Haemodynamic assessment and therapeutic studies in portal hypertension and ascites.

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Declaration

I declare that this thesis has been composed by me and that the work contained within it was performed by me, except where clearly stated otherwise. The entire work was performed while I held a Lecturer post at University of Edinburgh Department of Medicine at The Royal Infirmary of Edinburgh. The thesis has not been submitted for any other professional qualification.

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CONTENTS

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Abstract of thesis.

The development of portal hypertension and ascites in cirrhosis is associated with a variety of circulatory abnormalities. The aims of this thesis were to assess the haemodynamic changes of cirrhosis and their clinical consequences, and investigate the circulatory and clinical effects of therapies used in the management of portal hypertension and ascites.

Portal, systemic, cardiopulmonary and renal haemodynamics of 96 patients with alcohol related cirrhosis were measured. Their inter-relationship and predictive value for variceal haemorrhage and survival during a mean follow-up of 19 months was investigated. Severity of liver disease was related to the hepatic venous pressure gradient (HVPG), azgos blood flow (AzBF) and systemic hypotension. During follow-up, HVPG predicted survival and variceal bleeding.

Propranolol and isosorbide-5-mononitrate are widely used in the prophylaxis of variceal haemorrhage, but recent reports have suggested they may compromise renal function. Renal blood flow (RBF), HVPG, AzBF and systemic haemodynamics were measured in 26 cirrhotic patients before and after each drug or combination therapy. Despite significant changes in the other parameters, no fall in RBF was detected.

The novel vasodilating beta-blocker carvedilol offers potential in the treatment of portal hypertension, but little data currently exist. Portal, cardiopulmonary and systemic haemodynamics and renal function were assessed in 17 cirrhotic patients after acute and chronic therapy. Although carvedilol had a continued portal hypotensive effect after 1 month with no detrimental effect on liver blood flow or renal function, a significant minority of patients were unable to tolerate chronic therapy.

Adenosine-antagonism offer a new therapeutic approach to cirrhotic ascites and renal dysfunction. The effects on renal and systemic haemodynamics and renal function were assessed following administration of FK352 (a novel adenosine-1 antagonist) to 12 cirrhotic patients with ascites. An improvement in natriuresis, diuresis and RBF was detected.

The mechanism of an improvement in renal function following transjugular intrahepatic portosystemic stent-shunt (TIPSS) procedure remains unclear. The acute effects of TIPSS insertion on RBF, portal and cardiopulmonary haemodynamics were studied in 11 cirrhotic patients. Despite dramatic changes in portal pressure and cardiopulmonary parameters, no effect on RBF was detected.

The long-term clinical effects of TIPSS remain poorly described. The outcome of TIPSS procedure undertaken in 130 consecutive patients at our institution with a mean follow-up of 18 months are reported. Rates of variceal rebleeding, encephalopathy and shunt dysfunction are described.

Abbreviations used.

ADH	Antidiuretic hormone
AzBF	Azygos blood flow
CO	Cardiac output
ERPF	Estimated renal plasma flow
FHVP	Free hepatic venous pressure
HBF	Hepatic blood flow
HVPG	Hepatic venous pressure gradient
ISMN	Isosorbide-5-mononitrate
MAP	Mean arterial pressure
NO	Nitric oxide
PAH	Para-aminohippuric acid
PAP	Mean pulmonary artery pressure
PCWP	Pulmonary capilliary wedge pressure
PPG	Porto-systemic pressure gradient
PRA	Plasma renin activity
RAAS	Renin-angiotensin-aldosterone-system
RAP	Right atrial pressure
RBF	Renal blood flow
SNS	Sympathetic nervous system
SVR	Systemic vascular resistance
TIPSS	Transjugular intrahepatic portosystemic stent-shunt
UNaV	Urine sodium excretion rate
WHVP	Wedged hepatic venous pressure

Chapter 1.

INTRODUCTION

Patients with cirrhosis and portal hypertension exhibit a hyperdynamic circulation characterised by a raised cardiac output (CO) and low systemic vascular resistance (SVR). However, there is evidence of paradoxical renal vasoconstriction in addition to reduced sodium and water excretion, which can lead to ascites formation and impaired renal function. The aims of this thesis were to assess the inter-relationship and prognostic value of the circulatory abnormalities observed in cirrhosis, and to investigate the haemodynamic, renal and clinical effects of pharmacological and radiological interventions in the management of portal hypertension and ascites.

1 a The haemodynamic abnormalities in cirrhosis and the development of portal hypertension, ascites and renal dysfunction.

The development of portal hypertension appears critical in the initiation of the subsequent circulatory and haemodynamic changes in cirrhosis. However, the exact mechanisms behind these circulatory abnormalities and their relationship to the degree of portal hypertension and risks of variceal bleeding and death remain unclear.

1a i Pathophysiology of Portal Hypertension.

Increased hepatic resistance

The initiating factor in the development of portal hypertension is increased resistance to portal blood flow. In Western countries, the commonest cause is cirrhosis, where the main resistance to flow occurs in the hepatic sinusoids. Alternatively, resistance to flow in the portal or splenic veins or in the hepatic veins leads to pre-hepatic or post-hepatic portal hypertension respectively (see table 1).

Collateral vessels open and partially decompress the portal system. They arise most commonly in the retroperitoneal area, but are most visible and problematic when they occur at the gastro-oesophageal junction. In addition, collateral vessels arise at the peri-anal, peri-umbilical, splenorenal, ovarian, and choledochal regions, in the peritoneum and at areas of surgical anastamoses or ileostomy/colostomy sites. Normally 100% portal venous blood reaches the hepatic veins, but in cirrhosis this can be reduced to 13% (McIndoe 1928).

However, despite formation of these collaterals, portal hypertension is maintained by increased splanchnic arterial flow leading to increased portal blood flow (figure 1). As for any vascular system, according to Ohm's law, changes in pressure are defined by the equation:

$$P = Q \times R$$

where P is the portal pressure, Q is the splanchnic blood flow and R is the resistance of the portal venous system. Thus an increase in either vascular resistance or splanchnic flow will lead to increased portal pressure.

Table 1.

Causes of Portal Hypertension

Pre-Hepatic	Hepatic	Post-Hepatic
Portal vein thrombosis	*Sinusoidal:*	Budd-Chiari syndrome
Splenic vein thrombosis	Cirrhosis	Constrictive pericarditis
Tumour invasion of	Acute hepatitis	
portal/splenic veins	Fatty liver of pregnancy	
Lymphoproliferative disorders	Cytotoxic drugs	
Splenomegaly	*Pre-sinusoidal:*	
Arteriovenous fistula	Schistosomiasis	
	Congenital hepatic fibrosis	
	Idiopathic portal hypertension	
	Sarcoidosis	
	Vinyl chloride/arsenic/copper	
	Post-sinusoidal:	
	Venocclusive disease	
	Alcoholic central hyaline sclerosis	

Figure 1. (over page)

Schematic representation of the haemodynamic changes seen in portal hypertension and possible targets for pharmacological intervention:

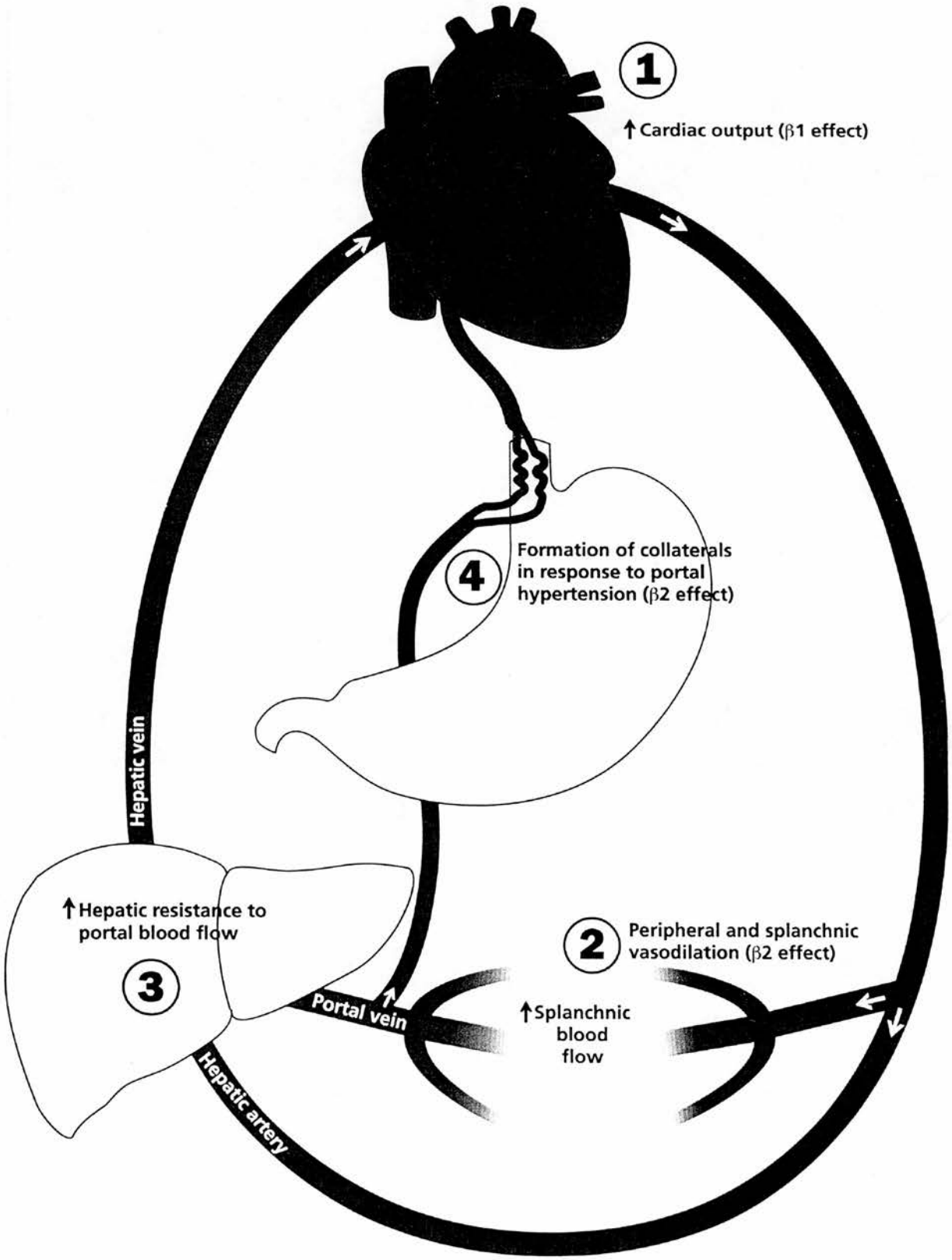
1) *Beta*-1 blockade (to reduce cardiac output).

2) *Beta*-2 blockade or vasoconstrictors (to reduce splanchnic blood flow).

3) Vasodilators (to reduce intrahepatic resistance).

4) *Beta*-2 blockade (to reduce variceal/collateral flow).

Figure 1


1
↑Cardiac output (β1 effect)
4
Formation of collaterals in response to portal hypertension (β2 effect)
Hepatic vein
↑Hepatic resistance to portal blood flow
3
2
Peripheral and splanchnic vasodilation (β2 effect)
Portal vein
↑Splanchnic blood flow
Hepatic artery

Stellate cells

Stellate cells (analogous to tissue pericytes) are found in the perisinusoidal space of disse. Following liver injury, these cells are transformed into contractile myofibroblasts which are central to the initiation of fibrogenesis (Friedman 1993). They express smooth muscle alpha-actin and produce collagen. Stellate cells also regulate sinusoidal resistance and flow in response to a variety of vasoactive substances, particularly endothelin and nitric oxide (NO) (Rockey 1997). Therefore, at least part of the resistance to portal venous flow is under dynamic control.

Circulating plasma endothelin levels are increased in cirrhosis, and endothelin causes a direct constriction of the hepatic sinusoid, probably via contraction of stellate cells (Zhang *et al* 1994, Rockey *et al* 1996). Increased endothelin receptor density has also been reported in the cirrhotic liver (Gandhi *et al* 1996). Nitric oxide can be produced by the stellate cells themselves, and exogenous or endogenous NO can prevent endothelin induced contraction of these cells, and can relax pre-contacted cells (Kawada *et al* 1993, Rockey *et al* 1995). The exact contibution of these and other substances such as carbon monoxide to the regulation of intrahepatic portal hypertension remains to be elucidated.

Increased splanchnic inflow

The resistance to portal flow is the "backward" component of portal hypertension. The "forward" component is the increased splanchnic inflow which occurs secondary to the peripheral vasodilatation seen in these patients. The low SVR and the associated raised CO lead to the characteristic hyperdynamic circulation of cirrhosis (Groszmann 1994). It has been suggested that the main site of this low SVR is in fact the splanchnic circulation (Marato *et al* 1993).

In addition to its potential role in the regulation of sinusoidal flow, NO has been implicated in the systemic circulatory abnormalities of cirrhosis. It has been proposed that vasodilatation results from increased levels of NO secondary to the raised endotoxin and cytokine levels seen in cirrhosis. However, this remains unproven and

studies have reported variable circulatory effects following administration of NO synthetase inhibitors to cirrhotic patients (Whittle *et al* 1992). Elevated levels or increased sensitivity to a number of other vasodilatory substances have also been reported in cirrhosis (see table 2).

Vascular hyporeactivity has also been well documented in cirrhosis and portal hypertension (Hadoke *et al* 1997). It is unclear whether this is secondary to an attenuated response to vasoconstrictors, defective postreceptor signal pathways or decreased basal cytosolic calcium levels (Tsai *et al* 1997).

It seems likely that the vasodilated circulation of cirrhosis is due to a disturbed balance between vasodilatory substances and vasoconstrictors (eg. endothelin, the renin-angiotensin-aldosterone and sympathetic nervous systems (RAAS and SNS), and anti-diuretic hormone). The relative contributions of the parenchymal liver disease itself and the intrahepatic, porto-systemic and intrapulmonary shunts to alterations in this balance remain unclear.

Table 2.

Systemic vasodilators with increased sensitivity or increased circulating levels in cirrhosis.

Glucagon

Nitric oxide

Endotoxin

Vasoactive intestinal polypeptide

Prostaglandins

Kinins

Atrial naturetic factor

Bile acids

Substance P

Encephalins

Adenosine

1a ii Pathophysiology of Cirrhotic ascites and renal dysfunction.

Underfill and overflow hypotheses

Patients with cirrhotic ascites have evidence of impaired sodium and water excretion in addition to their dilated systemic and constricted renal circulations (Henriksen 1995). The traditional "underfill" hypothesis of ascites formation proposed that transudation of fluid into the peritoneal cavity occurred secondary to hypoalbuminaemia and obstruction to blood and lymph flow caused by portal hypertension. The resulting diminished effective plasma volume caused activation of vasoconstrictors such as the RAAS, the SNS and antidiuretic hormone (ADH) to help maintain blood pressure. However, this theory does not explain the fact that cardiac output is classically high and sodium retention present in cirrhosis even before ascites develops.

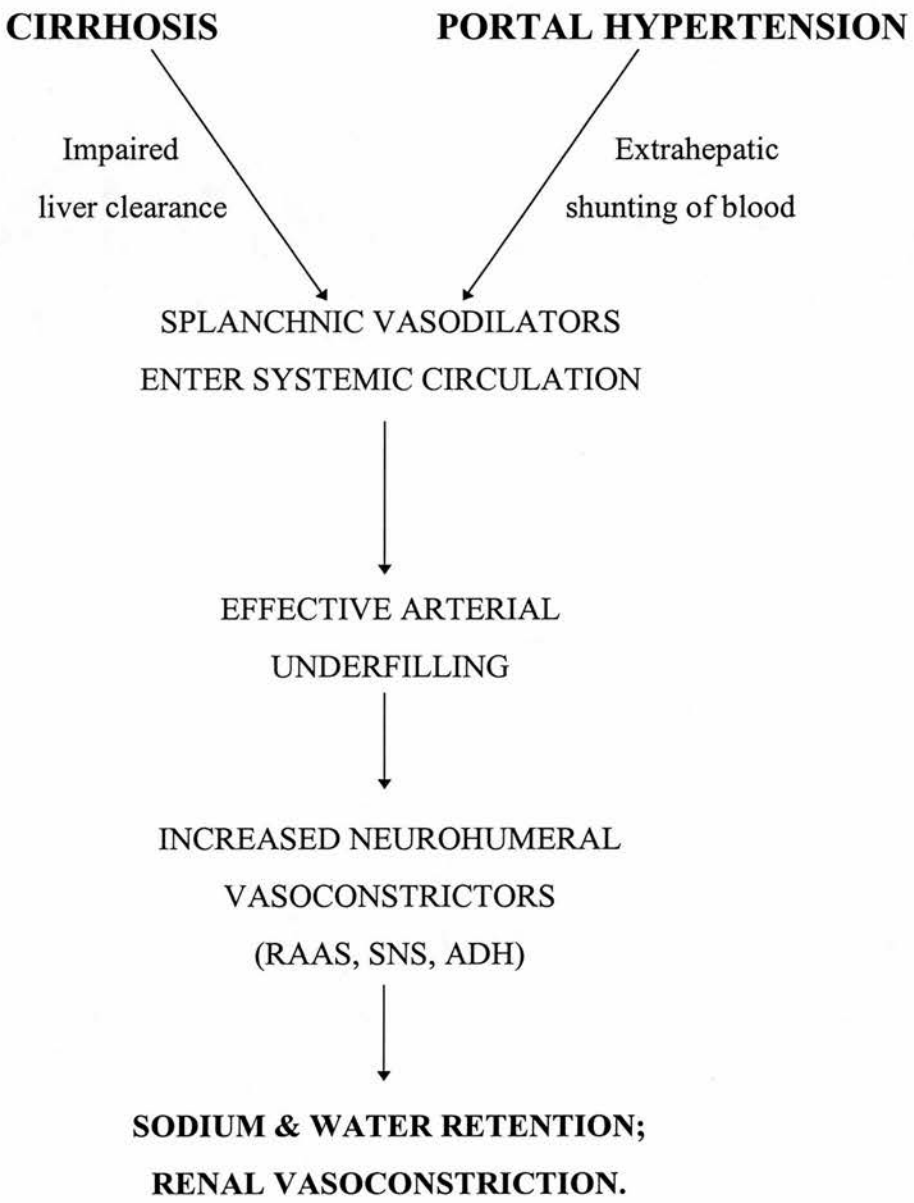
Therefore the "overflow" hypothesis was developed, suggesting that renal sodium and water retention was the primary event occurring as a result of an autonomic reflex in response to portal hypertension. The consequence was increased CO and eventually ascites formation. However this hypothesis does not explain the activation of RAAS, SNS and ADH seen in cirrhotic patients.

