo ultrasound allows measurement of wave velocity through liver
  M-Mode only → NO IMAGE

Wave velocity proportional to stiffness
  Young’s modulus (kPa)
  Faster the wave speed, stiffer the tissue
Several probe sizes available

- **S:**
  - S1: depth of measurement 15-40 mm, thoracic perimeter <45 cm (children)
  - S2: depth of measurement 20–50 mm, thoracic perimeter 45-75 cm (children)

- **M:** depth of measurement 25-65 mm, thoracic perimeter > 75 cm

- **XL:** depth of measurement 35 – 75 mm, uses 2.5Hz probe (others all 5Hz). Intended for use in BMI > 25 kg/m²

- Only M and XL available clinically in U.S.

- Probe choice significantly affects stiffness measurement

Software determines if measurement is successful/reliable

- 10 “valid” shots (“valid” = a value is obtained)

- Ratio of “valid” to total # of shots > 60%

- Variability of measurement (ICC) < 30% of median value

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1 Goldschmidt I, et al. JPGN 2013;57:109-113
Transient Elastography (FibroScan)
Transient Elastography ( FibroScan )

- **Limitations**
  - Poor performance in very obese patients
  - Not accurate when ascites present
  - In children, small intercostal space a problem without S probes
  - Only right lobe can be sampled

- **Advantages**
  - Quick
  - “Cheap” to buy, relatively “cheap” to perform (list price $125k)
  - Excellent reproducibility
  - Painless
  - Samples liver area ~100x that of a biopsy

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1 Cohen EB, Afdhal NH. *J Clin Gastroenterol* 2010;44:637-645
FibroScan: Performance Results in Children

- High interobserver agreement (~96%) \(^1\)
- Failure rates ~4-7%; unreliable rates ~15% \(^1-4\)
  - Increased with smaller age (<24 months) and increased BMI \(^5\)
- Normal mean liver stiffness = 4.5-4.7 kPa (upper limit normal = 6.5 kPa) \(^3,5\)
- Optimal cutoff for significant fibrosis 6.9 – 8.6 kPa \(^1,2\)
- Optimal cutoff for cirrhosis 12.5 kPa \(^2\)

\(^2\) Fitzpatrick E, et al. *JPGN* 2013;56:72-76
ARFI: Acoustic Radiation Force Impulse (Siemens, Philips, GE and Toshiba)

- Reference B-mode imaged obtained
- US probe emits an acoustic push-pulse (0.26 ms) at 2.67 MHz
- Localized tissue displacement occurs resulting in shear-waves propagating perpendicular to push-pulse
- Shear waves travel at ~1-10 m/s, slow enough to sample by separate detection waves
- SWV displayed on screen
- FDA would not allow kPa displayed on screen for some vendors (in Europe, it’s allowed)
Siemens ARFI

• 2 methods now FDA approved in children and adults

• Virtual Touch Quantification (VTQ)
  – Predefined 10x5 mm ROI box, right intercostal approach, 1-2 cm deep to liver capsule, mean of 10 SWV measurements recommended during breath-hold

• Virtual Touch IQ (VTIQ)
  – User defined box demonstrates relative SWVs in interrogated area in different colors; ROIs can then be placed inside box
Siemens ARFI

Images courtesy of Dr. Jonathan Dillman, Cincinnati Children’s Hospital Med Ctr
Philips ARFI

• FDA approved in children and adults – ElastPQ
  – However, FDA required depiction of correction factors based on depth from liver capsule

• Same basic mechanism of action and methods of acquisition as Siemens VTQ
Philips ARFI

12 yo with PSC. Note heterogeneity of SWVs and liver stiffness

Normal 19 year old
Toshiba ARFI
Toshiba ARFI
GE ARFI

Images Courtesy of Jeni Pearson, GE
ARFI: Acoustic Radiation Force Impulse

• Limitations
  – Still limited in obese patients, but better than TE
  – Variability between vendors
  – Variability of measurement at different depths
  – Small volume of liver interrogated
  – kPa not depicted (in U.S.)

