Editorial

The Emergence of Elastography for Cystic Fibrosis Liver Disease

Current recommendations [1,2] for screening of cystic fibrosis liver disease (CFLD) in people with cystic fibrosis (CF) include liver biochemistries, complete blood count and abdominal ultrasound to detect evidence of chronic hepatic inflammation and sequelae of cirrhosis, all of which have limited sensitivity and specificity [1,3]. In this issue of JCF, a longitudinal assessment for CFLD at two centers identified a prevalence of 8.8% by the age of 18 years [4]. Although elevated liver enzymes were associated with eventual CFLD, they were not predictive for development of disease, suggesting a need for alternative methods of diagnosing CFLD. Novel imaging methods have been proposed to improve upon our detection of clinically meaningful liver disease. Recently, a multicenter study of gray-scale research ultrasound found that heterogeneity of liver parenchyma (vs normal) was associated with a subsequent 9-fold increased incidence of developing a nodular pattern over four years [5], which may reflect a cirrhotic or advanced precirrhotic state. While nodularity on imaging may predict advanced liver disease in the hepatology field generally, these findings have not yet been fully elucidated in people with CF. In addition, there is emerging evidence that advanced CFLD with portal hypertension has a non-cirrhotic etiology as well [6-8]. Studies of liver explants and biopsies in children and adults have shown that oblitative portal venopathy and nodular regenerative hyperplasia represent an important pathophysiology of CFLD [6]. The assessment of disease progression prior to the development of portal hypertension in CFLD is challenging and has historically relied on invasive liver biopsy, but a single liver core biopsy typically represents only about 1/50,000 of the liver volume and with a patchy heterogeneous disease such as occurs in CFLD, sampling bias is a common problem [9,10].

Approaches to assessment of liver fibrosis using various imaging methods have grown and become rapidly innovative recently. Elastography is a technique that measures tissue deformation secondary to external stress applied using a probe. Elastography allows measurement of tissue stiffness reflective of the underlying pathology affecting tissue composition and can be measured by either ultrasound (USE) or magnetic resonance (MRE). In the resulting images, the least deformed regions are the stiffest, while the most deformed regions are the softest. With dynamic shear wave techniques, quantitative stiffness is assessed by tracking shear wave propagation through the liver, with stiffness values calculated by measuring shear wave velocity [11]. This technique is increasingly used to detect and stage hepatic fibrosis in the setting of diffuse liver disease. Ultrasound-based approaches include: transient elastography (TE), point shear wave elastography (SWE), and 2D SWE and all have been applied to relatively small cohorts of people with CF often in single center studies. Dynamic USE has two main approaches that are well established in the clinical practice. They are transient elastography (TE) using an extrinsic vibrating source at 40–50 Hz and shear wave elastography (SWE) using an acoustic radiation force at 100–500 Hz [11]. TE has the unique advantage as a point of care test that may be performed within clinic that is highly reproducible to measure liver stiffness in a short period of time (often <10 min). As a result, the cost of TE is much lower. The most commonly used device in current practice is Fibroscan™. SWE provides a full dimensional image-based approach compared to TE, which provides only a 2-D image without capability of capturing an anatomical image. Neither are ideal in morbidly obese patients or those with ascites, though impact on reproducibility appears to affect TE more [14]. With SWE, the operator can visualize the interrogated region in detail (e.g. evaluate texture of the liver, exclude masses, evaluate patency of large blood vessels and bile ducts) while conducting elastographic measurements, thus ensuring the proper position. SWE allows assessment of size and contour of the liver, detection of hypertrophy of the caudate lobe associated with advanced fibrosis and ability to detect and monitor focal lesions such as hepatocellular carcinoma or regenerative nodules. While TE may not provide as much anatomic information as SWE, it offers a standardized platform with universal threshold values for liver stiffness, whereas SWE measures may vary by vendor (using different shear wave frequencies) and must be interpreted accordingly [12]. SWE can be inherently limited due to its operator dependence; however, recent literature shows SWE techniques to have excellent reproducibility [12-15].

In a study published in this issue of JCF, SWE-determined LSM showed good diagnostic accuracy (AUC 0.79) in detecting CFLD in children comparing CF patients with and without CFLD (diagnosed according to guidelines) and healthy controls [16]. The accuracy improved (AUC 0.84) when combined with aspartate aminotransferase-to-platelet ratio index (APRI). Using a greater threshold LSM, SWE accurately discriminated advanced CFLD (AUC 0.95). These data complement another study of TE used in 160 consecutive children with CF and concluded that this modality showed an AUC of 0.87, using a cut-off value of 8.7 kPa (75% sensitivity and 100% specificity) to detect bridging fibrosis and/or cirrhosis (Metavir fibrosis stage F3-F4) [17]. TE technology also has the capability to quantify liver fat or steatosis using controlled attenuation parameter (CAP). Work by Bader et al. in adolescent and young adult patients with CF did not find that degree of steatosis associated with clinical markers of liver disease, however they
Table 1