Peripheral vasodilatation hypothesis

To explain these findings and contradictions, the alternative "peripheral vasodilatation" hypothesis was conceived (Schrier *et al* 1988). This suggests that arterial vasodilatation is the initiating event, leading to effective arterial underfilling which triggers neuro-humoral factors such as the RAAS, SNS and ADH causing retention of sodium and water. The arterial vasodilatation is thought to be due to cirrhosis and portal hypertension causing impaired liver clearance and extra hepatic shunting of splanchnic vasodilators (fig. 2). A number of putative vasodilators have been proposed to account for this perpheral vasodilatation in cirrhosis, although no specific causal relationship has been identified (table 2).

Figure 2.

The peripheral vasodilatation hypothesis in hepatic cirrhosis.



(Footnote: RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system; ADH: antidiuretic hormone.)

Humeral factors

Elevated levels of aldosterone, plasma renin activity (PRA) and angiotensin II have been reported in cirrhotic patients, suggesting a major role for the RAAS in the circulatory abnormalities of cirrhosis. Sodium excretion is inversely related to PRA, and higher levels of angiotensin II are found in patients with ascites compared with non-ascitics (Tobe *et al* 1993). Plasma noradrenaline levels are also raised in cirrhotic patients with ascites and are inversely related to renal blood flow suggesting that activation of the SNS also contributes to sodium retention and renal vasoconstriction (Henriksen *et al* 1984).

Raised ADH levels and decreased delivery of filtrate to the diluting segments reduces free water clearance in cirrhosis (Schedl *et al* 1960), and recent reports of ADH inhibition with opiod receptor agonists are of interest (Moreau *et al* 1996). Raised levels of endothelin-1 have also been reported in cirrhotic patients with ascites, and endothelin antagonists are under evaluation in this situation. Increased levels of adenosine have been shown to reduce sodium and water excretion in cirrhosis (Llach *et al* 1993) and adenosine-antagonism appears to improve renal sodium and water handling in animal studies (Kuan *et al* 1993). Therefore adenosine antagonism offers a novel therapeutic approach in cirrhosis.

Renal vascular and tubular changes

The pathogenesis of the renal dysfunction in cirrhosis is complex and poorly understood. In particular the paradoxical renal vasoconstriction in the face of systemic vasodilatation remains largely unexplained. The renal vasculature is particularly sensitive to angiotensin II mediated vasoconstriction (Arroyo *et al* 1991). Activation of the RAAS, the SNS and ADH secondary to splanchnic and peripheral arterial vasodilatation can reduce renal perfusion and sodium and water excretion as described above.

A number of studies have confirmed that renal sodium and water retention are early features of the renal dysfunction in cirrhosis and precede the development of ascites or a fall in the glomerular infiltration rate (GFR) (Jimenez *et al* 1985). This early sodium retention has been shown to correlate with the degree of hyperaldosteronism in cirrhotic patients (Arroyo *et al* 1979), however as water retention progresses, the reduced free water clearance leads to hyponatraemia and hypo-osmolarity. In the absence of excess diuretic therapy, the hyponatraemia seen in cirrhosis is due to water excess rather than sodium deficiency which therefore has implications for management. As described above, increased levels of ADH, endothelin and adenosine may contribute to the renal vascular and tubular abnormalities of cirrhosis.

Hepatorenal Syndrome

The hepatorenal syndrome (HRS) is characterised by uraemia, oliguria, hyponatraemia and low urinary sodium in the absence of renal histological changes in a patient with chronic liver disease. This syndrome is the end of the spectrum of renal abnormalities seen in cirrhotic patients and the definition has recently been updated by an International Working Party of Hepatologists (Arroyo *et al* 1996, see table 3).

Patients with hepatorenal syndrome have evidence of profound activation of the SNS and RAAS and raised levels of endothelin-1 leading to intense renal vasoconstriction

and reduced GFR (Arroyo *et al* 1983, Forrest *et al* 1996). The renal autoregulatory system and the protective intrarenal vasodilators including prostaglandins fail to maintain renal perfusion in response to the intrarenal vasoconstriction and systemic hypotension.

The hepatorenal syndrome occurs in patients with poor hepatic reserve who often have severe jaundice and hepatic encephalopathy and are a major management problem. Such patients have a grave prognosis and survival is uncommon beyond several weeks without liver transplantation, following which all renal abnormalities disappear.

Table 3.

International Ascites Club's diagnostic criteria for the diagnosis of Hepatorenal Syndrome.

MAJOR CRITERIA:

- Chronic/acute liver disease with advanced liver failure and portal hypertension.
- Low GFR (creatinine clearance <40ml/min.)
- Absence of shock/sepsis/nephrotoxic drugs.
- Absence of excessive gastrointestinal or renal fluid losses (weight loss > 500g/day in absence or >1kg/day in presence of peripheral oedema).
- No sustained improvement in renal function following diuretic withdrawal and plasma expansion with 1.5 l isotonic saline.
- Proteinuria <500mg/l and no evidence of obstructive uropathy/parenchymal renal disease.

ADDITIONAL CRITERIA:

- Urine volume <500ml/day.
- Urine sodium <10 mmol/l.
- Urine osmolality > plasma osmolality
- Urine red blood cells <50 per high powered field.
- Serum sodium <130mmol/l.

1 b. Clinical sequelae of portal hypertension.

1b i Variceal Haemorrhage

Although portal hypertension contributes to the development of ascites and hepatic encephalopathy, its most important complication is variceal haemorrhage. Longitudinal studies have suggested that most patients with cirrhosis will eventually develop varices (Christensen *et al* 1981). The rate of variceal bleeding in patients not receiving therapy in contolled clinical trials ranges from 15% to 68% (median 32%), with bleeding occuring most commonly within 2 years of follow-up (Pagliaro *et al* 1994, *et al*, Burroughs *et al* 1986). The mortality of a first variceal haemorrhage approaches 50%, and between 47% and 84% of survivors will have a recurrent bleed during a mean follow-up of 1-2 years (Pagliaro *et al* 1989). Reported mortality figures from recurrent bleeding range from 20% to 70% (Pagliaro *et al* 1989).

Therefore effective primary and secondary prophylactic therapy for variceal bleeding is worthwhile. For primary prophylaxis, identification of patients at high risk of bleeding would allow clinicians to target therapy to these patients, and avoid unecessary treatment of the large number of patients who will not bleed.

1b ii Risk factors for variceal bleeding

The portal pressure in an individual is dynamic rather than fixed. It demonstrates circadian changes with highest pressures nocturnally, and increases post-prandially, with alcohol intake, and in response to coughing, sneezing and exercise (Alvarez *et al* 1996, Garcia-Pagan *et al* 1996). Such variations may combine with local factors in the vessel walls to contribute to a surge in pressure which can lead to a variceal bleed. However, the exact mechanisms responsible for variceal bleeding remain unclear.

A number of clinical, endoscopic and haemodynamic parameters have been shown to predict variceal haemorrhage. The risk of a first bleed has been shown to increase with the severity of liver disease, endoscopic assessment of variceal size and the presence of red markings on the varices (NIEC 1988).

A "bleeding threshold" of a 12mmHg pressure difference between the portal vein and inferior vena cava has also been identified, with bleeding very unlikely at lower pressure gradients (Garcia-Tsao *et al* 1985). In addition, in patients who have had a variceal haemorrhage, the risk of rebleeding is low if a pressure gradient fall of 20% or greater is achieved (Feu *et al* 1995). Although the degree of portal hypertension as measured by the hepatic venous pressure gradient (HVPG) independently predicts bleeding (Merkel *et al* 1992), when the HVPG rises above 12mmHg there is no linear relationship between HVPG and bleeding risk.

There have been suggestions that the HVPG can predict mortality in patients with cirrhosis (Merkel *et al* 1992, Armonis *et al* 1997). Therefore it is possible that measurement of the HVPG or other haemodynamic parameters can be used in conjunction with the Childs-Pugh score to assess prognosis.

1b iii Cirrhotic Ascites.

The probability of survival 1 and 5 years after the first episode of cirrhotic ascites has been estimated at 50% and 20% respectively (Arroyo *et al* 1986) which emphasises the prognostic importance of ascites. In addition, the associated metabolic abnormalities such as hyponatraemia and renal impairment are often exacerbated by diuretic therapy.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is defined as infected ascitic fluid occuring in patients with ascites, in the absence of bowel perforation ot intra-abdominal abscess formation. Clinically an ascitic fluid polymorphonucleocyte count >250cells/mm^2, even in the absence of positive ascitic fluid culture is highly suggestive of SBP. The occurrence of SBP is associated with a one year survival of 30%, therefore such patients should be considered for liver transplantation (Altman *et al* 1995).

Refractory ascites

Approximately 10-20% patients with cirrhotic ascites are refractory to treatment with sodium restriction and diuretics (Gerbes 1993). It has recently been suggested that the definition of refractory ascites should include the two distinct conditions of "diuretic resistant" and "diuretic intractable" ascites (Arroyo *et al* 1996, table 4). Alternative therapeutic strategies include large volume paracentesis with intravenous colloid replacement (Gines *et al* 1988), TIPSS procedure (Ochs *et al* 1995), and the less popular peritoneo-venous shunts and extracorporeal ascitic concentration devices. Due to the associated advanced liver disease and limited success of alternative therapies, such patients should also be considered for transplanatation.

Hepatorenal syndrome

As previously described, the hepatorenal syndrome is the end of the spectrum of renal abnormalities in cirrhosis. This syndrome occurs in patients with poor hepatic

reserve who often have severe jaundice and hepatic encephalopathy and are a major management problem. Such patients have an ominous prognosis without liver transplantation, following which all renal abnormalities disappear.

Table 4.

Definitions and Diagnostic Criteria of Subtypes of Refractory Ascites

Diuretic-resistant Ascites:

Ascites that cannot be mobilised or the early recurrence of which cannot be prevented because of lack of response to sodium restriction and intensive diuretic therapy.

Diuretic-intractable Ascites:

Ascites that cannot be mobilised or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage.

Diagnostic criteria:

Treatment period required: patients must be on intensive diuretic treatment for at least one week.

Lack of response: mean weight loss < 200g/day during last 4 days of intensive diuretic treatment and urinary sodium excretion <50mmol/day.

Dietary sodium restriction: a 50mmol sodium diet.

Intensive diuretic treatment: spironolactone 400mg/day plus frusemide 160mg/day (or equivalent doses of other diuretics).

Early ascitic recurrence: within 4 weeks of initial mobilization.

Diuretic-induced complications:

- development of encephalopathy in absence of other precipitating factors
- increase in serum creatinine by >100% to above 200mmol/l
- decrease in serum sodium by >10mmol/l to <125mmol/l.
- decrease in serum potassium to <3mmol/l or increase >6mmol/l despite appropriate measures to normalize potassium levels.

1 c. Beta blockers and nitrates in the management of portal hypertension and their effects on the kidney.

The most widely used drugs in the prevention of variceal haemorrhage are propranolol and other nonselective beta-blockers. Recent reports have also assessed nitrates in this situation. Propranolol reduces portal pressure and collateral blood flow in cirrhosis and numerous studies have confirmed its efficacy as prophylaxis against portal hypertensive related gastrointestinal bleeding (Pascal *et al* 1987, Lebrec *et al* 1988, Hayes et al 1990, Conn *et al* 1991, Poynard *et al* 1991, D'Amico *et al* 1995). However, approximately 40% patients will not have a portal hypotensive response to beta-blockade (Garcia-Tsao *et al* 1985).

Nitrates such as isosorbide-5-mononitrate (ISMN) are long acting venodilators that reduce portal pressure and hepatic vascular resistance (Hayes *et al* 1988, Navasa *et al* 1989, Garcia-Pagan *et al* 1990). They reduce the risk of variceal bleeding (Angelico *et al* 1993, Bertoni *et al* 1994), and are often used as alternative therapy for patients who are intolerant to beta-blockade. Recent reports have suggested that the combination of propranolol and nitrates may be the optimum portal hypotensive therapy (Garcia-Pagan *et al* 1991, Vorbioff *et al* 1993, Merkel *et al* 1997).

Ideally, haemodynamic assessement of the reduction in portal pressure in response to drug therapy should be undertaken by measurement of the hepatic venous pressure gradient (HVPG). This is particularly important in patients with alcoholic cirrhosis in whom a spontaneous fall in of > 20% is possible with abstinence (Vorbioff *et al* 1996). Although a reduction in the resting pulse rate by 25% is often used to guide the dosage of beta-blockers, the splanchnic haemodynamic effects of beta-blockers are unpredictable and correlate poorly with the systemic effects.

1c i Primary prophylaxis of variceal bleeding

Beta-blockers

Nine controlled studies incorporating a total of 999 patients and summarised in 4 meta-analyses (Hayes *et al* 1990, Poynard *et al* 1991, Pagliaro *et al* 1992, D'Amico *et al* 1995) have confirmed the efficacy of beta-blockers over placebo in the prevention of a first variceal haemorrhage. Most investigators have studied propranolol in this role, although nadolol has been used in some studies. The risk of bleeding is reduced by approximately 45% with beta-blocker therapy and in most studies there is a trend towards improved survival (Lebrec *et al* 1997). There appears to be a consistent benefit to patients with moderate or large oesophageal varices from all aetiologies of liver disease. Side effects of beta-blockers were reported in 15-50% patients, although only a minority withdrew from therapy (D'Amico *et al* 1995).

Two studies have compared propranolol with sclerotherapy in the prevention of a first variceal haemorrhage (Andreani *et al* 1990, PROVA 1991). One showed reduced bleeding in the propranolol group at two years (Andreani *et al* 1990) but no difference was detected in the other. Propranolol is also superior to a combination of propranolol and sclerotherapy in this situation (PROVA 1991). The benefits of band ligation over sclerotherapy have been confirmed (Laine *et al* 1995), therefore trials must compare this with propranolol in the primary prophylaxis of variceal haemorrhage. To date only one study (published in abstract form) has compared banding with propranolol in this situation (Sarin *et al* 1997). No significant difference in the bleeding rate was detected.

Nitrates

In 1993, Angelico et al suggested that nitates may be as efficacious as beta-blockers in the primary prophylaxis of variceal bleeding, offering an alternative to those patients who are intolerant of beta-blockers (Angelico *et al* 1993). Although the recently published long term follow-up of this study confirmed that variceal bleeding rates were similar in both groups, an increased mortality was obseved in elderly

patients given nitrates (Angelico *et al* 1997). Another recent study reported a reduced incidence of first variceal haemorrhage in patients given a combined regime of nitrates and beta-blockers compared with those given beta-blockers alone (Merkel *et al* 1996). No effect on survival was seen. This suggests that this drug combination may be the optimum therapy in the primary prophylaxis of variceal bleeding, but confirmatory studies are awaited particularly in view of the possible adverse effect of nitrates recently reported by Angelico.

1c ii Prevention of variceal rebleeding.

Following survival from an initial variceal bleed, the majority of patients will rebleed, the risk being highest in the first few weeks. To reduce this risk, further treatment such as pharmacological therapy, endoscopic methods of variceal obliteration or creation of a portosystemic shunt is required.

Beta-blockers

Similar to the situation for the primary prophylaxis of variceal haemorrhage, non-selective beta-blockers are the most widely used drugs in the prevention of rebleeding after a variceal haemorrhage. Most experience is with propranolol, although some investigators have used nadolol. A total of 828 patients in 13 randomised trials, summarised in 4 meta-analyses (Pagliaro *et al* 1989, Hayes *et al* 1990, D'Amico *et al* 1995, Bernard *et al* 1997) have confirmed the efficacy of beta-blockers in the prevention of variceal rebleeding. Most studies suggest an improvement in survival compared with placebo. Overall, beta-blockers appear to reduce the risk of rebleeding by approximately 40% and mortality by 20% (Lebrec *et al* 1997).

Nine randomised studies compared beta-blockers with sclerotherapy in the prevention of variceal rebleeding, and most reported similar efficacy although the studies showed substantial heterogeneity (D'Amico *et al* 1995). However, complications were more frequent and severe with sclerotherapy. There is no clear evidence of a benefit from combined beta blockade and sclerotherapy compared with either treatment alone.

Beta-blockers & Nitrates

The addition of nitrates (usually ISMN) to beta-blockers improves the portal hypotensive response (Garcia-Pagan *et al* 1990). A recent study reported reduced rebleeding when this drug combination was used in comparison with endosopic

sclerotherapy (Villanueva *et al* 1996). However, studies are required to compare pharmacological therapy with band ligation for the prevention of rebleeding, since this is now the endoscopic treatment of choice.

1c iii Renal effects of propranolol and nitrates in cirrhosis.

Any reduction in renal function is critical in cirrhotic patients, because they are already at risk of renal impairment due to reduced RBF, glomerular filtration rate (GFR) and sodium and water excretion (Epstein 1988). Recent suggestions that beta-blockers and nitrates may have deleterious renal effects in cirrhosis include reports of reduced renal sodium excretion (Vorbioff *et al* 1993, Rector & Reynolds 1984, Salmeron *et al* 1993) and reduced renal perfusion (Ljubicic *et al* 1992, Bolognesi *et al* 1994, Henriksen & Ring-Larsen 1993) following administration of these drugs. This is important in view of their increasing use in the prophylaxis of variceal haemorrhage.