• Advantages
  – SWV provided with a gray-scale ultrasound image
  – Not affected by ascites
  – Push-pulse focused at region of interest
  – Good reproducibility
  – Portable
  – Quick
ARFI: Performance Results in Pediatric Livers

- Good reliability (ICC 0.77) \(^1\)
- ~5% failure rate \(^1\)
- Mean normal SWV between 1.12 and 1.19 m/s (range 0.73 – 1.45 m/s) \(^1,2\)
- Optimal cutoff for significant fibrosis = 1.34 – 1.39 m/s (85% sens/82% spec; AUC 0.83) \(^3,4\)
- Optimal cutoff for cirrhosis = 2.25 m/s (AUC 0.98) \(^3\)

ARFI: Other Uses

- Accurate prediction of biliary atresia in liver disease in neonates
- Accurate prediction of severity of liver fibrosis in infants with biliary atresia after Kasai
- Accurate prediction of need for transplantation after Kasai
  - Two consecutive ARFI measurement > 2 m/s

Shear Wave Elastography (SSI)

- Acoustic radiation force pulses generated by transient ultrasound waves
- Localized tissue perturbation at multiple tissue depths occurs resulting in shear-waves propagating perpendicular to push-pulse
- Raw radiofrequency data resulting from small tissue displacements captured at super fast frame rates (~5,000-10,000/sec; 100x faster than typical US frame rates)
- Using Doppler techniques, SWV captured
Shear Wave Elastography: Supersonic Imagine

- FDA approved in children and adults
- User adjustable color box (up to 3x3 cm) placed 2-6 cm deep to capsule during breath-hold from right intercostal approach
- 10 mm² circular ROI placed in box
- Stiffness in kPa displayed
Shear Wave Elastography (SSI)

- Limitations
  - Limited in obese patients, worse than ARFI but better than TE
  - Variability of measurement at different depths
  - Small volume of liver interrogated

- Advantages
  - Stiffness provided with a gray-scale ultrasound image
  - Not affected by ascites
  - Portable
  - Quick
  - Excellent interobserver agreement
SSI: Performance in Liver

1. In adults, 29% failure rate, 60% in patient with BMI > 30kg/m$^2$  
2. Excellent interobserver agreement (ICC = 0.95)  
3. Normal liver stiffness in adults = 4.4±0.9kPa (range 2.6-6.2kPa)  
4. Optimal cutoff for significant fibrosis in adults = 7.1 kPa (90% sens/70% spec; AUC 0.92)  
5. Optimal cutoff for any fibrosis in children = 10.6 kPa (92% sens/94% spec; AUC 0.95)  

Teenager with normal liver stiffness

Teenager with NAFLD and severe liver fibrosis
## Ultrasound Elastography Cutoffs in Children

*Be very cautious*

<table>
<thead>
<tr>
<th>Fibrosis staging</th>
<th>TE (KPa)</th>
<th>ARFI (m/s)</th>
<th>2D-SWE (KPa)</th>
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<tbody>
<tr>
<td>F0</td>
<td>2.5-5.9</td>
<td>0-1.19</td>
<td>0-7.39</td>
</tr>
<tr>
<td>F1</td>
<td>6-7.19</td>
<td>1.2-1.39</td>
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</tr>
<tr>
<td>F2</td>
<td>7.2-9.59</td>
<td>1.4-1.59</td>
<td>7.4-8.69</td>
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<tr>
<td>F3</td>
<td>9.6-14.49</td>
<td>1.6-1.99</td>
<td>8.7-9.19</td>
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<tr>
<td>F4</td>
<td>&gt;14.5</td>
<td>&gt;2</td>
<td>&gt;9.2</td>
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First systematic review of pediatric literature

