ADVANCES IN ENDOSCOPY

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Endoscopic Ultrasound–Guided Portosystemic Pressure Gradient and Endo-Hepatology

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G&H What defines portal hypertension, and why can it develop in patients with cirrhosis?

KC Portal hypertension reflects the gradient of blood pressure between vessels coming in and out of the liver. The portal vein enters the liver, and the hepatic vein leaves it. Each of these veins has a pressure, and the gradient is the difference between the two. Normal blood pressure gradient is anything less than 5 mm Hg. A gradient above 5 mm Hg defines portal hypertension.

Many factors can cause portal hypertension. The most common is cirrhosis, and most of the time, portal hypertension is a complication of liver cirrhosis. Other causes include posthepatic obstruction to blood flow (right-sided heart failure, hepatic vein thrombosis) and prehepatic obstruction to blood flow (schistosomiasis, idiopathic noncirrhotic portal hypertension, portal vein thrombosis).

G&H What are the consequences of untreated portal hypertension?

KC The dilation of vessels in the portal vein system results in esophageal and gastric varices. Engorged vessels can rupture and bleed, with the potential to cause severe bleeding that can result in shock and death. As mentioned, the typical scenario is that of a person with liver cirrhosis. Portal hypertension develops, followed by varices. Varices rupture, and the afflicted person starts vomiting blood and ends up in the emergency room.

The other complication of portal hypertension is ascites because the liver is under such pressure that it cannot absorb the fluid in the abdomen. Encephalopathy and change in mental status also can develop because of toxin accumulation.

G&H How was portal venous pressure assessed before the introduction of endoscopic ultrasound–guided technology?

KC Portal venous pressure was determined indirectly via measurement of the hepatic vein pressure. The most common method of calculating this pressure is by measuring the transjugular hepatic venous pressure gradient (HVPG). To perform this procedure, an interventional radiologist makes an incision and places a catheter into the internal jugular vein and passes it down to the superior vena cava and the inferior vena cava, and then continues into 1 of the 3 branches of the hepatic vein—usually the right hepatic vein—to measure its pressure (ie, free hepatic vein pressure). A further step is added to indirectly measure the portal vein pressure, which cannot be measured directly because it is not accessible through the skin but, rather, only via the intestinal tract. With the catheter in place in the hepatic vein, the interventional radiologist inflates a balloon on the catheter tip and

performs a wedged hepatic vein pressure measurement, which assesses the pressure inside the sinusoids. The sinusoids eventually connect to the portal vein; therefore, the wedged hepatic vein pressure indirectly reflects the portal vein pressure.

The HVPG has been the gold standard for diagnosing portal hypertension, but it is not perfect. It is a fairly invasive procedure and is undergone by only a small proportion of patients with conditions associated with portal hypertension. Additionally, almost no patients undergo HVPG in a serial fashion, such as once a year, to assess liver health and the effectiveness of medication. The relative inaccessibility of this tool leaves an important unmet need for diagnosis and disease monitoring, considering the worldwide morbidity and mortality caused by liver disease, cirrhosis, and liver cancer. Endoscopic ultrasound (EUS)-guided portosystemic pressure gradient (PPG) and the new field of endo-hepatology fill this gap.

G&H What led to the breakthrough of EUS-guided vascular catheterization in the assessment of portal venous pressure?

KC EUS has been used since the 1980s, providing access to key organs, such as the pancreas, liver, and gallbladder, via the gastrointestinal tract. Compared with the pancreas, the liver has been relatively neglected by endosonographers. EUS makes it possible to identify and assess flow in all of the vessels in and around the liver. I began to think about leveraging this technology to directly measure portal venous pressure. My team began conducting proof-of-concept studies in animals. In exploring technologies that would be compatible with an endoscope and needle, we examined transducers mounted to the tip of a very long guidewire. The guidewire could be passed through a needle and placed in a vessel, allowing for pressure measurement.

Thus, we knew that it was possible to visualize the vessels using EUS, pass a needle tip into the vessels via the fine-needle aspiration (FNA) technique, and measure the pressure via the wired transducer, but the technique needed to be refined. The transducer-tipped guidewire was very delicate; the tip could easily sheer off. In addition, it was expensive. We theorized that by attaching a manometer to the needle and filling the needle with fluid such as saline, we could potentially obtain measurements of hepatic and portal vein pressures.

From Cook Medical's division of reproductive health, we were able to acquire several manometers that were used for in vitro fertilization. This technique proved to be successful in our animal studies. We were able to capture pressures with a 19-gauge needle, which is the largest gauge for FNA, and then decided to explore whether it was possible to use a smaller needle. We went from 19- to 22-gauge and then from 22-gauge to 25-gauge. The 25-gauge needle worked as well as the other sizes, and we thought that it would be the safest for puncturing vessels to measure venous pressure.