Beta-blockers

The renal effects of beta-blockers are complex due to their haemodynamic and neurohumoral actions. In addition to their portal hypotensive action, they reduce cardiac output and increase systemic vascular resistance, but have minimal effect on MAP (Henriksen *et al* 1992). Propranolol therapy leads to increased circulating noradrenaline which can cause sodium and water retention (Best & Halter 1985), however reduced levels of renin, angiotensin and aldosterone (beta-1 blockade) are also observed which increase salt and water excretion (Bernardi *et al* 1989).

In addition, renal vasoconstriction due to beta-2 blockade has been suggested as a mechanism by which beta-blockers may impair RBF and GFR (Wilkinson 1982). However, the clinical significance of these changes remain unclear and data on cirrhotic patients are limited.

Nitrates

Nitrates are venodilators that reduce cardiac output and MAP in cirrhosis (Navasa *et al* 1989, Salmeron *et al* 1993, Merkel *et al* 1987). There has been concern that this associated fall in blood pressure and resulting activation of the RAAS and sympathetic nervous system may compromise renal function in patients with advanced liver disease. Nitrate therapy has been shown to reduce renal plasma flow, GFR, and sodium and water excretion and increase renin and aldosterone values in cirrhosis (Salmeron *et al* 1993, Salerno *et al* 1996). Combination therapy with propranolol and nitrates has also been shown to worsen ascites to a greater extent than propranolol alone (Vorbioff *et al* 1993).

However, two recent reports have shown no effect on GFR, free water clearance, activity of the RAAS or ascites outcome in patients given combined ISMN and propranolol therapy, or combined ISMN and nadolol therapy compared with nadolol alone (Morrillos *et al* 1994, Merkel *et al* 1995).

Therefore the published evidence on whether beta-blockers and nitrates have deleterious renal effects in cirrhosis is conflicting although concern remains regarding their safety in this patient population. It is unclear whether any adverse renal effect is secondary to intra-renal changes or impaired renal perfusion consequent on the systemic haemodynamic effects of these drugs.

1 d. Alternative drug therapies for portal hypertension.

Although propranolol is the pharmacological agent used most widely in the primary prophylaxis of variceal haemorrhage and the prevention of rebleeding, many cirrhotic patients are unable to take this drug due to contraindications or intolerance (Silvain *et al* 1985). Ever since Bathal and Grossman confirmed that vasodilator therapy modulated the increased vascular resistance in the cirrhotic liver, nitrates and other vasodilators have been investigated as treatments for portal hypertension (Bathal & Grossman 1985). However, the recently reported adverse effect of nitrates on survival in elderly patients is a major concern (Angelico *et al* 1997).

Although haemodynamic and clinical studies have suggested that the combination of a beta-blocker and ISMN is the optimum therapy for portal hypertension, doubts remains about the compliance, tolerability and renal effects of such a drug combination in cirrhotic patients. Therefore the search continues for other drugs which reduce portal pressure and are well tolerated in cirrhosis.

1d i Vasodilating beta-blockers

Carvedilol is a novel vasodilating non-selective beta-blocker. In addition to its non-selective beta-blocking effects, it is a weak alpha-1 receptor antagonist and exhibits calcium channel antagonism (Sponer *et al* 1992, Zweiten 1993). Recent reports have shown that this drug has beneficial acute effects on portal pressure in cirrhosis (Forrest *et al* 1996, Sekiyama *et al* 1997) and may indeed have a greater portal hypotensive effect than propranolol (Banares *et al* 1997).

Carvedilol has two enantiomers, R (+) and S (-). Cirrhotic patients have an increased S- to R- ratio, resulting in more beta-blockade compared with control subjects (Neugebauer *et al* 1992). The beneficial beta-blockade in cirrhotic patients with portal hypertension may be combined with reduced intrahepatic and collateral

resistance due to the alpha-blockade. In addition, improved RBF and GFR has been described in hypertensive patients given carvedilol, probably due to the alpha-antagonism (Dupont *et al* 1987). It remains unclear as to whether carvedilol has beneficial haemodynamic effects after chronic administration to cirrhotic patients and whether it can be tolerated in this patient group.

One other study assessed nipradilol, another vasodilating beta-blocker, in cirrhotic patients (Sugano *et al* 1995). However, only patients with Childs A or B liver disease were investigated and renal function was not assessed. In addition, less than two thirds of patients had a >10% fall in HVPG following acute administration of nipradilol, compared with 81% after carvedilol (Forrest *et al* 1996).

1d ii Alpha-agonists

Clonidine is a centrally acting alpha-2 adrenoreceptor agonist which reduces sympathetic activity in cirrhosis. Studies have shown a reduction in CO, MAP and portal pressure in cirrhotic patients given clonidine (Willett *et al* 1986, Albillos *et al* 1992, Roulot *et al* 1992). Its effect seems to depend on a reduction in the portosystemic collateral circulation and the drug is relatively well tolerated. However, in a comparative haemodynamic study in patients with large varices, clonidine had minimal portal haemodynamic effects despite major beneficial effects with propranolol (Tincani *et al* 1995).

1d iii Alpha-blockers

Prazosin, an alpha-adrenoreceptor antagonist has been investigated in cirrhotic patients. The rationale for its use is the increased sympathetic tone present in the splanchnic vascular bed in cirrhosis, and the direct reationship between the degree of portal hypertension and the activity of the SNS (Willet *et al* 1985). A reduction in

HVPG and improvement in hepatic perfusion with no systemic circulatory effects has been reported (Mills *et al* 1984, Albillos *et al* 1995). However, increased sodium and water retention was observed (Albillos *et al* 1995).

1d iv Vasodilators

Molsidomine is a preferential venodilator that relaxes vascular smooth muscle by increasing intracellular concentrations of cGMP. It has been shown to have a moderate portal hypotensive effect following acute administration to cirrhotic patients (Vinel *et al* 1990, Ruiz del Arbol *et al* 1991). However, a recent study reported no greater effect on HVPG with combined molsidomine and propranolol compared with propranolol alone (Garcia-Pagan *et al* 1996).

1d v Other drugs

Diuretics reduce blood volume and cardiac output and can therefore be used to reduce portal pressure (Okumura *et al* 1991). Five-hydroxy-tryptamine ($5\text{-}HT_2$) receptor antagonists and angiotensin converting enzyme inhibitors have shown portal haemodynamic effects (Koshy *et al* 1992, Ibarra *et al* 1992), but problems with encephalopathy and systemic hypotension have been encountered (Vorbioff *et al* 1989, Pariente *et al* 1985).

A number of other drugs including angiotensin-II blockers, endothelin receptor antagonists, nitric oxide synthetase inhibitors and pentoxifylline have been shown to have a portal hypotensive effect in small studies. However, little data exist and none of these drugs have been shown to be superior to propranolol.

1 e. The therapeutic potential of adenosine-antagonism in cirrhotic ascites and renal dysfunction.

1e i Background

Adenosine is an endogenous nucleoside produced locally by the intracellular degradation of ATP in response to hypoxia. It has potent vasoactive properties and may be involved in the pathogenesis and maintenance of renal failure, with intra-renal haemodynamic and tubular effects (Spielman *et al* 1982, Balakrishnan *et al* 1996). Adenosine-1 receptors are present on the afferent renal artery and proximal renal tubule and stimulation of these inhibit adenyl cyclase, resulting in renal vasoconstriction and sodium and water retention in animal models (Agmon *et al* 1993, Takeda *et al* 1993). Adenosine-2 receptors are found in the vasculature of the systemic circulation and stimulation leads to vasodilatation via activation of adenyl cyclase (Stiles 1992).

Balakrishnan and colleagues recently reported a decline in urine flow, natriuresis, free water clearance and GFR following administration of adenosine to healthy subjects (Balakrishnan *et al* 1996). These effects are similar to the abnormalities seen in cirrhotic patients and it has been suggested that adenosine has a major role in the haemodynamic and particularly the renal changes of cirrhosis (Milani *et al* 1983, Llach *et al* 1993).

1e ii Effects of adenosine in cirrhosis

Increased oxygen demand and tissue hypoxia are found in cirrhosis (Martini *et al* 1972, Moreau *et al* 1988) which lead to the systemic release of vasodilating substances including adenosine (Ohisalo 1987, Olsson & Pearson 1990). However in the kidney, adenosine acts as a vasoconstricting metabolite, reducing renal perfusion,

GFR and sodium excretion via adenosine-1 receptors on the afferent renal artery and the proximal tubular cells (Balakrishnan *et al* 1996, Agmon *et al* 1993, Takeda *et al* 1993, Edlund *et al* 1994). Cirrhotic patients have an increased number of adenosine receptors and increased sensitivity to adenosine (Hall & Granger 1986, Paul *et al* 1993, Hasegawa *et al* 1989).

Llach et al reported that increasing extracellular adenosine levels by administration of dipyridamole to cirrhotic patients reduced sodium and free water excretion (Llach *et al* 1993). In their study, renal plasma flow and GFR were also reduced in patients with ascites and high basal renin levels. Animal studies have confirmed that stimulation of adenosine-1 receptors on the renal artery and proximal tubule cells leads to similar renal effects to those found in cirrhosis, with renal vasoconstriction and sodium and water retention (Agmon *et al* 1993, Takeda *et al* 1993, Holz & Steinhausen 1987). This suggests that adenosine-1 specific antagonism may be beneficial in the treatment of the renal abnormalities of cirrhosis.

1e iii Adenosine-antagonism in cirrhosis

Methylxanthines such as theophylline and aminophylline are non-specific adenosine-1 and -2 antagonists. Studies have shown that they improve RBF (as measured by thermodilution or 133-Xenon washout methods), GFR, urine volume and sodium and water excretion in cirrhosis, with variable effects on systemic haemodynamics (Milani *et al* 1983, MacMathuna *et al* 1990, Moreau *et al* 1992, Forrest *et al* 1997). However, these drugs are far from ideal for use in cirrhosis because of their side-effects which include tachycardia, gastrointestinal disturbances, arrhythmias and convulsions. In addition, xanthines are poorly cleared in cirrhosis, and at higher plasma levels they act via phosphodiesterase inhibition with variable clinical effects (Fredholm 1980). However, specific adenosine-1 blockade may be beneficial in cirrhotic patients with impaired sodium and water excretion or functional renal impairment.

Previous use of adenosine-1 specific antagonists in animal studies demonstrated amelioration of the acute renal failure induced by glycerol, endotoxin and cisplatin (Kellet *et al* 1989, Knight *et al* 1991, Knight *et al* 1992). Kuan reported an increased diuresis and natriuresis, but minimal systemic effects in rats given an adenosine-1 antagonist (Kuan *et al* 1993). Administration of an adenosine-1 antagonist has been shown to attenuate the oliguria, hypofiltration, and electrolyte retention induced by adenosine in an animal model, suggesting that adenosine-1 antagonism may protect the kidney from the undesirable haemodynamic and tubular effects of adenosine (Barrett & Wright 1994). However, to date no study has investigated the effects of an adenosine-1 antagonist in cirrhotic patients.

1 f. Transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of variceal haemorrhage and cirrhotic ascites.

Since the first description of the transjugular intrahepatic portosystemic stent-shunt procedure (TIPSS) in 1988 (Rossle et al 1988), there have been numerous reports describing its use in the management of complications of portal hypertension. However, much of this literature involves assessment in small numbers of patients and therefore it has been difficult to determine the exact role of TIPSS.

1 f i Variceal haemorrhage

Acute bleeding

The first reports of TIPSS procedure were in the management of oesophageal variceal haemorrhage (Richter *et al* 1990, Zemel *et al* 1991, Ring *et al* 1992, Simpson *et al* 1993). The treatment of uncontrolled variceal haemorrhage or recurrent oesophageal variceal haemorrhage remain the main indications for TIPSS placement. Although there is a lack of prospective randomised trials, TIPSS procedure appears preferable to shunt surgery or oesophageal transection as a rescue procedure for uncontrolled variceal haemorrhage refractory to endoscopic therapy in view of the less invasive technique and lower reported complications and mortality (Jalan *et al* 1995). Successful TIPSS placement leads to immediate haemostasis in up to 100% patients with uncontrolled variceal haemorrhage (McCormick *et al* 1994, Jalan *et al* 1995, Sanyal *et al* 1996). However rebleeding, encephalopathy and shunt dysfunction occur at a variable rate during follow-up (see table 5).

Table 5.

Summary of four major series reporting follow-up in patients with TIPSS insertion.

	Helton et al 1993	Rossle et al 1994	Coldwell et al 1995	LaBerge et al 1995
Number of patients	59	100	96	90
Childs C patients (%)	56	22	35	47
Emergency procedure (%)	39	10	-	33
Mean follow-up (mo.)	7	12	<6	14
Rebleeding (%)	31	18	15	18
Encephalopathy (%)	17	15	29	-
Shunt dysfunction (%)	18	33	33	29
Mortality-30 day (%)	-	3	14	16
Mortality-overall (%)	25	10	23	38

Recurrent bleeding

Recurrent variceal haemorrhage despite adequate endoscopic therapy is also an accepted indication for TIPSS placement, especially for patients with Childs B or C disease in whom shunt surgery is poorly tolerated (Shiffman *et al* 1995). However, it is only in the past 2-3 years that randomised trials comparing TIPSS procedure with endoscopic therapy for the prevention of rebleeding following a variceal bleed have been reported. Seven of these trials have been published as full papers (Cabrera *et al* 1996, Rossle *et al* 1997, Sanyal *et al* 1997, Cello *et al* 1997, Sauer *et al* 1997, Jalan *et al* 1997, Merli *et al* 1998) and 3 in abstract form only (G d'EAIH 1995, Garcia-Villarreal *et al* 1996, Sauer *et al* 1997).

In these studies, patients were randomised to receive TIPSS or definitive endoscopic therapy a variable time (up to 11 days) following control of the initial bleed by endoscopic or pharmacological means. All except two studies which used band ligation (Jalan *et al* 1997, Sauer *et al* 1997), used sclerotherapy as the endoscopic treatment. Three studies added propranolol to the endoscopic treatment arm (G d'EAIH 1995, Rossle *et al* 1997, Sauer *et al* 1997). These studies are summarised in table 6.

Eight of these studies found a significant reduction in rebleeding following TIPSS compared with endoscopic therapy with the other 2 showing no difference between the groups. There were no differences in mortality in 8 of the trials, with one finding an increased mortality in the TIPSS group (Sanyal *et al* 1997) and another an increased mortality in the sclerotherapy group (Garcia-Villarreal *et al* 1996). In some trials, patients who rebled in the endoscopy group were "rescued" by TIPSS insertion, thereby reducing the chance of demonstrating a difference in survival. Rates of encephalopathy were higher in the TIPSS group in most studies, but was generally easy to manage.

Table 6.

Summary of the ten trials comparing TIPSS with endoscopic therapy for the prevention of rebleeding following a variceal haemorrhage.

	no. TIPSS/sclero.	F-up(mo)	Rebleeding (%)+	H. enceph.(%)+	Survival (%)+
Rossle, 1997♣	61/65	13	15 vs 45*	36 vs 18°	90 vs 89 (1yr)
Sauer, 1997♣	42/41	18	23 vs 57*	29 vs 13°	69 vs 67
G d'EAIH, 1995♣	32/33	12	41 vs 61	-	50 vs 48
Cabrera, 1996	31/32	15	23 vs 52°	33 vs 13°	80 vs 84
Sanyal, 1997	41/39	33	22 vs 21	29 vs 13°	71 vs 82°
Cello, 1997	24/25	19	12 vs 48°	50 vs 44	79 vs 84 (30 day)
Merli, 1998	38/43	18	24 vs 51°	55 vs 26♦	76 vs 81
Garcia-Villarreal, 1996	18/19	15	11 vs 47♦	26 vs 22	94 vs 56♦
Jalan, 1997#	31/27	16	10 vs 52*	36 vs 33	58 vs 63
Sauer, 1997#	16/17	7	18 vs 54° (1yr)	25 vs 12	89 vs 91 (1 yr)

♣ used concomitant propranolol in sclerotherapy arm.

used band ligation as endoscopic therapy.

+ results expressed as TIPSS group vs endoscopy group.

° $p<0.05$ ♦ $p<0.01$ *$p<0.001$

Shunt insufficiency and the subsequent need for surveillance of the stent remain a major limitation of TIPSS (see below) and must be taken into account when comparing TIPSS with other treatment modalities. Little data exist regarding the cost-effectiveness of the various treatments for variceal haemorrhage, although two of the TIPSS vs endoscopic therapy trials for prevention of rebleeding (Jalan *et al* 1997, Cello *et al* 1997) concluded that there were no significant differences in total costs on long-term follow-up. Although TIPSS procedure appears promising in preventing rebleeding from oesophageal varices, further data are required to further define its role in this situation.

Gastric varices.

Endoscopic methods for treating bleeding gastric varices remain unsatisfactory. Recent reported benefits of gastric variceal injection of bovine thrombin or tissue adhesives appear promising but require comfirmation with larger studies (Ramond *et al* 1989, Williams *et al* 1994). In view of the perceived benefits of TIPSS over shunt surgery, TIPS

1 f ii Refractory ascites

In most series, refractory ascites is the second most common indication for TIPSS placement after variceal haemorrhage. Over the past 3 years, numerous abstracts and 8 published papers (Ferral *et al* 1993, Villarreal *et al* 1993, Ochs *et al* 1995, Wong *et al* 1995, Somberg *et al* 1995, Quiroga *et al* 1995, Crenshaw *et al* 1996, Forrest *et al* 1996) have assessed the efficacy of TIPSS for refractory ascites. The findings are broadly similar and indicate that TIPSS improves renal function and urinary sodium excretion. Most patients have at least a partial improvement in their ascites with reduced diuretic requirements.

