use them, especially in high-risk patients (those with ASA grade ⩾3, regardless of age)? In our experience, routine measurement of coagulation indices before ERCP is a waste of time and money. Significant bleeding after endoscopic sphincterotomy is rare these days, even in the presence of therapeutic anticoagulation. This likely reflects improvements in the technology of electrocautery. The UK guidelines regarding coagulation screening for ERCP should be reviewed and revised. Informed consent is the keystone of safe ERCP practice. Every ERCP should be performed for a solid indication: it is not a game. When obtaining informed consent, the risks, benefits and alternatives need to be explained. Some experts are advocating that patients be given physician-specific ''score cards'' detailing the experience of the endoscopist, as well as his or her success and complication rates.[10] Although it is hard to prove, the involvement of trainees in ERCP probably increases the risk of failure and complications, and it certainly prolongs the procedure. Patients' willingness to have trainees participate in ERCP should not be assumed. They should be asked ''up front'' whether they agree, and their wishes respected—without debate—should they decline.

This study casts a harsh spotlight on British ERCP. We commend those who participated, for their willingness to give honest answers. The results are first-and-foremost a ''wake-up call'' for British GI, but they also offer a unique opportunity for those who perform and teach ERCP around the world to look at their own practices. The way forward is clear: fewer, carefully selected trainees should be trained in the management of HBP disorders in regional specialist centres, with ERCP being only one component of that training. The numbers being trained in ERCP should match the number of gastroenterology consultant posts requiring these skills that open up each year. All gastroenterology trainees should be taught how to use a duodenoscope. Those with interest and proven facility with endoscopes should compete for limited opportunities to learn ERCP. After an assessment period during which 50–100 ERCPs are to be performed, further selection should take place to identify those trainees most likely to benefit from a dedicated year (or more) of advanced training in HBP disorders, including the full range of diagnostic and therapeutic ERCP skills. With the availability of less- and non-invasive imaging techniques, such as EUS and magnetic resonance cholangiopancreatography, to look at the biliary tree and pancreas, solely diagnostic ERCP is becoming a rarity. We recommend that EUS be taught concurrently with ERCP, as these techniques are complementary. EUS is increasingly important in both the diagnosis and staging of biliary and pancreatic cancer, and its therapeutic applications are increasing daily. Finally, this study reveals that the sickest patients having ERCP in the UK do not always have the benefit of adequate monitoring. Monitored anaesthesia care using propofol and general anaesthesia increase the cost of ERCP, but enhance its performance and safety. We suggest that UK endoscopy units should look at alternatives to standard conscious sedation for the comfort and safety of their most vulnerable patients.

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Survival in cirrhosis

Cardiovascular determinants of survival in cirrhosis

Samuel S Lee, Hongqun Liu

Diastolic response as the strongest determinant of mortality after TIPS

My heart,
Where either I must live or bear no life,
The fountain from which my current runs
Or dries up

William Shakespeare, Othello

Cirrhosis is a fatal condition. Although mild cirrhosis can be associated with prolonged survival, most diseases that induce cirrhosis progress, at variable rates, to end-stage liver failure. Deaths from hepatic failure, variceal bleeding and infection are common in advanced cirrhosis, and even the rate of sudden unexplained death is increased compared with that in a normal population.[1] Moreover, patients with cirrhosis are well known to be fragile, and do poorly after invasive or stressful procedures. It is logical and intuitive to assume that the sickest patients—that is, those with the most advanced degree of liver failure—will have the poorest outcome after challenges. Indeed, this is what virtually all studies on risk factors for

morbidity and mortality in cirrhosis show.[2] Mortality following a variceal bleed is strongly correlated with the degree of liver dysfunction as estimated by the Child–Pugh score, with death rates of 10–15% in class A, 20–30% in class B and 40–50% in class C patients. Similar correlations have been shown using the Model End-stage Liver Disease (MELD) score to estimate liver function. Cardiovascular surgery carries greater risks in those with advanced liver dysfunction than in those with mild liver dysfunction.[3]

In all these studies, the assumption was made that deaths were wholly or predominantly due to liver failure. Indeed, a recent exhaustive systematic review of the entire world literature to 2006, analysing 118 studies that examined risk factors predictive of death in patients with cirrhosis, found that liver function, as assessed by the Child–Pugh score or the MELD score, consistently emerged as the best predictor of mortality in the majority of studies.[2] However, virtually no studies have examined cardiac contractile function as a predictor of mortality, except by indirect measures such as cardiac output or diastolic arterial pressure.