We developed an animal model of portal hypertension, and had consistent successful results, which were published in 2016 in *Gastrointestinal Endoscopy*. We went on to launch a pilot human study that included 28 patients between the ages of 18 and 75 years who had a history of liver disease or suspected cirrhosis. We used a linear endoscope, a 25-gauge FNA needle, heparinized saline, and a compact manometer with noncompressible tubing that had a digital readout.

We had complete (100%) technical success and no adverse events. The portal pressure gradient ranged from 1.5 to 19 mm Hg and had statistically significant ($P<.05$ or stronger) correlation with clinical parameters of portal hypertension, including the presence of varices, portal hypertension–associated gastropathy, and thrombocytopenia. In most of the patients, EUS-guided liver biopsies were performed during the procedure as well, demonstrating that combining a portal pressure gradient measurement and liver biopsy in the same session was safe. Results of the study were published in 2017 and 2018 in *Gastrointestinal Endoscopy* and *VideoGIE*, respectively. Other studies and meeting presentations followed, with enthusiasm in the specialty for this new technology.

G&H Is the technology currently available, and is special training needed to use it?

KC The device, known as EchoTip Insight (Cook Medical), was approved by the US Food and Drug Administration in January 2020. A postmarketing multicenter, multinational study is now underway.

EUS-PPG can be performed quickly and safely by any endosonographer, making it more accessible for patients. They no longer need to be referred to specific interventional radiology centers, which may be difficult to find in some parts of the country and world.

The patient is positioned supine, and the manometer is placed at the patient's midaxillary line. The hepatic venous pressure is measured first, with the middle hepatic vein being the most common site because of its larger size and proper alignment with the trajectory of the needle. The needle is flushed with saline or heparinized saline, which equilibrates within a closed system between the manometer and the blood vessel. The measurement is repeated 3 times to establish a precise mean measurement. The needle is withdrawn under Doppler flow visualization. Then the portal venous pressure is measured by targeting the umbilical portion of the left portal vein.

A transgastric-transhepatic approach is used to puncture the portal vein with the 25-gauge FNA needle, and the method described for the hepatic vein is applied.

G&H How has EUS-guided vascular catheterization impacted clinical practice, and how might this new technology impact patient care in the future?

KC As EUS-PPG becomes more widely available, we will gain fuller knowledge regarding who else could benefit. In addition to portal pressure measurement, applications of EUS-guided vascular catheterization may include angiography, transhepatic intrahepatic portosystemic shunt creation, and portal vein sampling for the staging of pancreatic cancer.

A synergistic technology that I have been involved with is the development of EUS-guided liver biopsy. Traditionally, liver biopsy involved percussing the liver and placing a large needle into the site suspected to be the correct place. Up to 10% of patients experience subcapsular bleeding and pain with this method. With EUS-guided procedures, the needle can be placed precisely to avoid puncturing large blood vessels, and tissue can be acquired safely. It is also possible to measure liver stiffness with EUS using a technology known as shear wave elastography (SWE), thus enabling 3 procedures (SWE, PPG, biopsy) to be performed during the same session with endo-hepatology.

With obesity and thus fatty liver becoming an epidemic, more tools will be needed to obtain meaningful and safe liver biopsies, measures of liver stiffness, and PPG measurement. In the past, patients suspected of having nonalcoholic fatty liver disease or nonalcoholic steatohepatitis were often not tested for portal hypertension or given a liver biopsy. They were simply told to go home and lose 30 to 50 pounds and see if their condition improved. Patients were not given precise prognostic information, resulting in a lack of motivation; meanwhile, progressive disease could ensue.

Now, patients can undergo an endo-hepatology workup in which varices and portal hypertensive gastropathy can be easily detected on esophagogastroduodenoscopy, and EUS-PPG and EUS-guided liver biopsy can provide a firm diagnosis with evidence-based recommendations and prognoses. For example, a patient with a body mass index of 31 who is on the verge of liver failure but does not qualify for laparoscopic gastric bypass or a sleeve gastrectomy may be told to lose a significant amount of weight but simply cannot achieve that goal. An endoscopic sleeve gastroplasty may then be recommended. After weight loss, a follow-up endo-hepatology workup may show that portal pressure has normalized, liver fat has resolved, and fibrosis is improving and reversing. This is not a hypothetical scenario; I have seen a number of such cases. Thus, by leveraging 2 new subspecialties in gastroenterology—endo-hepatology and endo-bariatrics—superior outcomes may be achieved in many patients. Early diagnosis and minimally invasive interventions can reverse the path to significant morbidity and even death.

Disclosures

Dr Chang has consulted for Apollo Surgical, Boston Scientific, Cook Medical, EndoGastric Solutions, Erbe, Mauna Kea, Mederi, Medtronic, Olympus, Ovesco, Pentax, and Torax.

Suggested Reading

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