The mechanism of ascites reduction following TIPSS placement remains unclear. Possibilities include a reduction in the activity of the RAAS despite worsening of the hyperdynamic circulation (Wong *et al* 1997) and a hepatorenal reflex directly linking portal pressure and renal perfusion (Jalan *et al* 1997).

Most studies assessing TIPSS procedure for refractory ascites report a high incidence of hepatic encephalopathy and a high mortality due to the advanced liver disease present in these patients. In view of their poor prognosis, any patient with refractory ascites should also be considered for orthotopic liver transplantation.

Two studies (Ochs *et al* 1995, Lebrec *et al* 1996), have reported results of randomised trials comparing TIPSS with paracentesis. Lebrec et al reported that TIPSS procedure was effective in the control of refractory ascites, but only in patients with Childs C disease (Lebrec *et al* 1996). Survival was actually lower in patients treated with TIPSS, possibly due to a reduction in hepatic perfusion. They concluded that the improvement in ascites following TIPSS placement was due to neurohumeral factors controlling naturesis, which depended on hepatic sinusoidal pressure. Ochs and colleagues reported that TIPSS was more effective than paracentesis in the control of refractory ascites with a reduced period of hospitalisation (Ochs *et al* 1995). No difference in survival between the two groups was observed.

In addition, one study presented in abstract form randomised patients with refractory ascites to receive either TIPSS or a peritoneovenous shunt (Zervos *et al* 1996). The authors found that both treatments were equally effective in palliating ascites but no difference in survival was detected. Patients treated with peritoneovenous shunts had fewer days in Intensive Care.

Currently TIPSS procedure should probably not be considered a routine treatment for refractory ascites, and its use for this indication is best limited to controlled trials. These studies should compare TIPSS placement with paracentesis or peritoneovenous shunt insertion and should also assess quality of life issues.

1f iii Hepatorenal syndrome.

Patients with hepatorenal syndrome have a poor prognosis without orthotopic liver transplantation. Several short reports describing the use of TIPSS in a small number of such patients have suggested it may improve renal function, reduce the need for haemodialysis and prolong the waiting time to liver transplantation (Lake *et al* 1993, Spahr *et al* 1995, Sturgis *et al* 1995). However mortality is very high in this patient group due to their advanced liver disease and the use of TIPSS can only provide at best a temporary reprieve.

1f iv Complications of TIPSS procedure

Hepatic encephalopathy

One of the major concerns that was anticipated about TIPSS placement is the increased risk of hepatic encephalopathy due to the portosystemic shunting of blood and reduced hepatic sinusoidal perfusion. New or worsening encephalopathy has been reported in 15-29% patients in the large TIPSS cohort studies (table 5). Unlike the chronic debilitating encephalopathy reported by the early shunt surgery series, post-TIPSS encephalopathy has been relatively easy to manage by protein restriction and lactulose therapy. However for the minority of patients who develop refractory encephalopathy, successful treatment by shunt reduction or occlusion has been reported (Hauenstein *et al* 1995, Haskal *et al* 1995, Rose *et al* 1995).

Studies that have prospectively assessed the development of encephalopathy following TIPSS placement have suggested that the incidence is highest in the first 3 months after shunt placement and improves thereafter, presumably due to gradual narrowing of the stent (Sanyal *et al* 1994, Riggio *et al* 1996). Using multivariate analysis, encephalopathy following TIPSS procedure has been shown to be predicted by its presence prior to the procedure, hypoalbuminaemia, non-alcohol aetiology of cirrhosis, advanced age, female gender and low post-procedural PPG (Sanyal *et al* 1994, Jalan *et al* 1995, Somberg *et al* 1995, Riggio *et al* 1996). Such patients must be carefully assessed prior to and following TIPSS procedure, and perhaps should have narrower stents placed and be given prophylactic lactulose and protein restriction.

It remains difficult to achieve the optimal balance between the reduction in portal pressure required to minimize the risk of variceal bleeding, maintain hepatic perfusion and avoid post-procedural encephalopathy.

Shunt insufficiency

The frequent occurrence of shunt insufficiency and therefore the need for repeated assessment of shunt patency during follow-up is probably the major limitation of TIPSS. The major cohort studies describe shunt insufficiency in 29-33% patients during follow-up, with consequent risks of variceal rebleeding or ascites reaccumulation (table 5). A prospective study which carefully assessed shunt patency during follow-up revealed a 1 year shunt insufficiency rate of 53% (Lind *et al* 1994). Patency can be maintained in the vast majority of patients by a combination of balloon angioplasty, shunt extension or parallel TIPSS placement (LaBerge *et al* 1995), but the challenge is to detect the shunt insufficiency before clinical consequences occur.

It must be remembered that reports of shunt insufficiency following TIPSS procedure depends to a large extent on both the frequency and method of assessing shunt patency and the definition of "shunt insufficiency" used. A variety of different definitions have been used in the literature, but the most clinically appropriate one appears to be:

any narrowing of the shunt leading to a rise in the PPG to >12 mmHg, above which the risk of variceal bleeding increases (Groszmann *et al* 1990), or a 20% rise in immediate post TIPSS PPG for those patients with a low initial portal pressure.

The pathogenesis of shunt dysfunction remains poorly understood. Early shunt occlusion is usually due to thrombosis within the stent, but longer term shunt insufficiency is usually related to the development of pseudo-intimal hyperplasia causing stenosis within the stent or the hepatic vein (LaBerge *et al* 1993). It has been suggested that the creation of a transient biliary venous fistula by transection of a bile duct at the time of the TIPSS procedure may lead to shunt stenosis or occlusion due to the thrombogenic nature of bile (Haskal *et al* 1994, Jalan *et al* 1996).

Direct portography remains the "gold standard" in the assessment of shunt patency following TIPSS procedure (Sanyal *et al* 1997). Although several studies have suggested that duplex sonography is highly sensitive and specific at detecting shunt

stenosis (Ferral *et al* 1993, Chong *et al* 1993, Foshager *et al* 1995, Dodd *et al* 1995), other authors have reported poor detection of shunt dysfunction by ultrasonography as compared with portography (Hasegger *et al* 1994, Ferguson *et al* 1995, Bartolone *et al* 1996). One report highlighted the possible benefits of magnetic resonance angiography in the assessment of TIPSS patency (Eustace *et al* 1994), but currently this has limited availability.

A number of studies have suggested benefit from heparin or phenprocoumon in the reduction of early shunt occlusion following TIPSS placement (Krause *et al* 1994, Sauer *et al* 1995). However, the best hope of reducing the need for continual shunt assessment is probably the development of covered stents which have shown improved patency in swine (Nishimine *et al* 1995). Until such stents are available, the cost, time and invasive nature of direct portography must be weighed against the possible deficiencies of ultrasonography in detecting shunt dysfunction.

Haemodynamic effects

Following TIPSS placement, there is a worsening of the hyperdynamic cirrhotic circulation with increased cardiac output and decreased systemic vascular resistance (Azoulay *et al* 1994, Colombato *et al* 1996, Van Der Linden *et al* 1996). It is unclear as to how permanent these haemodynamic changes are. They are thought to occur as a result of the increased venous return to the heart from the decompressed splanchnic circulation.

The effects of these systemic haemodynamic changes on the renal circulation remain poorly understood. Although TIPSS placement has been shown to improve natriuresis and ascites control, any worsening of the systemic vasodilatation might be expected to further reduce renal perfusion. Alterations in the concentrations of humeral factors or the presence of an hepato-renal reflex may over-ride such an effect.

A recent study suggested that the major haemodynamic effect of TIPSS placement is the development of pulmonary hypertension, since this correlated with the decreased

PPG (Van der Linden *et al* 1996). In this study, transient shunt occlusion also returned all haemodynamic parameters except pulmonary artery pressure to baseline. The authors postulated that both mechanical and neurohumeral factors were involved in these changes. The clinical implication is that TIPSS should be used with caution in patients with known right heart failure or pulmonary hypertension.

Chapter 2.

THE METHODOLOGY OF THE HAEMODYNAMIC MEASUREMENTS IN CIRRHOTIC PATIENTS

The haemodynamic catheters were placed via a 7.5 french gauge right femoral venous introducer sheath (Baxter Healthcare Corporation, USA), inserted after infiltration of local anaesthetic (5-10 ml. 2% lignocaine). All catheters were positioned under fluoroscopic guidance. Heart rate and mean arterial pressure (MAP) were recorded using a Merlin patient monitoring system (Hewlett Packard Europe, Geneva, Switzerland).

2 a Azgos blood flow

Azgos blood flow (AzBF) was measured using a double thermister reverse thermodilution catheter (Webster Laboratories, California, U.S.A.). The catheter was positioned in the azgos vein and real time AzBF measured by transfering the thermister signals through a custom built interface and processing them in an IBM compatible PS2-286 microcomputer system as previously described (Hayes *et al* 1993). Measurements were taken over 30 seconds with the patient breathing normally at rest.

2 b Renal blood flow

Unilateral renal blood flow (RBF) was measured using the same reverse thermodilution, double thermister catheter described above for AzBF measurement. The catheter was positioned in the left renal vein (unless otherwise stated) since this is longer than the right which allows easier positioning to ensure the proximal thermister is within the lumen of the renal vein. The position was confirmed by injection of 5mls dilute contrast media (Conray 280, May & Baker Ltd., Dagenham, U.K.). The thermister signals were transfered through the microcomputer system as described above to give real time measurements of unilateral real time RBF.

2 c Hepatic venous pressure gradient

A Sidewinder II torque balloon catheter (Cordis Corporation, U.S.A.) was positioned in the right hepatic vein. Free and wedged hepatic venous pressure (FHVP and WHVP) were measured in triplicate to give mean values, and hepatic venous pressure gradient (HVPG) was calculated as:

$$HVPG = WHVP - FHVP.$$

2 d Cardio-pulmonary haemodynamics

Right heart catheterisation was undertaken using a Swan-Ganz catheter (Baxter Healthcare Corporation, U.S.A.). Right atrial pressure (RAP) was measured, then the catheter was positioned in the pulmonary artery to measure mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). With the catheter then free in the pulmonary artery, cardiac output (CO) was measured by the standard thermodilution technique and systemic vascular resistance (SVR) calculated as:

$$SVR = 79.96 \times (MAP-RAP) / CO.$$

2 e Estimated hepatic blood flow

Via a peripheral vein, an intravenous bolus of 10mg indocyanine green (ICG) was given prior to an infusion of 0.2mg/min ICG. Following an equilibration period of 40 mins, 3 simultaneous samples were taken from the right hepatic vein (using the Sidewinder II balloon catheter descibed above for HVPG measurement) and right femoral vein to calculate estimated hepatic blood flow (HBF), (provided the hepatic extraction of ICG was > 10%):

HBF = (ICG Clearance/ICG Extraction) / (1-Haematocrit)

Chapter 3.

ANALYSIS OF HAEMODYNAMIC PARAMETERS IN ALCOHOL-INDUCED CIRRHOSIS AND PREDICTIVE VALUE FOR VARICEAL HAEMORRHAGE AND DEATH

3a Introduction

The prognosis of cirrhotic patients depends largely on the severity of the liver disease. However, it has been suggested that haemodynamic assessment of the systemic, cardiopulmonary and particularly the portal circulation may offer additional indicators of prognosis (Gluud *et al* 1988, Armonis *et al* 1996).

The aim of this study was to clarify the relationship between systemic, cardiopulmonary and portal haemodynamic parameters in patients with alcohol-related cirrhosis, and assess their prognostic value with regard to variceal bleeding and survival.

3 b Methods

3 b i Patients

From November 1992 to September 1996, 96 patients with alcohol-related cirrhosis underwent haemodynamic assessment either as baseline measurements prior to acute pharmacological intervention trials or as part of detailed assessment of their liver disease. Cirrhosis was diagnosed by liver biopsy or by clinical assessment (varices or ascites in the absence of other causes and in the prescence of chronic biochemical derangement of liver function tests). Full patient characteristics are shown in table 7.

Twenty-four patients had suffered a previous variceal bleed and were on long-term variceal obliteration programmes with band ligation. Three patients were in a similar programme as part of a study assessing band ligation in the primary prophylaxis of variceal haemorrhage. No patient was encephalopathic and none had suffered a variceal bleed in the 10 days prior to haemodynamic assessment. All patients were haemodynamically stable at the time of study and none were taking haemodynamic altering medications except for diuretic therapy (n=51).

Table 7.

Patient characteristics at time of haemodynamic study (n=96).

Sex (M/F)		63/33
Age (years):		
	mean±SEM	55.6±1.0
	range	35-80
Childs-Pugh score:		
	mean±SEM	9.0±0.2
Childs grade (%):		
	A	15 (15.6)
	B	36 (37.5)
	C	45 (46.9)

3b ii Haemodynamic measurements

Ethical approval was given by Lothian Ethics Committeee and all patients gave informed written consent. On the day of study, a full clinical examination was undertaken and blood taken for measurement of serum bilirubin and albumin, and prothrombin time. Due to the complexities of multiple catheter placement, all haemodynamic measurements were not undertaken at each study.

Heart rate and MAP were recorded in all patients. Hepatic venous pressure gradient (HVPG) was measured in 82 patients and AzBF and RBF in 62 and 42 respectively. Right atrial pressure (RAP), CO and SVR were also measured in 28 patients.

Patients were followed up at 3-monthly intervals or earlier if complications arose. Mean±SEM follow-up to most recent clinical review, death or liver transplantation (n=2) was 19.3±1.5 months and episodes of endoscopically proven variceal haemorrhage during follow-up were recorded.

3b iii Data Analysis

Results are expressed as mean±SEM. Relationship between variables was assessed using Spearmans correlation, and comparisons between groups analysed by unpaired Students t-test and Mann-U-Whitney test for parametric and non-parametric data respectively.

Patients were grouped into Childs Class A/B and Childs Class C for survival analysis, into HVPG<12mmHg and >12mmHg for bleeding analysis and into HVPG<16mmHg or >16mmHg for both bleeding and survival analysis. These groups were chosen because it has been suggested that variceal bleeding does not occur at HVPG<12mmHg (Garcia-Tsao *et al* 1985), and that HVPG of 16mmHg may be a threshold value above which bleeding and death is more likely (Merkel *et al* 1992). Survival and bleeding were compared between groups using Kaplan-Meier method with log rank test.

Cox's regression was used to test the univariate and multivariate significance of the haemodynamic parameters described above in addition to serum albumin, bilirubin, prothrombin time, the presence of ascites, the CPS, diuretic therapy and the occurence of a previous variceal bleed in predicting variceal bleeding and death.

3 c Results

3c i Baseline values

The baseline values of the haemodynamic measurements are shown in table 8. Both the HVPG and AzBF correlated with CPS ($r=0.38$, $p=0.001$ and $r=0.29$, $p<0.05$ respectively; figs. 3 and 4) but not with other haemodynamic parameters. CPS was also related to heart rate, MAP, CO and SVR ($r=0.38$, $p<0.001$; $r=-0.28$, $p<0.01$; $r=0.40$, $p<0.05$; $r=-0.44$, $p<0.05$ respectively). CO and SVR also both correlated with heart rate ($r=0.55$, $p<0.005$ and $r=-0.62$, $p<0.005$ respectively) but not with other haemodynamic measurements. There was no relationship between RBF and any other haemodynamic parameter or CPS.

Table 8.

Baseline haemodynamic measurements.

Measurement	Mean±SEM
MAP (mmHg)	90.51±1.38
CO (l/min)	6.90±0.30
SVR (dynes-s-cm^{-5})	1055.91±82.72
HVPG (mmHg)	16.69±0.59
AzBF (ml/min)	474.68±43.07
RBF (ml/min)	398.98±38.83

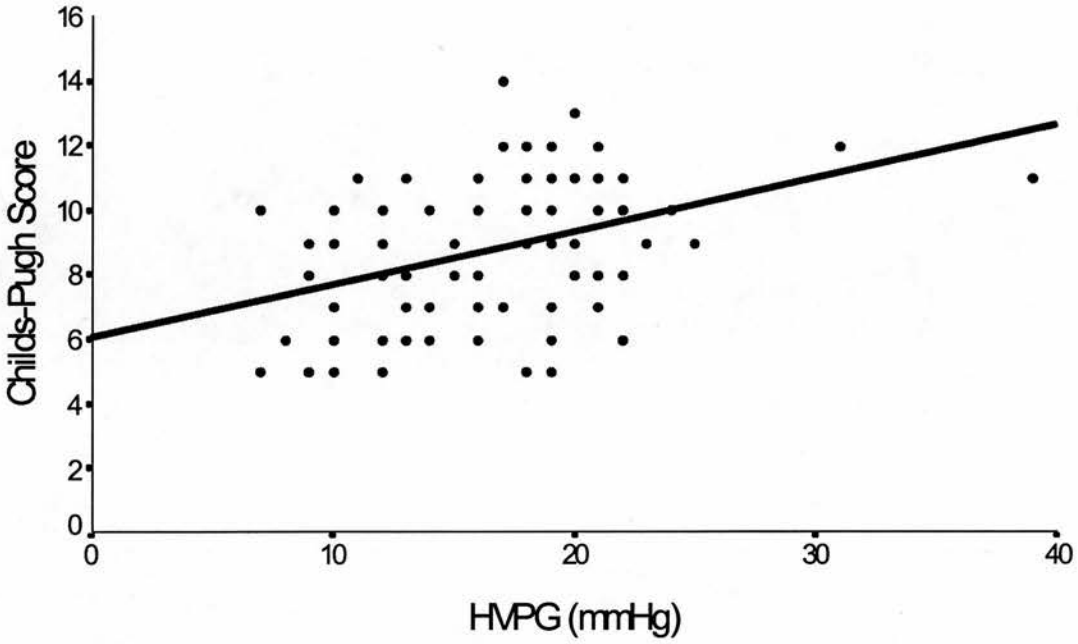


Figure 3.