Transjugular intrahepatic portosystemic shunt (TIPS) insertion has become increasingly popular over the past decade as a non-operative approach to treat resistant ascites or intractable variceal bleeding in patients with cirrhosis. TIPS insertion poses a significant cardiovascular challenge, as it suddenly shifts a significant amount of splanchnic venous blood to the systemic veins—that is, increases preload. Not surprisingly, this procedure, almost invariably performed in patients with advanced liver dysfunction, is also associated with high mortality. A meta-analysis of 330 patients in five randomised trials of TIPS in refractory ascites revealed a 1-year and 2-year mortality of 38% and 50%, respectively.[4] Yoon *et al*[5] reported that after TIPS, 31% of patients died within 30 days of stent insertion, and 59% died during a 35-month follow-up period. Multivariate analysis showed that only hyperbilirubinaemia and increased serum creatinine were independent predictors of death.[5] However, cardiac function was not examined in that study. Another study, using multivariate analyses showed that creatinine level >1.7 mg/dl and uncontrolled variceal bleeding were independently associated with 30-day mortality after TIPS.[6] This study also did not consider cardiac function.

All deaths, of course, ultimately involve some form of cardiac arrest as an agonal event. Even deaths due to liver failure from sepsis, multi-organ failure, adult respiratory distress syndrome, and so on, eventually result in cardiac arrest. Given this line of reasoning, it is perhaps understandable that the agonal event would not merit consideration as the primary causative factor in death. This type of thinking may explain the previously unnoticed 'hole' in the hepatology literature—that is, ignoring the possible role of the heart.

In view of this background, the pioneering nature of the study by Cazzaniga *et al*[7] (***see page 867***) can be appreciated. They prospectively examined the prognostic utility of not just the usual indices of liver function such as MELD score, but also cardiac function parameters such as the diastolic E/A ratio in patients undergoing a TIPS procedure.[7] Only early diastolic (E)/late-diastolic filling velocity (A) <1 at day 28 post-TIPS and baseline MELD score were univariate predictors of 1-year mortality. On multivariate analysis, only the day 28 E/A was a significant predictor of death. The E/A ratio is the echocardiographic measurement of the E (early) wave velocity of blood filling the ventricle during the initial part of diastole divided by the velocity of late diastolic filling wave (called A wave as the ''atrial kick'' predominates during this stage). As the failing or hypertrophic ventricle loses elasticity and compliance, the normally dominant ''sucking'' inflow during early diastole diminishes, and the late-diastolic atrial kick becomes increasingly important for filling. An E/A <1 is generally considered abnormal. The E/A is well accepted as a simple, reproducible measure of diastolic compliance and is often the first ventricular contractile abnormality in cardiac patients with congestive heart failure.[8]

The normal heart should easily accommodate the mild-to-moderate increase in preload induced by a TIPS insertion. This inability to accommodate an increased preload is yet another evidence of the existence of a syndrome now emerging from years of obscurity, cirrhotic cardiomyopathy.[9–11] When first described almost two decades ago, cirrhotic cardiomyopathy was a scientific ''homeless waif''. Many doubted its existence, and it seemed to have little or no clinical relevance as severe congestive heart failure is rare in cirrhosis. Over the past few years, that situation has changed dramatically. The explanation for the rarity of overt heart failure is the marked peripheral vasodilatation, which reduces ventricular afterload and thus ''auto-treats'' the patient. Recently, compelling evidence of a significant role of inadequate cardiac contractile responsiveness in the pathogenesis of hepatorenal syndrome has been reported in two studies by Ruiz-del-Arbol *et al*[12 13]. Firstly, they showed that insufficient cardiac response to infection in patients with spontaneous bacterial peritonitis contributed to the development of hepatorenal syndrome after infection resolution.[12] Secondly, among 66 patients with tense ascites, a subgroup of 27, who went on to develop hepatorenal syndrome, could be distinguished by a lower baseline cardiac output than the group that did not.[13] As underscored in our accompanying editorial,[14] these data strongly suggest that an insufficient cardiac response to infection stress or other stimulus in the patient with advanced cirrhosis reduces arterial pressure and renal perfusion and thus contributes to the pathogenesis of hepatorenal syndrome.