<table>
<thead>
<tr>
<th>Transient Elastography</th>
<th>Shearwave Elastography</th>
<th>MR Elastography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technically easy and relatively fast with good reproducibility, performed in clinic</td>
<td>Technically easy with good reproducibility, performed by sonographer</td>
<td>Standardized technique across magnet strengths and vendor specific machines, performed by technician and radiologist</td>
</tr>
<tr>
<td>Can be performed in younger patients and at the bedside without sedation</td>
<td>Can be performed in younger patients and at the bedside without sedation</td>
<td>Breath-holding required for MR Elastography sequence, hence may need sedation in younger patients</td>
</tr>
<tr>
<td>Abundant literature specific to pediatric CFLD, validated technique in pediatrics</td>
<td>Emerging literature for diagnosing and staging hepatic fibrosis in CFLD</td>
<td>Normative data and cut-off values specific to CF not yet available, but being studied</td>
</tr>
<tr>
<td>Limited performance in obese patients and those with ascites</td>
<td>Limited performance in obese patients and those with ascites</td>
<td>Easily performed in obese patients and those with ascites</td>
</tr>
<tr>
<td>Lacks full 2-D imaging, thus provides no anatomical information. However, can capture fat fraction</td>
<td>Displayed in real-time, 2-D ultrasound which allows for evaluation of anatomy, vasculature, and steatosis</td>
<td>Post-processing on elastograms is performed at each slice level, providing a global assessment of the liver</td>
</tr>
<tr>
<td>A 50-MHz wave is passed into the liver from a small transducer on the end of an ultrasound probe. Manual compression responsible for some operator dependence</td>
<td>Shear waves are generated using acoustic radiation force. Manual compression responsible for some operator dependence</td>
<td>The low frequency waves are generated by a mechanical drum placed over the abdominal wall overlying the liver</td>
</tr>
</tbody>
</table>

Interestingly report higher CAP in those with CFLD (n = 44), but not in those with evidence of cirrhosis and portal hypertension (n = 15), suggesting that steatosis may be replaced with fibrosis in more advanced CFLD [18]. While informative, small studies such as these need validation in larger prospective studies.

MRE is a phase-contrast based method that utilizes low frequency (60 Hz) mechanical waves to indirectly assess stiffness of the entire liver. A passive driver is secured to the chest/forehead abdominal wall over the liver of the patient during the exam. As the mechanical waves enter the liver, their wavelength changes in response to the underlying tissue stiffness [19]. Subsequently, in post-processing, a stiffness heat map (warmer colors reflect increasing stiffness) of the liver, referred to as an elastogram, is generated [20,21]. MRE and USE each have their advantages (Table 1). MRE acquisition is a two-dimensional algorithm wherein four axial slices are acquired during a breathhold of 20-30 seconds (Fig. 1), although free breathing versions should become available soon. Three-dimensional MRE acquisition is being investigated, which will allow assessment of the entire liver volume, as opposed to just four cross-sectional slices and may help identify the pattern of fibrosis in CFLD that can be quite heterogeneous. It is important to understand that USE and MRE data on liver stiffness measurements (LSM) cannot be extrapolated to one another, since the physics and frequencies captured are distinct for each modality [22].

Early experience with MRE has shown that the technique is both feasible and robust in pediatric patients when utilizing 2-D gradient-recalled echo MRE [23]. There are emerging data on threshold values for hepatic stiffness in pediatric patients without liver disease, with a recent paper reporting higher LSM in healthy children compared to healthy adults [24]. Mean hepatic stiffness value for their study population (81 children, 8-17 years) was significantly greater than reported values for healthy adult subjects. Although the current literature on MRE in pediatric CFLD is sparse, a recent article reported elevated LSM on all four pediatric patients with documented CFLD who underwent MRE. One patient with splenomegaly and portal hypertension had the highest LSM [20].

While many studies that demonstrate increasing liver stiffness (albeit TE or SWE) with liver fibrosis severity validated by liver biopsies, it should be acknowledged that liver stiffness can be confounded by venous congestion, inflammation, steatosis, and a non-fasting state [11,25]. Importantly, portal hypertension in CFLD, the most severe form, may be secondary to multilobar cirrhosis [2,8] or non-cirrhotic etiologies such as obliterator portal venopathy and nodular regenerative hyperplasia (NRH) [6,26]. NRH resembles cirrhosis radiologically, so differentiating the two by liver biopsy and/or elastography may influence management in regard to therapeutic options such as liver transplant or portosystemic shunts [26,27]. TE and MRE are being studied in CF multi-center studies (ELASTIC-CF, NCT03001388 and CFLD MRE, NCT02979340) in hopes of better understanding the utility and interpretation of liver stiffness in CFLD. Elastography offers another tool that can be
References