Graph showing correlation between Childs-Pugh Score and hepatic venous pressure gradient (HVPG) (r=0.38, p=0.001).

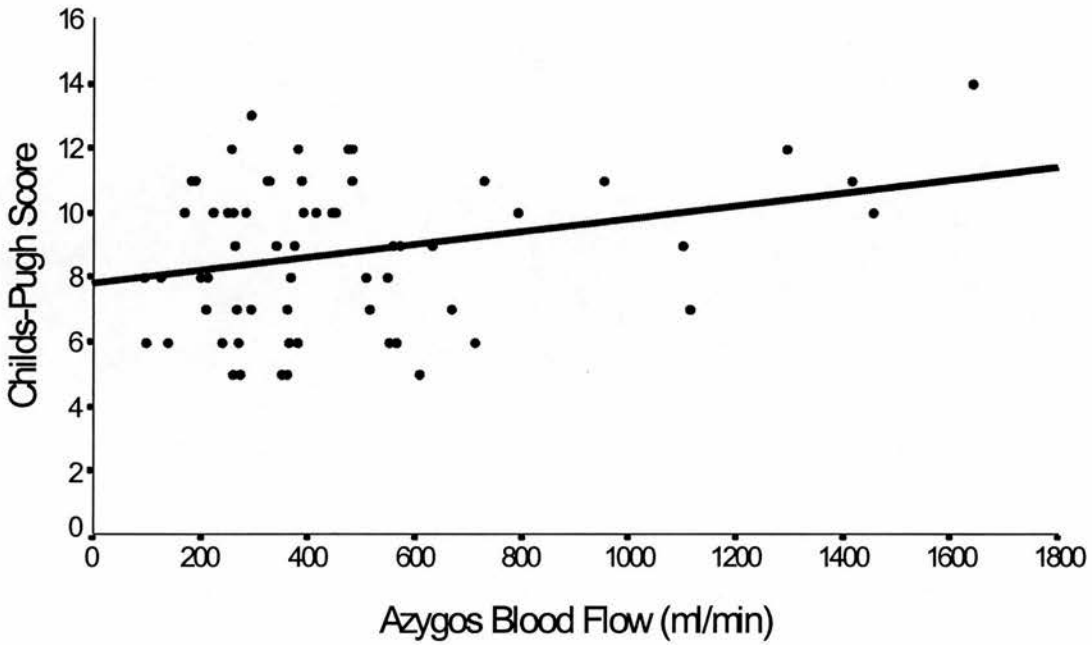


Figure 4.

Graph showing correlation between Childs-Pugh Score and Azygos blood flow ($r=0.29$, $p<0.05$).

3 c ii Variceal bleeding

During follow-up, 16 patients suffered a variceal haemorrhage (only one of whom had a baseline HVPG of <12mmHg). Variceal bleeding occurred in 7 (29.2%) patients who had previously bled and 9 (12.5%) who had not (p=NS). Baseline HVPG was higher in those patients who subsequently bled compared with those who did not (18.7±1.2 vs 16.3±0.7mmHg; $p<0.02$) and bleeding was more likely to occur in those with a baseline HVPG>12mmHg compared with those with HVPG<12mmHg ($p<0.05$; fig. 5) and also in those with HVPG>16mmHg compared with those with HVPG<16mmHg ($p<0.05$). Variceal bleeding was only predicted in the univariate or multivariate analysis by HVPG ($p<0.01$).

Baseline CO was higher in those patients who bled during follow-up compared with those who did not (10.7±0.7 versus 6.7±0.3 l/min; $p<0.01$), but AzBF, RBF, SVR, HR, MAP and CPS were no different between those who subsequently bled and those who did not.

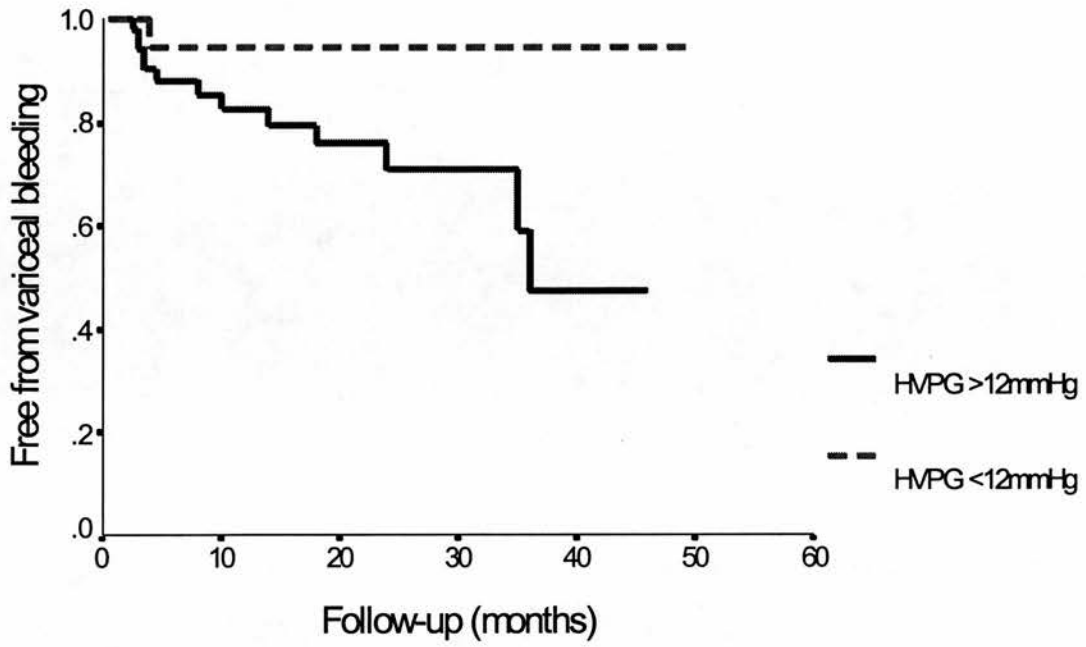


Figure 5.

Kaplan-Meier analysis comparing variceal bleeding during follow-up between patients with HVPG<12mmHg and those with HVPG>12mmHg ($p<0.05$).

3c iii Survival

During follow-up, 38 patients died. Survival was significantly greater in patients with Childs grade A or B compared with Childs C disease ($p<0.0001$) (fig. 6), and in those with baseline HVPG <16mmHg compared with HVPG >16mmHg ($p=0.001$) (fig. 7). Baseline CPS and HVPG were higher in patients who died during follow-up compared with those who survived (10.3 ± 0.3 versus 8.2 ± 0.3 ($p<0.001$); and 19.2 ± 1.0 versus 15.1 ± 0.7mmHg ($p=0.001$) respectively). Baseline AzBF, RBF, CO, SVR or MAP was not different between those who died and survived on follow-up.

Variables predicting death in the univariate analysis were CPS ($p<0.0001$), prothrombin time ($p<0.0001$), HVPG ($p=0.0001$), presence of ascites ($p<0.001$), serum albumin ($p<0.001$), serum bilirubin ($p<0.05$), and diuretic therapy ($p<0.05$). No other haemodynamic parameter predicted death. On multivariate analysis, only the CPS and HVPG retained independent predictive significance ($p<0.0001$ and $p<0.05$ respectively).

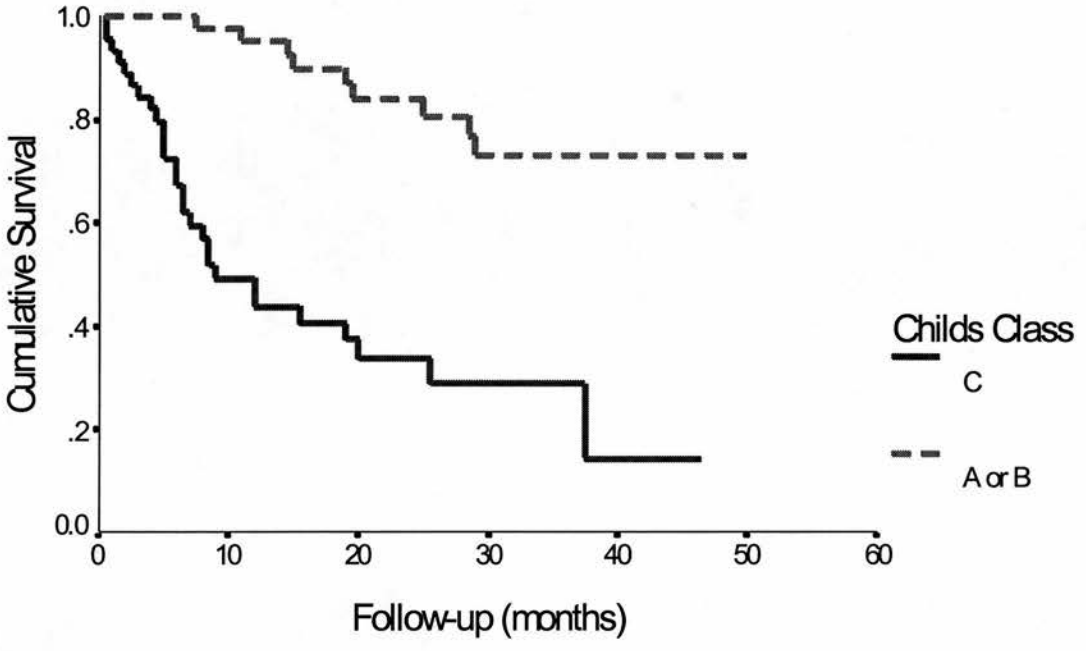


Figure 6.

Kaplan-Meier analysis comparing cumulative survival between patients with Childs grade A or B liver disease with those with grade C disease ($p<0.0001$)

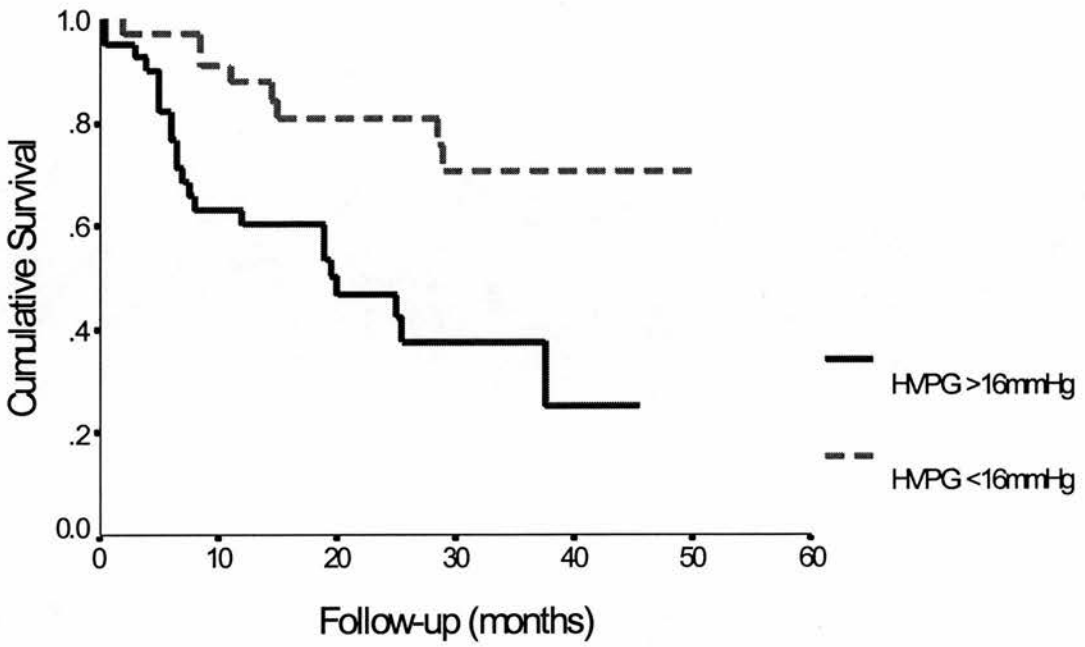


Figure 7.

Kaplan-Meier analysis comparing cumulative survival between patients with HVPG<16mmHg and those with HVPG>16mmHg (p=0.001).

3 d Conclusions

This large study indicates a strong relationship between severity of liver disease and the associated haemodynamic changes including a fall in MAP and SVR, and a rise in HVPG, CO and AzBF in patients with alcoholic cirrhosis. Measurement of HVPG is also shown to have strong prognostic value in such patients.

Death and variceal bleeding were more likely in patients with HVPG>16mmHg than in those with lower HVPG, and bleeding extremely uncommon in patients with HVPG<12mmHg. Perhaps most significantly, HVPG was the only haemodynamic or clinical parameter (including CPS) which predicted bleeding on multivariate analysis, and the CPS was the only parameter to have greater independent predictive value than HVPG for survival.

Chapter 4.

ACUTE RENAL, PORTAL AND SYSTEMIC HAEMODYNAMIC EFFECTS OF PROPRANOLOL AND ISOSORBIDE-5-MONONITRATE IN CIRRHOSIS

4 a Introduction

Beta-blockers and nitrates are the drugs most commonly used in the prophylaxis of variceal haemorrhage. However, several recent studies have suggested that these drugs may compromise renal function in cirrhosis. The aim of our study was to investigate the effect of propranolol, ISMN and the combination of both drugs on renal blood flow and systemic and splanchnic haemodynamics in patients with cirrhosis.

4 b Methods

4b i Patients

All patients gave informed written consent, and the study was approved by the Lothian Ethics Committee. Twenty-six patients (12 female, mean age 51.1±1.9 years (range 33-70), mean CPS 9.2±0.6) with cirrhosis were studied. Eighteen patients had ascites at the time of study which was clinically graded as mild, moderate or severe (see table 9). Diagnosis of cirrhosis was based on liver biopsy (20 patients) or the presence of chronic liver biochemical abnormalities and endoscopically proven varices (6 patients). Cirrhosis was alcohol related (ALD) in 21 patients, secondary to primary biliary cirrhosis in 2 patients and primary sclerosing cholangitis, sarcoid and alpha-1-antitrypsin deficiency in 1 patient each.

No patient had biochemical evidence of renal dysfunction prior to study (serum urea > 6.6 mmol/l or serum creatinine > 150 umol/l) and none were receiving vasoactive medication at the time of study. In addition, no patient had suffered a gastrointestinal haemorrhage within the previous 4 months.

4b ii Haemodynamic measurements

Studies were undertaken in the Department of Medicine catheter laboratory, on fasted patients in the supine position. HVPG was measured, then unilateral (left) RBF and AzBF in each patient. The thermodilution catheter was then left in position for the duration of the study.

When recruited for the study, patients were matched for age and CPS for each therapeutic regimen (table 9). Nine patients were then given 80 mg oral propranolol, 8 patients 20 mg oral ISMN and 9 patients both therapies. One hour later AzBF was again recorded, then the reverse thermodilution catheter was manouevred back into the initial position in the left renal vein and repeat measurement of RBF undertaken.

Finally, measurement of HVPG was repeated. The sheath was then removed and firm pressure applied until haemostasis was obtained. Heart rate and MAP were also recorded for the duration of the study and for 4 hours thereafter. In all cases, the duration of the study was less than 3.5 hours.

Table 9.

Characteristics of patients given propranolol, isosorbide-5-mononitrate (ISMN) or combination therapy.

	Propranolol	ISMN	Propranolol/ISMN
	(n=9)	(n=8)	(n=9)
Age (yrs):	52.7±2.3	50.5±2.8	51.1±1.9
Childs-Pugh score:	9.2±1.0	9.4±1.5	9.1±1.1
No. with ascites (mild or moderate/severe):	5/0	4/1	7/1
Serum Creatinine (umol/l), mean (range):	83.1 (63-136)	92.1 (65-142)	88.8 (66-126)
Aetiology (ALD/other):	8/1	6/2	7/2

(ALD = Alcohol related liver disease)

4b iii Data Analysis

Results are expressed as mean±SEM or range were indicated. For parametric data, paired Student's *t*-test and Pearson's correlation were used. Wilcoxon signed ranked test and Kendall correlation were used for non-parametric variables. A p-value of < 0.05 was taken to be significant.

4 c Results

4c i Baseline values and systemic haemodynamic changes

All patients completed the study without difficulty and no side effects were observed or reported. There was no statistical difference between the three therapeutic groups with regard to baseline RBF or other haemodynamic parameters. Baseline RBF did not correlate with CPS, HVPG or ascites severity. Changes in heart rate and MAP for each therapy group at one hour following medication are shown in table 10.

Table 10.

Systemic haemodynamic effects of acute administration of propranolol, ISMN and combined therapy

	Propranolol		ISMN		Propranolol/ISMN	
	pre	*post*	*pre*	*post*	pre	post
Heart rate (bpm):	81.6±3.9	71.7±4.2 [I]	86.8±3.5	91.0±3.3	79.9±4.8	71.4±4.4
MAP (mmHg)	82.6±3.4	78.2±3.3	84.5±3.3	76.9±3.6 [I]	78.1±4.6	68.7±3.4 [I]

[I] $p<0.005$ versus pre-drug value

4 c ii Splanchnic and renal haemodynamic effects of propranolol

Following administration of propranolol, there was a fall in HVPG from 16.3±2.2 to 12.9±1.9 mmHg ($p=0.05$) and in AzBF from 471.5±85.8 to 293.4±42.6 ml/min ($p<0.01$) (fig. 8). There was no effect on RBF (454.1±77.3 versus 413.9±60.3 ml/min) (fig. 9).

4 c iii Splanchnic and renal haemodynamic effects of ISMN

ISMN therapy led to a fall in HVPG from 14.9±1.9 to 11.0±1.3 mmHg ($p<0.01$), but no effect on either AzBF (573.4±183.1 versus 576.0±145.1) ml/min) (fig. 8) or RBF (302.5±49.4 versus 301.7±58.8 ml/min) (fig. 9).