Cirrhotic cardiomyopathy may also help determine outcomes after liver transplantation. Before the syndrome was widely recognised, transplant physicians were puzzled by the apparently inexplicable appearance of sometimes severe cardiac dysfunction in the postoperative period, often in patients with no previous history or risk factors for heart disease. Moreover, despite careful cardiac workup and exclusion of those with overt heart disease, 12–56% of patients develop clinically- or radiographically-evident pulmonary oedema during the postoperative period.[15] It is now becoming increasingly clear that these problems reflect the presence of underlying cirrhotic cardiomyopathy.[15 16]

An expert working group is developing a consensus definition of cirrhotic cardiomyopathy, with the results expected in 2007. For now, it can be generally defined as attenuated systolic and diastolic ventricular contractile responses to stress stimuli in the absence of a primary heart disease in the patient with cirrhosis. Other associated features can include electrophysiological repolarisation changes including prolonged electrocardiographic QT interval and enlargement or hypertrophy of cardiac chambers.

Several studies have reported an abnormal cardiac response to TIPS insertion, ranging from mild contractile or diastolic dysfunction[17 18] to precipitation of overt heart failure. Such heart failure has been reported sporadically as individual case reports,[15] as well as in randomised trials. For example, in a randomised trial comparing TIPS with repeated large-volume paracentesis to treat resistant ascites, heart failure was reported in 12% of the TIPS group,[19] versus none in the paracentesis group. However, heart failure was not reported in four other randomised trials of TIPS in refractory ascites. Moreover, many patients actually

improve some indices of cardiac function after TIPS. Like most populations afflicted with end-stage liver failure, the patients who receive TIPS are heterogeneous. Indeed, this study suggests that TIPS insertion serves as a significant cardiac challenge that may distinguish those with cirrhotic cardiomyopathy from those who have relatively intact cardiac function. The overall effect of TIPS was beneficial to cardiac function, as the mean baseline E/A of 0.97 increased to a mean of 1.19 4 weeks later, and the number of patients with E/A <1 decreased from 18 to 10. However, after 1 year of follow-up, the only deaths were observed in the 10 patients with E/A <1 (6 died). In other words, the presence of cirrhotic cardiomyopathy unmasked by the TIPS challenge identified a subgroup with a very poor medium-term prognosis.

A preliminary report generally supports the findings of the Italian study. A retrospective combined analysis of 101 consecutive patients undergoing TIPS from 1997–2005 in the authors' centre and in Toronto found that the baseline E/A was the only factor on multivariate analysis predictive of mortality after TIPS.[20] As that study was retrospective, the 4-week post-TIPS E/A data was not available. However, these results again suggest the prognostic significance of diastolic dysfunction.

The central question posed by the study of Cazzaniga *et al*[7] is which organ failure played a greater role in post-TIPS mortality: the liver or the heart? This observational study cannot definitively answer this question, and the authors are therefore appropriately cautious in their interpretation and extrapolation of the results. Trying to answer this question is enormously complicated by the positive correlation between degree of liver failure and diastolic dysfunction. Several studies have demonstrated that the extent of cirrhotic cardiomyopathy worsens as liver disease progresses.[11] Thus, the degree of systolic contractile dysfunction,[21] diastolic changes[22 23] and electrophysiological abnormalities such as QT prolongation[24] are greater in those with more advanced liver failure. The correlation between degree of liver failure and cardiac response was also observed in this study, with a positive interaction between MELD score and the E/A ratio at day 28. However, the most obvious conclusion of the multivariate analysis is that the diastolic response to TIPS is the strongest determinant of post-procedure mortality.

No deaths were due to overt cardiac failure in the study. Does this cast doubt on the notion that cirrhotic cardiomyopathy played a central role in mortality? We believe not. First, overt severe heart failure is rare in cirrhosis for the reasons mentioned previously. Second, the most common cause of death was hepatorenal syndrome, and all such cases were observed in the group with post-TIPS diastolic dysfunction. The contributory role of cardiac dysfunction in pathogenesis of hepatorenal syndrome has been noted above.

These intriguing results need to be confirmed in a larger cohort of patients. Another question that the study raises is how to predict poor outcomes from baseline factors rather than variables occurring after TIPS insertion. Two-dimensional echocardiography is non-invasive and inexpensive; we believe that that all patients undergoing TIPS should have this examination 4 weeks later, and those who have diastolic dysfunction must be carefully followed. Finally, this study underscores the need to examine cardiac function as a prognostic factor not just in TIPS but also in patients with cirrhosis undergoing cardiovascular stresses such as haemorrhage, shock, infection and surgery, particularly liver transplantation.

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