27 studies

Ultrasound elastography able to diagnose cirrhosis, distinguish healthy from fibrotic liver, and showed consistent liver stiffness values in children without liver disease (<1.19 m/s, < 5.6-6.5 kPa)
General Issues with US Elastography

- Vendors urge 10 measurements in same spot to reduce variability in measurements, but this is “cheating”
- Different estimates of shear wave speed in same liver obtained with different measurement systems at different depths
- Differences cause confusion, inability to easily compare different techniques/vendors, and lack of technology adoption
- Providing common SWV estimate among systems, validated on same standardized phantoms, would make technology more clinically viable
- Thankfully, there’s a group of very smart people in industry and radiology working on this
  - RSNA/QIBA SWS (shear wave speed) Committee
QIBA Technical Committee for Shear Wave Speed (SWS) Measurement

Claude Cohen-Addie, MS, Brian Garra, MD, Timothy J. Hail, PhD, Andrew Milkowski, MS, Mark Palmeri, MD, PhD,
David Cosgrove, MD, Anthony Samir, MD, Keith Wear, PhD, Paul Carson, PhD, Daniel C. Sullivan, MD

Purpose of the Group:
To create and support implementation of a QIBA Profile for Shear Wave Speed for a quantitative biomarker in ultrasound imaging.

The characterization of a disease with any medical device relies on a three-part relationship among the pathology, tissue properties, and medical device as a means to estimate the physical property and corresponding pathology.

The QIBA Technical Committee for SWS is divided into three subcommittees to evaluate the interactions between pathology, tissue physical properties, and ultrasound instrumentation in order to create the QIBA Profile.

Clinical Applications and Biological Targets Subcommittee

General Charge:
• Determine how SWS may be used in clinical practice for what types of pathology
• Determine confounding parameters

Dependencies or potential Confounding factors:
• Anatomy
• Physiology
• Exam Conditions
• Patient’s Conditions
• Measurement protocol
• Operator Dependence / Experience

Phantom Development Subcommittee

General Charge:
• Determine the appropriate ultrasound elastography phantom material properties and phantom design needed to adequately assess SWS measurement performance
• Develop/Test/Select ultrasound phantoms

Dependencies:
Phantom materials
Phantom structure/architecture

Medical Device

General Charge:
• Establish a set of standards to allow for comparison of SWS across vendors
• Evaluate system dependencies

Dependences:
• SW frequency content
• SW reconstruction artifacts
• Displacement / Velocity imaging algorithm
• Measurement protocol
• Operator Dependence / Experience

Outcomes

QIBA Profile Components
Specific claims of what can be accomplished
Details: What procedures and system settings are necessary for the claims to be achieved. A device following all procedures and using proper system parameters is said to comply with Profile.

QIBA/UPICT (Uniform Protocols for Imaging in Clinical Trials) is a consensus-derived process used to facilitate the development and maintenance of widely acceptable, consistent imaging protocols (including imaging quality control procedures) for use in clinical trials across a range of disease states, anatomic sites, and imaging modalities. QIBA/Protocols adheres to this standardized structure, whenever possible.

System Dependencies Subcommittee

Frequency range of the shear wave measurements provided by manufacturers

Do pathology changes result in changes to physical properties of tissue?

Ultrasound measurements can be used to infer the pathological state of the tissue being examined

Altered physical characteristics produce changes that are measurable using ultrasound devices

Pathology

Physical Characteristics

Nemours.

qibawiki.rsna.org/images/8/83/QIBA_2012_Ultrasound_SWS_QIBA_RSNA.pdf
Recent food intake increases liver stiffness by ~30% 1,2

- Related to alterations in portal and hepatic arterial blood flow
- Patients should be NPO for at least 2, preferably 4 hours

Anesthesia increases liver stiffness 3

- Likely secondary to increased blood flow to liver from agents such as propofol

“It is the duty of everyone in the world to do what is within his power to alleviate human suffering.”

Alfred I. duPont

THANK YOU

Questions/Comments?
daniel.podberesky@nemours.org
SAM Questions