4 c iv Splanchnic and renal haemodynamic effects of combination therapy

Following administration of the combination of propranolol and ISMN, HVPG fell from 15.1±1.8 to 8.9±1.1 mmHg ($p=0.002$) and AzBF fell from 612.5±187.6 to 358.2±57.0 ml/min ($p<0.05$) (fig. 8). Again, there was no effect on RBF (419.2±62.6 versus 415.1±61.1 ml/min) (fig. 9).

When the 18 patients with ascites were considered alone, there remained no effect on RBF of any therapy when these patients were grouped together, or when analysed in treatment subgroups.

Figure 8 (over page)

Graph showing the changes in hepatic venous pressure gradient (HVPG) and azygos blood flow (AzBF) 1 hour following a single dose of propranolol, ISMN or combined therapy.

Figure 8

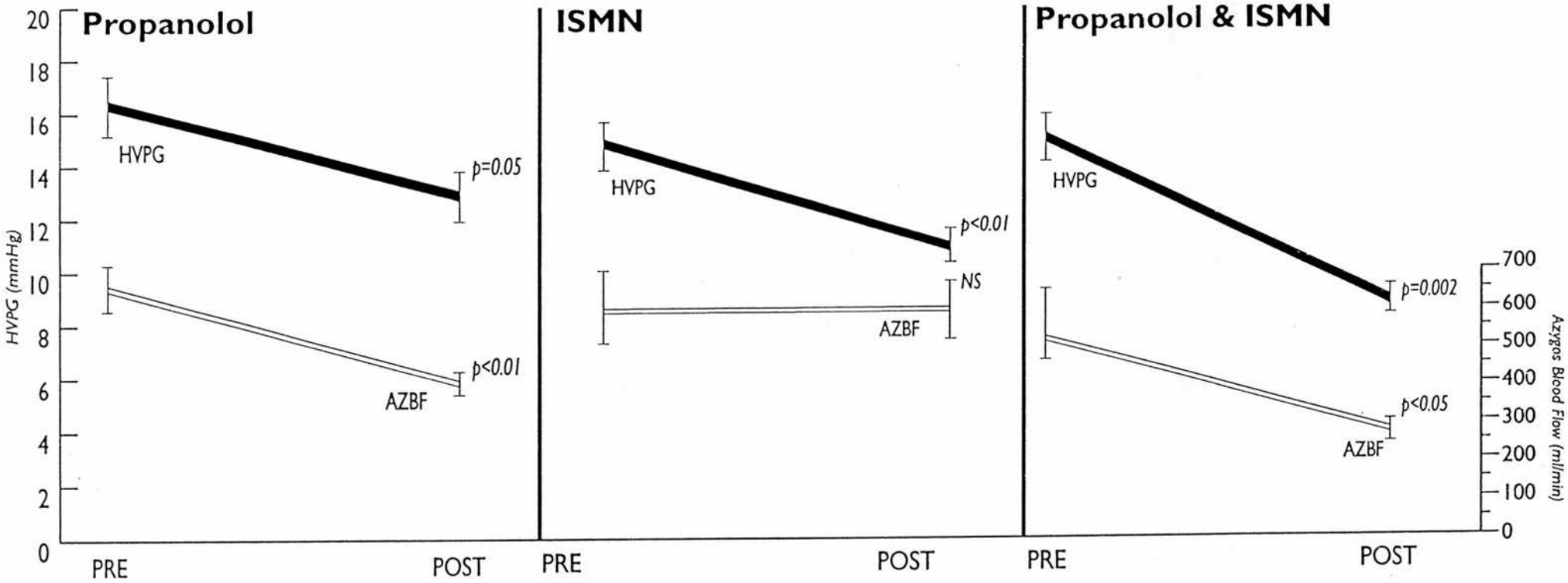
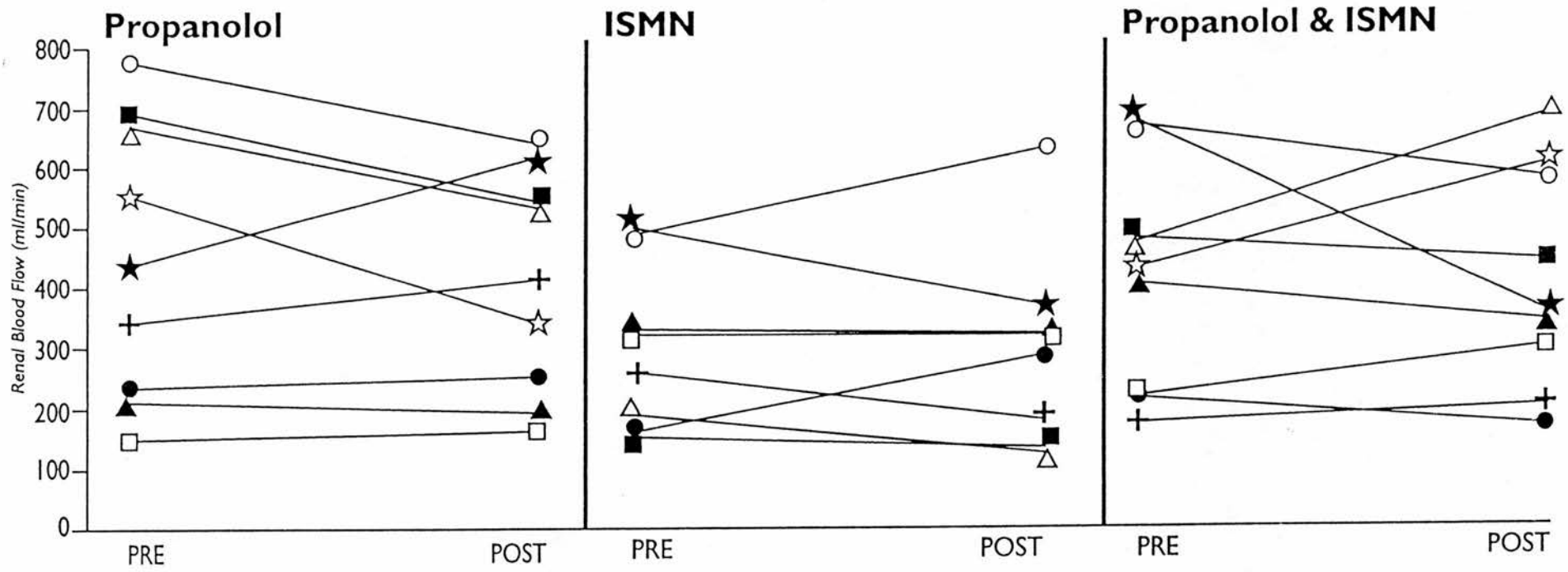

Propanolol
ISMN
Propanolol & ISMN
HVPG (mmHg)
Azygos Blood Flow (ml/min)
20
18
16
14
12
10
8
6
4
2
0
700
600
500
400
300
200
100
0
HVPG
AZBF
p=0.05
p<0.01
p<0.01
NS
p=0.002
p<0.05
PRE
POST
PRE
POST
PRE
POST

Figure 9 (over page)

Graph showing no significant change in unilateral renal blood flow 1 hour following a single dose of propranolol, ISMN or combined therapy.

Figure 9


Propanolol
ISMN
Propanolol & ISMN
Renal Blood Flow (ml/min)
800
700
600
500
400
300
200
100
0
PRE
POST
PRE
POST
PRE
POST

4 d Conclusions

We undertook this study to assess the acute effect of propranolol, ISMN and the combination of both drugs on RBF in cirrhotic patients. Despite the anticipated drop in MAP with ISMN and combination therapy, and the significant changes in HVPG and AzBF with these drugs, no effect on RBF was detected with either drug alone or in combination.

Any effect on renal function following administration of these drugs to cirrhotic patients does not appear to occur secondary to an acute fall in RBF.

Chapter 5.

ACUTE AND CHRONIC HAEMODYNAMIC AND RENAL EFFECTS OF CARVEDILOL, A VASODILATING BETA-BLOCKER IN CIRRHOSIS

5 a Introduction

Carvedilol is a novel vasodilating non-selective beta-blocker with weak alpha-1 receptor and calcium channel antagonism. Recent reports have shown that acute administration of carvedilol can reduce portal pressure in cirrhosis (Forrest *et al* 1996, Sekiyama *et al* 1997), but no information exists as to the chronic effects of carvedilol in this patient population. The aim of our study was to assess the acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis.

5 b Methods

5b i Patients

All patients gave informed written consent to the study which was approved by the Lothian Medicine and Oncology Ethics Committee. Seventeen patients (mean age 55.2±2.8 years) with known cirrhosis and current or previously documented oesophageal varices were studied. Sixteen patients had alcohol related cirrhosis, and one Primary Biliary Cirrhosis. Eight patients had Childs-Pugh grade A, five grade B and four grade C liver disease.

Eleven patients had ascites (6 moderate, 5 mild). Seven patients had previously suffered a variceal bleed and had undergone obliteration of their varices by band ligation. Eight patients had undergone band ligation as primary prophylaxis against variceal haemorrhage as part of an ongoing study, and two had grade I oesophageal varices for which they had received no treatment.

5b ii Study Protocol

Patients underwent assessment of their portal and systemic circulations prior to and 60 minutes following 25mg oral carvedilol. They then received 12.5mg carvedilol daily (at 0900), increased to 25mg after 3 days if tolerated for four weeks. At this stage, repeat assessment of their portal and systemic circulations were undertaken prior to rechallenge with 25mg carvedilol. The last morning dose (on the day of the second invasive procedure) had been omitted. In addition their renal function was assessed at baseline and after 4 weeks carvedilol therapy. Patients compliance with drug therapy was assessed by questioning and a tablet count.

5b iii Haemodynamic measurements

Haemodynamic measurements were undertaken with the patient in the fasted state in the supine position. Cardiac output (CO) and SVR were measured, then FHVP and WHVP to calculate HVPG. In addition, HBF was measured using the ICG clearance method described earlier.

All the above measurements were repeated 60 minutes following administration of 25mg oral carvedilol. Heart rate and MAP were measured at 15 minutes during the study.

Following 4 weeks carvedilol therapy, these parameters were again measured prior to and 60 minutes following re-challenge with 25mg oral carvedilol.

5b iv Assessment of renal function

Prior to commencement of the study, a 24 hour urine collection was obtained for measurement of urine volume, urine sodium excretion and creatinine clearance. Following 4 weeks carvedilol therapy, a further 24 hour urine collection was obtained to repeat these analyses.

5b v Data Analysis

Results are expressed as mean±SEM. Paired Students t-test and Pearson's correlation were used for parametric data, and Wilcoxon signed rank test and Spearman correlation for non-parametric data.

5 c Results

5c i Tolerability

Seven patients were unable to complete 4 weeks carvedilol therapy and return for the second study. Two had an immediate hypotensive response to the first dose of 25mg carvedilol with asymptomatic falls in blood pressure to 60/40 and 65/35 mmHg respectively, maximal at 90-120 minutes following drug administration. However, both had a spontaneous rise in blood pressure within 2 hours with no untoward effects, but they received no further carvedilol. One other patient had an asymptomatic gradual fall in BP to 85/50 after 8 days of therapy despite keeping the dose of carvedilol at 12.5mg, therefore the drug was discontinued.

Three patients resumed alcohol drinking, stopped therapy and failed to attend for the repeat study. One other patient changed employment during the study period and was unable to take time off to attend for the repeat study and therefore discontinued carvedilol after 3 weeks without experiencing any side-effects.

Of the 10 patients who completed 4 weeks of carvedilol therapy and attended for the second haemodynamic study, 8 were able to take 25mg daily with no ill effects and 2 were changed to the lower dose (12.5mg daily) due to mild hypotension and dizziness (n=1) or mild breathlessness (n=1). One further patient had an asymptomatic BP of 90/50 at the baseline haemodynamic measurements at 4 weeks, and he was therefore not rechallenged with the drug. No untoward effects were reported and his BP rose spontaneously after discontinuation of the drug.

5c ii Splanchnic haemodynamic response

Following acute administration of carvedilol, there was a mean fall in HVPG of 20.8% from a baseline value of 16.3±1.2 to 13.2±1.3mmHg ($p<0.001$), and a continued effect at 4 weeks compared with baseline (mean fall of 16.3% to 12.9±1.7mmHg) ($p=0.001$) (fig. 10). Following rechallenge at 4 weeks, there was a further slight fall in HVPG to 11.2±1.5mmHg ($p<0.05$ compared to the baseline value at 4 weeks) (fig. 10).

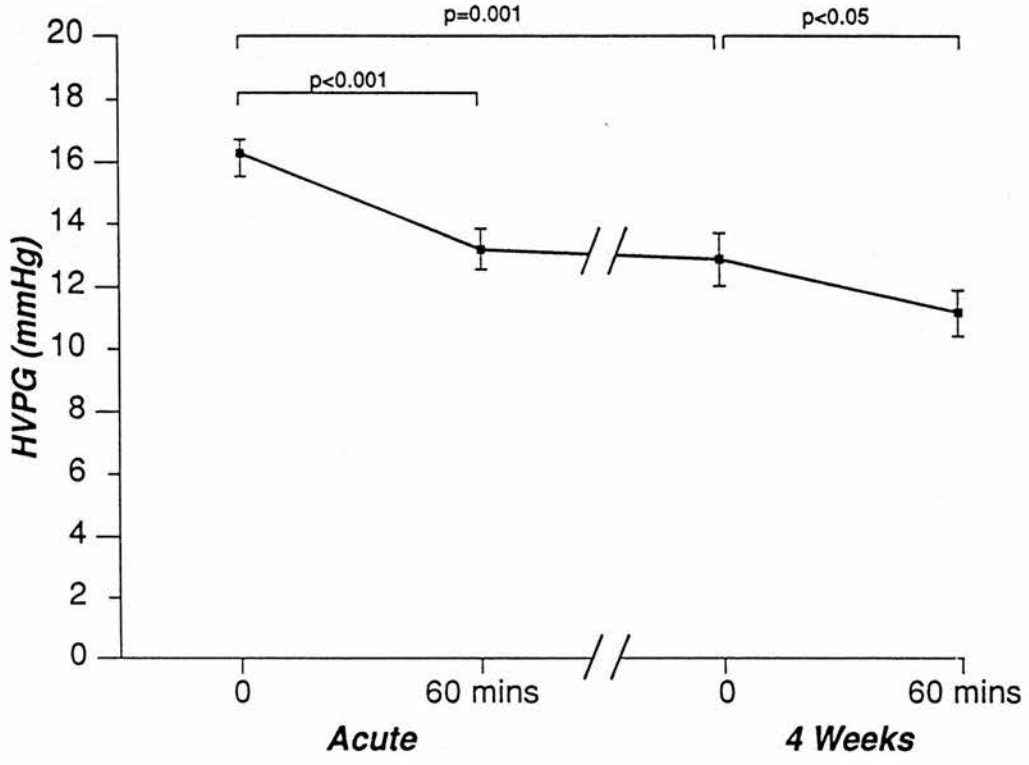
Thirteen (76.5%) patients had an acute fall in HVPG of 10% or more and 7 (41.2%) a fall of 20% or more. After 4 weeks therapy, 6 (60%) patients had a fall in HVPG of 10% or more compared with baseline, and 4 (40%) a fall of 20% or more. The FHVP did not change significantly from baseline at any time point, and the fall in HVPG was accounted for by a drop in WHVP (table 11). There was no difference in the reduction in HVPG between the patients who had suffered a previous variceal bleed, and those who had not.

There was no change in HBF after acute or chronic administration of carvedilol or on rechallenge of the drug (table 11).

Figure 10 (over page)

Graph showing reduction in hepatic venous pressure gradient (HVPG) following acute and chronic administration of carvedilol and after rechallenge at 4 weeks.

Figure 10


p=0.001
p<0.05
p<0.001
20
18
16
14
12
10
8
6
4
2
0
HVPG (mmHg)
0
60 mins
0
60 mins
Acute
4 Weeks

5c iii Systemic haemodynamic response

There was a fall in HR after acute and chronic drug administration, but no effect on rechallenge at 4 weeks (table 11). Similarly, MAP fell acutely and after 4 weeks therapy, but there was also a further fall on rechallenge (fig. 11). Cardiac output fell after acute administration of carvedilol, but the drop in CO after 4 weeks therapy failed to reach significance, and there was no further effect on rechallenge (table 11). The acute and chronic changes in CO did not correlate with the drop in HVPG or WHVP. There were no effects on RAP or SVR after acute or chronic carvedilol administration, or on rechallenge at 4 weeks (table 11).

5c iv Effect on renal function

There were no changes in urine volume, natriuresis or creatinine clearance following 4 weeks carvedilol therapy (table 12).

Table 11. **Effect of acute and chronic (4 weeks) carvedilol therapy on WHVP, FHVP, HBF and systemic haemodynamics.**

	ACUTE		*CHRONIC*	
	baseline	**+60mins.**	**baseline**	**+60mins.**
WHVP (mmHg)	21.1±1.4	17.8±1.6*	17.4±1.2°	14.9±1.8°♦
FHVP (mmHg)	4.8±0.5	4.6±0.7	4.5±0.8	3.7±0.9
HBF (ml/min)	1052.8±201.8	1109.8±236.3	964.0±332.8	999.7±327.4
HR (bpm)	77.4±3.5	75.1±3.3'	65.1±3.2*	62.1±3.6*
RAP (mmHg)	2.8±0.5	2.1±0.5	1.2±0.6	1.1±1.0
CO (l/min)	6.8±0.7	6.3±0.5°	6.1±0.6	6.1±0.7°
SVR (dynes.cm)	1016.3±78.1	1019.2±68.9	1073.4±125.4	1068.7±137.6

(°$p<0.05$; ' $p<0.005$; *$p<0.001$ compared with baseline value of acute study; ♦$p<0.05$ compared with baseline of chronic study)

Figure 11 (over page)

Graph showing reduction in mean arterial pressure (MAP) following acute and chronic administration of carvedilol.

Figure 11

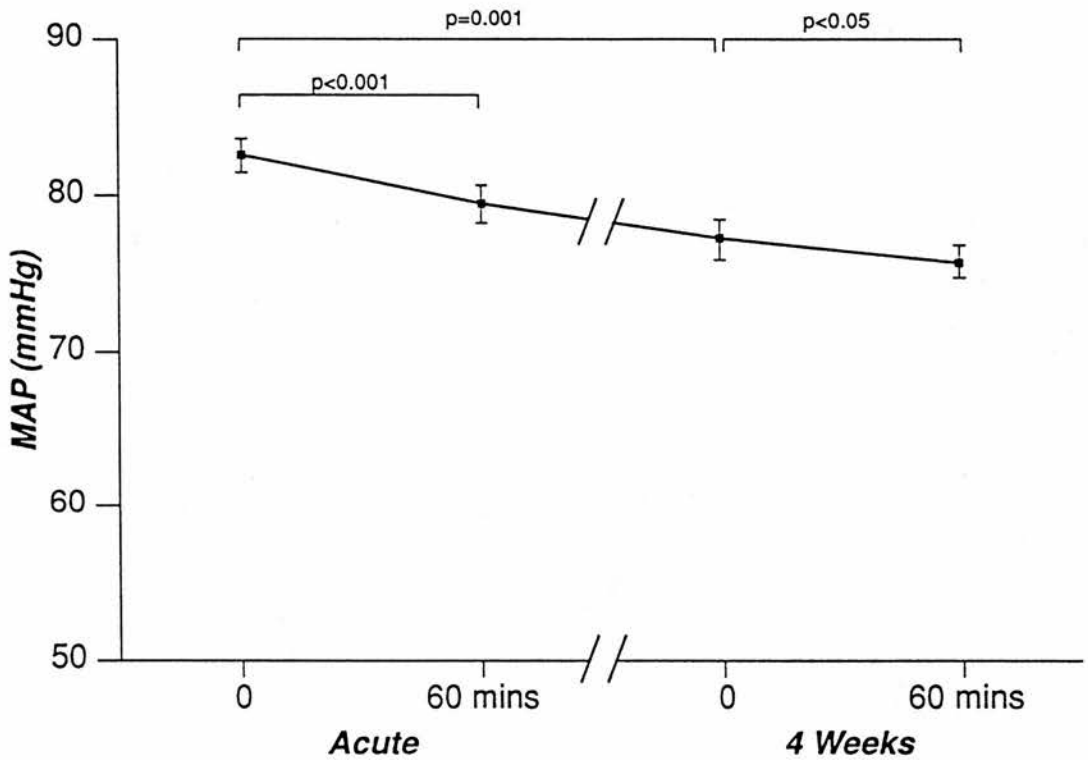

p=0.001
p<0.05
p<0.001
90
80
70
60
50
MAP (mmHg)
0
60 mins
0
60 mins
Acute
4 Weeks

Table 12.

Table showing no difference in urine volume, natriuresis and creatinine clearance before and after 4 weeks carvedilol therapy.

	baseline	4 weeks
Urine volume (ml/day)	1668.7±214.8	1880.9±309.6
Sodium excretion (mmol/day)	126.2±25.7	151.9±33.5
Creatinine clearance (ml/min)	114.6±27.9	190.5±49.7

5 d Conclusions

These results confirm the beneficial effect on HVPG of acute administration of carvedilol and show a consistent portal hypotensive effect following chronic therapy. No detrimental effect on hepatic blood flow or renal function was observed. However, a substantial minority of patients were unable to tolerate four weeks therapy with carvedilol.

Chapter 6.

HAEMODYNAMIC AND RENAL EFFECTS OF FK352 (A NOVEL ADENOSINE-1 ANTAGONIST) IN CIRRHOTIC PATIENTS WITH ASCITES

6 a Introduction

It has been suggested that adenosine plays a role in the renal abnormalities of cirrhosis, acting via adenosine-1 receptors on the renal artery and proximal tubule cells.

FK352 is a novel pyrazolopyridine derivative, which has been characterised in vitro as a highly selective adenosine-1 receptor antagonist. In animal studies, it has been shown to increase renal blood flow, diuresis and natriuresis, and its safety profile has been confirmed in healthy volunteers. However, adenosine-1 antagonists have never previously been investigated in patients with cirrhosis.

The aim of this study was to investigate the effects of FK352 on renal and systemic haemodynamics and renal function in cirrhotic patients with ascites.

6 b Methods

6b i Patients

Twelve patients (8 men) with alcohol-induced cirrhosis and ascites were studied. The mean age was 51.3±2.4 years and mean CPS 8.2±0.5 (8 Childs class B, 4 Childs class C). Cirrhosis was confirmed by biopsy in 9 patients and by the combination of oesophageal varices and chronic derangement in biochemical liver function tests in the absence of portal vein thrombosis in 3. All patients had earlier confirmation of ascites by ultrasonography and at the time of study, ascites was clinically graded as moderate (n=7) or mild (n=5). None of the patients were taking vasoactive medications and all were on dietary salt restriction.

Ten patients were on diuretic therapy prior to the study. Eight were taking spironolactone at a mean dose of 119mg/day (1 of whom was also taking 40mg frusemide daily) and 2 were taking amiloride at a mean dose of 6.7mg/day (1 of whom was also taking 40mg frusemide daily). Spironolactone was stopped 1 week, and amiloride and frusemide 3 days prior to the study. No patient had biochemical evidence of renal impairment (defined as serum urea > 6.6 mmol/l or serum creatinine > 150 mmol/l). Patients abstained from alcohol, cigarettes and caffeine containing substances for 24 hours prior to the study.

6b ii Study protocol

The study was approved by the Lothian Ethics Committee and all patients gave informed written consent. This was a Phase II open labelled pilot study, designed primarily to assess the efficacy and safety of FK352. A dose escalation was built into the study to identify any obvious trend towards a dose-response.

On the morning of the study, patients received a light breakfast (2 slices of toast and half a pint of milk). At 0800, they were required to drink 1 litre of water, then transferred to the Haemodynamic Suite where they remained supine until completion of the study. A urinary catheter was inserted and a loading dose of *p*-aminohippuric acid (PAH) (450mg) and inulin (3.5g) administered via a peripheral vein. This was followed at 0900 by a constant infusion of PAH (16mg/min) and inulin (20mg/min).

A single bolus injection of FK352 (10mg for the first 4 patients, 25mg the next 4 patients and 50mg the final 4 patients) was administered over a 2 minute period through a separate peripheral vein at 1200. PAH and inulin infusions were continued for 120 minutes following drug administration.

6b iii Plasma and urine analyses

Sixty minutes following commencement of the PAH and inulin infusions, 30 minute urine collections were obtained for the 2 hours prior to and the 2 hours following administration of FK352. Patients were required to drink 100 mls water during each of these 30 minutes periods. The urine collections were used to measure flow rate (V) and concentrations of PAH and inulin. Plasma was sampled at the mid-point of these 30 minute urine collections to measure PAH and inulin concentrations and therefore calculate inulin clearance (estimated GFR) and PAH clearance (estimated renal plasma flow (ERPF)) for each 30 minute period:

clearance = (Urine concentration) x V / (Plasma concentration).

Four patients also had renal venous PAH concentrations measured prior to and following FK352 to measure the PAH extraction coefficient { = (Peripheral PAH concentration - Renal vein PAH concentration) / (peripheral PAH concentration)}. In these 4 patients, this was used to give the corrected ERPF:

corrected ERPF = ERPF/PAH extraction coefficient.

.

In addition, plasma and urine osmolality, sodium and potassium concentration were also measured to calculate the sodium excretion rate (UNaV, where UNa is the urine concentration of sodium), potassium excretion rate and free water clearance for each 30 minute period:

free water clearance = V - (Urine osmolality) x V / (Plasma osmolality).

Plasma and urine was also collected at 15 minutes prior to and 15, 45 and 105 minutes following administration of FK352 to measure plasma angiotensin II, renin activity (PRA), adrenaline, noradrenaline and plasma and urine cAMP levels. At the end of the study, the PAH and inulin infusions were discontinued and the urinary catheter removed.

6b iv Laboratory analysis

Blood samples for PRA, angiotensin II, adrenaline, noradrenaline and cAMP determinations were collected on ice. The supernatant serum from all blood samples and the urine samples for cAMP measurement were stored at -70 degrees centigrade until analysis. PRA was measured by I^{125} radioimmunoassay of angiotensin I generation (Biodata Diagnostics, Roma, Italy), and angiotensin II by radioisotope assay with solid phase separation step (Nichols Institute Ltd., Newport, U.K.). Catecholamines were measured by high performance liquid chromatography and cAMP by radioimmunoassay (Incstar Ltd., Wokingham, U.K.). PAH and inulin were measured using high performance liquid chromatography with fluorometric detection and spectrophotometric technique respectively as previously described (Li Kam Wa *et al*, 1993).

6b v Haemodynamic measurements

Right heart catheterisation was undertaken to measure CO and SVR, 30 minutes prior to and 120 minutes following administration of FK352. Using the reverse thermodilution catheter, unilateral RBF was measured 15 minutes prior to and 15, 45, 75 and 105 minutes following administration of FK352, with the thermodilution catheter left in position between recordings. During the study, continuous electrocardiograph monitoring was employed and heart rate and MAP recorded at 15 minute intervals.

Following completion of the study (<6 hours in all cases), the femoral sheath was removed and pressure applied until haemostasis was obtained. The patient was then transferred to the ward and monitoring of heart rate and MAP was undertaken for a further 4 hours. The patients were observed overnight and reviewed at 1 week for clinical and biochemical assessment.

6b vi Data Analysis

Data are expressed as mean values ±SEM. In view of the repeated measurements on each patient, the drug effect was analysed by AUC based on percentage change from the mean baseline value. If the AUC was significant ($p<0.05$), the Students t-test was carried out to compare the mean pre-drug level with the value at each post-dose time point using the Bonferroni correction for multiple comparisons.

Therefore, the parameters with 4 post-dose time points (V, UNaV, potassium excretion rate, free water clearance and RBF) had a significance level of $0.05/4=0.0125$, and those with 3 post-dose time points (PAH and inulin clearance and hormone parameters) had a significance level of $0.05/3=0.0167$. The relationship between RBF and ERPF and the corrected ERPF was assessed using Spearman correlation with a significance level of $p<0.05$.

6 c Results

All patients tolerated the drug well and completed the study without difficulty. No clinical or biochemical abnormalities were detected at 24 hours or at the 1 week review. No dose response was detected, therefore all results were analysed for the 12 patients together.

6c i Changes in Renal Function

Following FK352 administration, UNaV increased by a mean of 199.9±43.0% ($p<0.001$) from a baseline mean of 185.9±62.6 to a maximum of 563.1±139.1 μmol/min and remained elevated for at least 2 hours (figure 12). Urine flow rate increased by 51.2±17.5% ($p<0.02$) from a mean of 6.49±0.80 to a maximum of 12.43±2.25 ml/min immediately following drug administration before returning towards baseline (figure 13). There was a slight rise in free water clearance by 92.7±53.8% from a mean of 3.56±0.56 prior to FK352 to 7.17±1.60 ml/min immediately following drug administration before returning towards baseline. However this did not reach statistical significance ($p=0.11$).

There was no change in potassium excretion rate following FK352 with a rise of 10.0±6.8% from a baseline of 60.84±9.88 μmol/min. Similarly, no change was observed in PAH or inulin clearance over the study period, with a change of 3.8±10.6% and -3.8±3.8% from baseline values of 592.2±60.8 ml/min and 113.8±12.8 ml/min respectively. In the 4 patients in whom it was measured, the PAH extraction coefficent ranged from 0.21-0.81, with a mean change in the corrected ERPF following FK352 of -1.3±12.6% from a baseline value of 454.8±150.3ml/min.

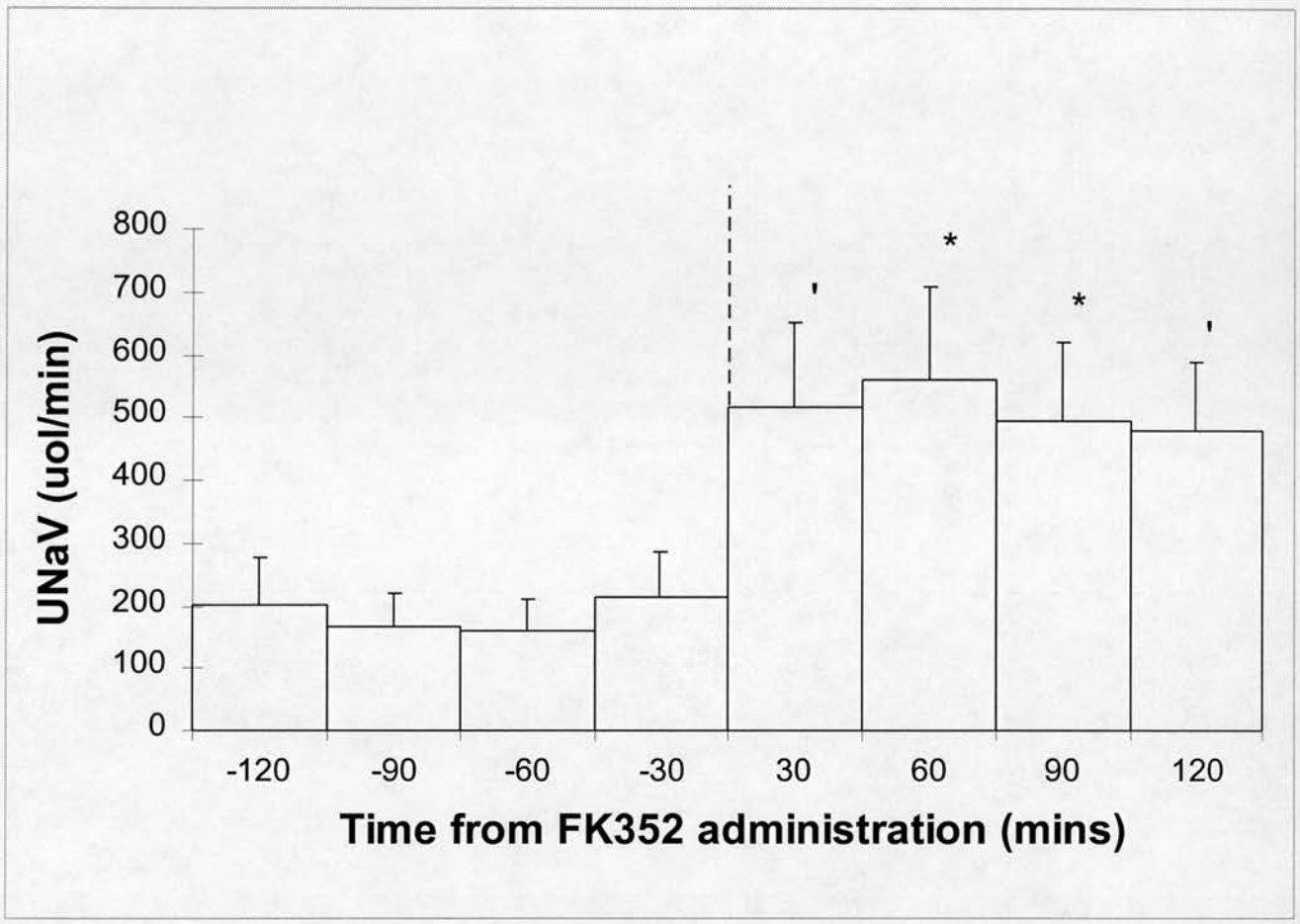


Figure 12.

Graph showing changes in absolute sodium excretion (UNaV) following administration of FK352 (AUC $p<0.001$).

{Application of the Bonferroni correction for multiple comparisons at individual post-dose time points gives significance level of $p=0.0125$. Therefore the individual significant values are: *$p<0.001$ and ' $p<0.005$ vs. mean pre-FK352 value}.

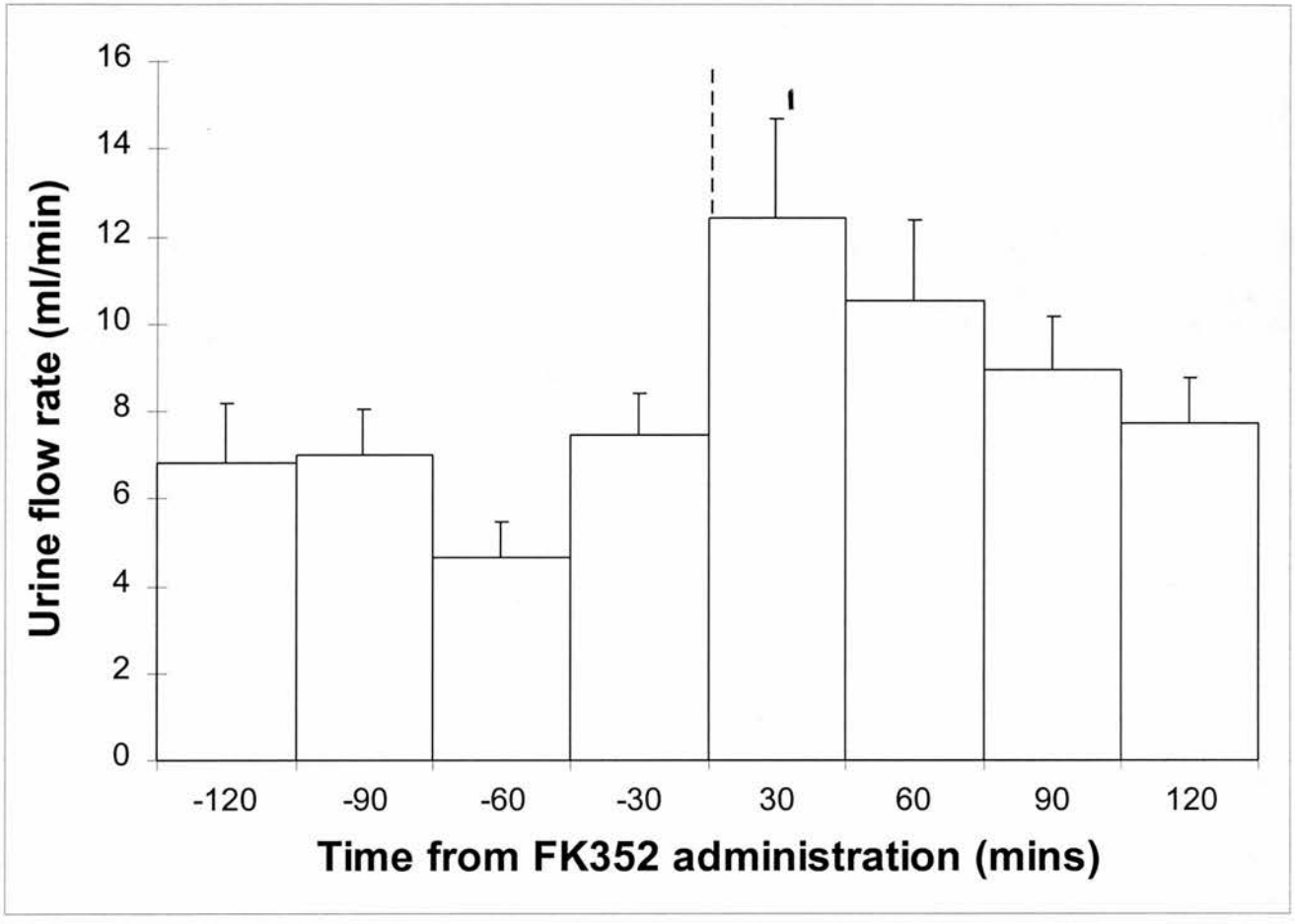


Figure 13.

Graph showing changes in urine flow rate following administration of FK352 (AUC $p<0.02$).

{Application of the Bonferroni correction for multiple comparisons at individual post-dose time points gives significance level of $p=0.0125$. Therefore the only individual significant value is ' $p<0.005$ vs. mean pre-FK352 value)

6c ii Haemodynamic changes

Real time unilateral RBF increased by 42.3±12.5% ($p<0.01$) from 445.4±99.1 to a maximum of 634.0±109.2 ml/min following FK352 (figure 14). There was no correlation between RBF and ERPF, but RBF correlated with the corrected ERPF ($p<0.05$). There was no change in heart rate or MAP during the study. Similarly, cardiac output (6.42±0.45 l/min pre- and 6.38±0.47 l/min post-FK352) and systemic vascular resistance (1025.3±92.7 dynes.s/cm^5 pre- and 1020.2±102.0 dynes.s/cm^5 post-FK352) remained unchanged.

6c iii Plasma and urine analytes

Plasma cAMP, Angiotensin II and PRA increased following FK352 by a mean of 10.8±3.2% ($p<0.01$), 36.9±11.3% ($p<0.01$) and 247.9±82.6% ($p<0.02$) respectively, but no change was observed in plasma adrenaline or noradrenaline or urine cAMP levels (table 13).

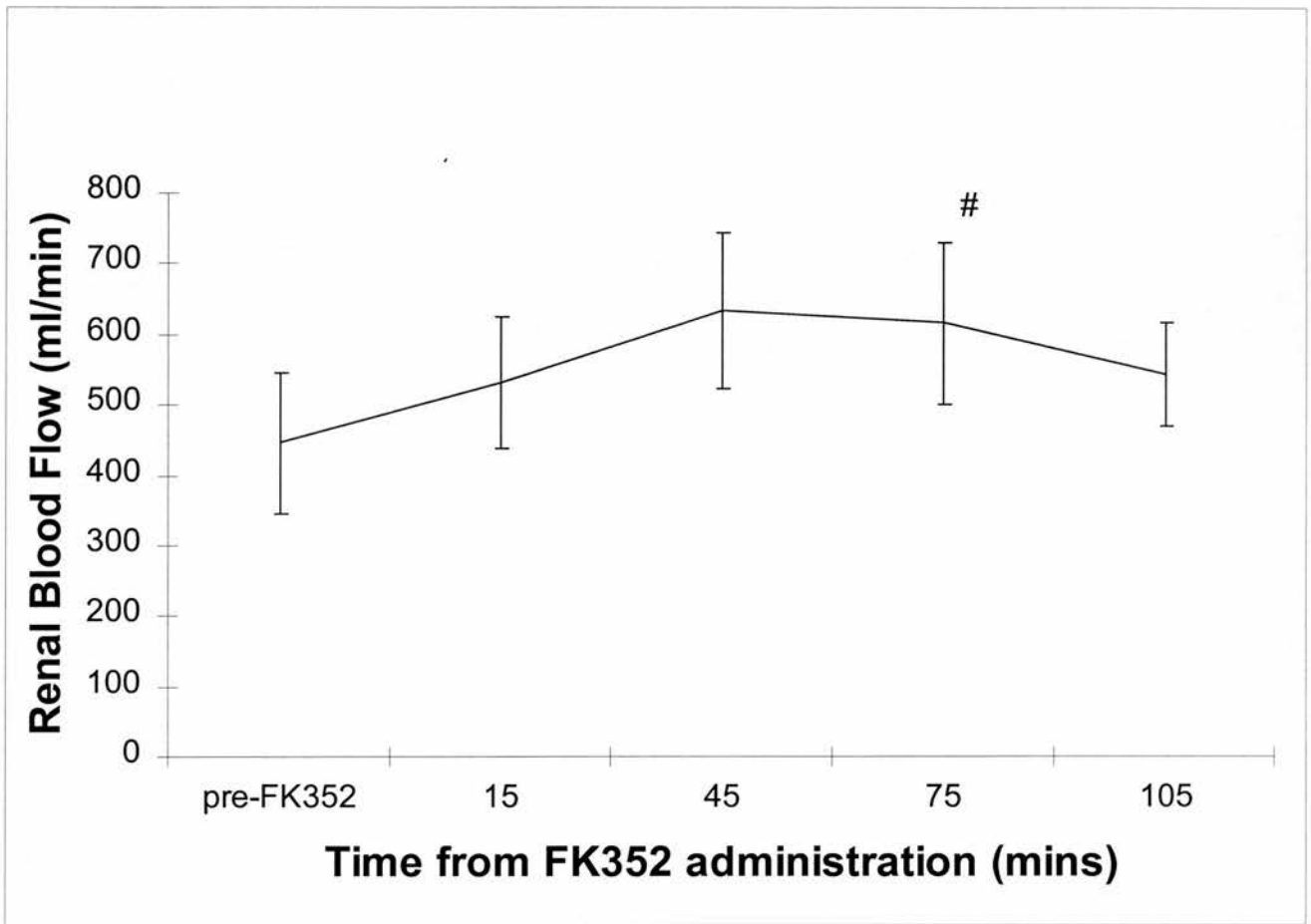


Figure 14.

Graph showing change in unilateral renal blood flow following FK352 administration (AUC $p<0.01$).

{Application of Bonferroni correction for multiple comparisons at individual post-dose time points gives significance level of $p=0.0125$. Therefore the only individual significant value is: # $p=0.011$ vs. mean pre-FK352 value}.

Table 13.

Table showing percentage change from baseline for angiotensin II, PRA, catecholamines and cAMP following FK352 administration.

{Application of Bonferroni correction for multiple comparisons at individual post-dose time points gives significance level of p=0.0167. Therefore the only individual significant values are: ' p<0.005, • p<0.002, ♦ p<0.01 and + p=0.013}

		Time after FK352 administration (minutes)			
	Baseline value	**15**	**45**	**105**	**AUC p value**
PRA	4.14±1.75 ng/ml/hr	202.7±63.7♦	243.7±87.0	349.9±117.7+	p<0.02
Angiotensin II	30.80±7.67 pg/ml	35.8±10.2'	41.1±17.8	40.7±9.7•	p<0.01
Adrenaline	0.18±0.04 nmol/l	-2.2±12.8	30.3±27.5	30.4±26.0	NS
Noradrenaline	2.76±0.41 nmol/l	0.2±6.3	2.5±5.6	-1.9±9.1	NS
Plasma cAMP	7.53±0.46 nmol/l	8.9±5.3	13.2±3.2•	11.2±4.1	P<0.01
Urine cAMP	1072.00±468.37 nmol/l	-14.4±9.3	-15.5±11.3	14.6±27.2	NS

6 d Conclusions

We have demonstrated an improvement in urine flow and natriuresis following administration of an adenosine-1 specific antagonist (FK352) to cirrhotic patients with ascites. There was also a significant increase in RBF as measured by the reverse thermodilution technique, but no change in ERPF or GFR as measured by PAH or inulin clearance respectively. Unlike most diuretics, a trend to an increase in free water clearance was also observed.

This is the first use of this drug in cirrhotic patients and it would appear that adenosine-1 antagonism can ameliorate some of the haemodynamic and renal tubular abnormalities seen in cirrhotic patients with ascites.

Acknowledgement: I would like to thank Fugisawa Pharmaceutical Company Ltd. for provision of FK352, Data Analysis and Research Limited (Lanarkshire, U.K.) for statistical analysis, and Dr. A. Cumming (Department of Renal Medicine, Royal Infirmary of Edinburgh) for specialist advice on the running of this study.

Chapter 7.

ACUTE HAEMODYNAMIC EFFECTS OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT-SHUNT (TIPSS) INSERTION IN CIRRHOTIC PATIENTS

7 a Introduction

Insertion of TIPSS dramatically reduces portal pressure and has significant systemic haemodyanamic effects. Although TIPSS procedure worsens the peripheral vasodilatation observed in cirrhosis, it also reduces the severity of ascites, increases sodium excretion and may temporarily improve renal function in patients with the hepato-renal syndrome. These findings suggest a link between the renal abnormalities of cirrhosis and portal hypertension.

Portal venous infusion of glutamine in an animal model has been shown to reduce RBF, which was reversed by renal denervation and section of the hepatic vagal fibres (Lang *et al* 1991). The authors proposed the existence of an hepato-renal reflex with afferent hepatic vagal and efferent renal sympathetic fibres. In addition, an acute increase in portal pressure caused by TIPSS occlusion in cirrhotic patients has been shown to cause an immediate reduction in RBF which correlated with the increase in the PPG (Jalan *et al* 1997).

Due to its immediate effect on portal pressure, TIPSS procedure provides a model to investigate the relationship between portal hypertension and RBF. The aim of this study was to assess the effect on RBF and other haemodynamic parameters of an acute reduction in portal pressure by elective TIPSS placement in cirrhotic patients.

7 b Methods

7b i Patients

The study was approved by the local ethics committee and all patients gave informed written consent. Eleven unselected cirrhotic patients undergoing elective TIPSS placement for recurrent oesophageal variceal haemorrhage (n=9) or refractory ascites (n=2) were studied. All patients were haemodynamically stable at the time of the TIPSS procedure and none had suffered a gastrointestinal haemorrhage within the previous 48 hours. In addition, no patient was receiving vasoactive medications and none were ventilated.

Ten patients had alcohol related cirrhosis, mean age was 55.4±3.9 and mean CPS was 8.7±1.0. Full patient characteristics are shown in table 14.

Table 14.

Patient characteristics.

Male/Female		8/3
Age (mean±SEM)		55.4 ±3.9 years
Childs-Pugh score (mean±SEM)		8.7±1.0
Childs Class (n):		
	A	4
	B	3
	C	4
Aetiology (n):		
	alcohol related	10
	autoimmune hepatitis	1

7b ii Haemodynamic measurements

On transfer to the catheter suite, intravenous midazolam and pethidine were administered and a reverse thermodilution catheter positioned via a femoral introducer sheath to measure baseline unilateral RBF. This catheter was kept in this position for the duration of the study.

A right internal jugular introducer sheath was then inserted (using 5mls 2% lignocaine local anaesthesia), and right heart catheterisation undertaken to measure RAP, PAP, PCWP, CO and SVR. This catheter was then removed.

TIPSS placement was undertaken in the routine manner as previously described in detail (22). One (n=6) or two (n=5) Wallstents were inserted to reduce the PPG below 12mmHg or reduce it by 20% if the initial PPG was <12mmHg (1 patient). Ten millimetre stents were used in 7 patients and 12mm stents in 4. Successful and uncomplicated stent placement was achieved in all patients.

With the reverse thermodilution catheter remaining in position, measurement of RBF was repeated at 5, 15, 30, 45 and 60 minutes following stent insertion. Thirty minutes following stent placement, right heart catheterisation was repeated to remeasure RAP, PAP, PCWP, CO and SVR. After these measurements were completed, all catheters and introducers were removed and pressure applied to obtain haemostasis.

Electrocardiography, pulse rate and oximetry were monitored continuously during the study, and MAP recorded at 15 minute intervals. After completion of the study, patients were transfered to the ward for further routine observation.

7b iii Data Analysis

Results are expressed as mean±SEM. Paired Students t-test for parametric and Wilcoxon Signed Rank test for non-parametric data were used to analyse changes in haemodynamic parameters. Pearson and Spearman correlation tests were used to assess the relationship between parametric and non-parametric data respectively. A significance level of 0.05 was chosen.

7 c Results

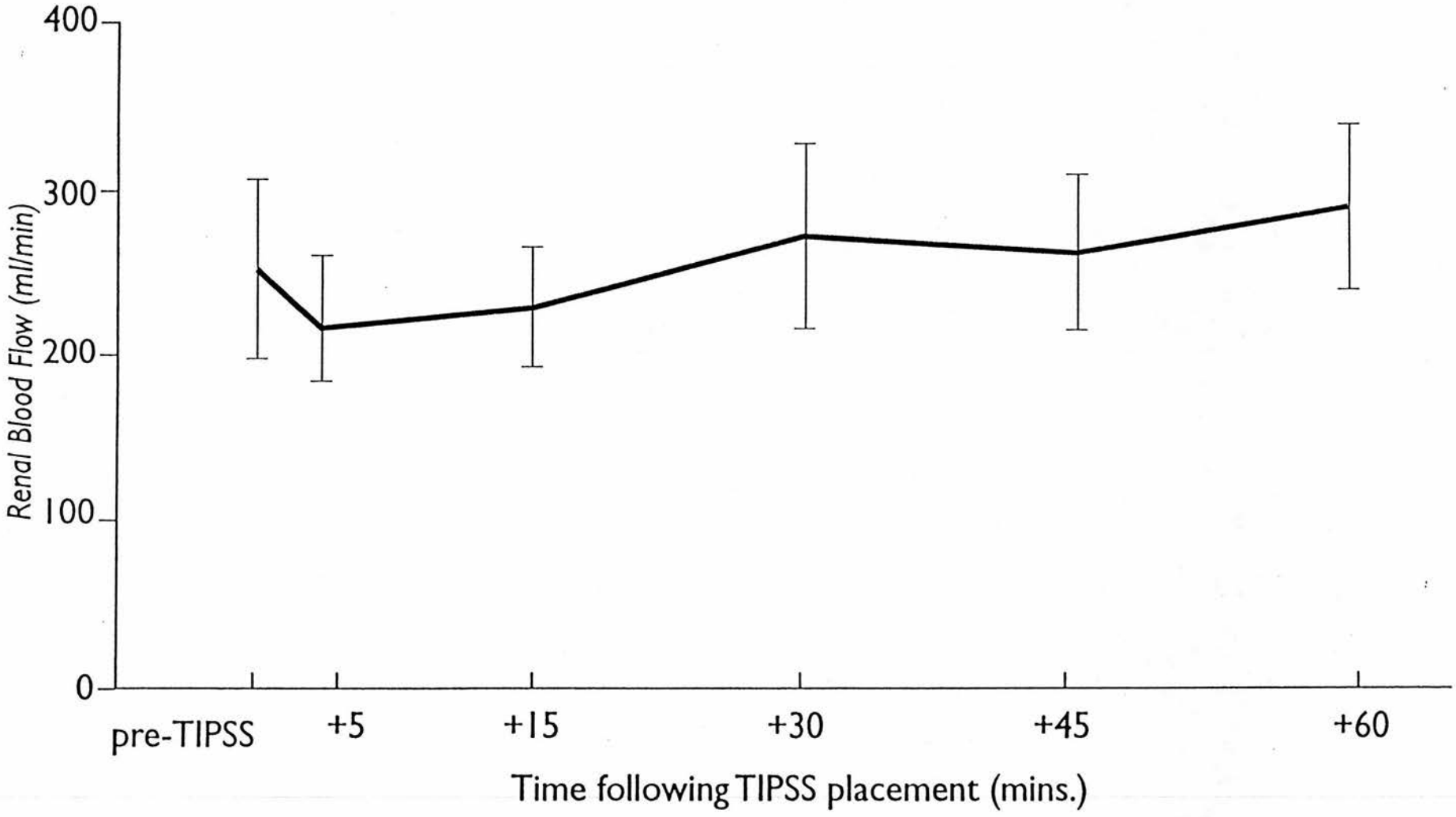
7 c i Splanchnic and renal haemodynamics

The PPG fell from 21.7±2.1 to 5.5±1.1 mmHg ($p<0.001$) following TIPSS insertion.

Compared with the baseline value of 252.5±54.2 ml/min, there was no change in RBF at any time following TIPSS placement (figure 15). Values of unilateral RBF at 5, 15, 30, 45 and 60 minutes were 202.5±34.3, 229.5±35.8, 272.9±55.9, 262.6±46.5 and 290.7±49.7 ml/min. respectively. There was actually a slight decrease in unilateral RBF/CO % from 4.5±1.0 to 3.7±0.7 % after TIPSS insertion.

Figure 15 (over page)
Graph showing no significant change in unilateral renal blood flow up to 60 minutes following TIPSS placement.

Figure 15


400
300
200
100
0
Renal Blood Flow (ml/min)
pre-TIPSS
+5
+15
+30
+45
+60
Time following TIPSS placement (mins.)

7c ii Systemic haemodynamics

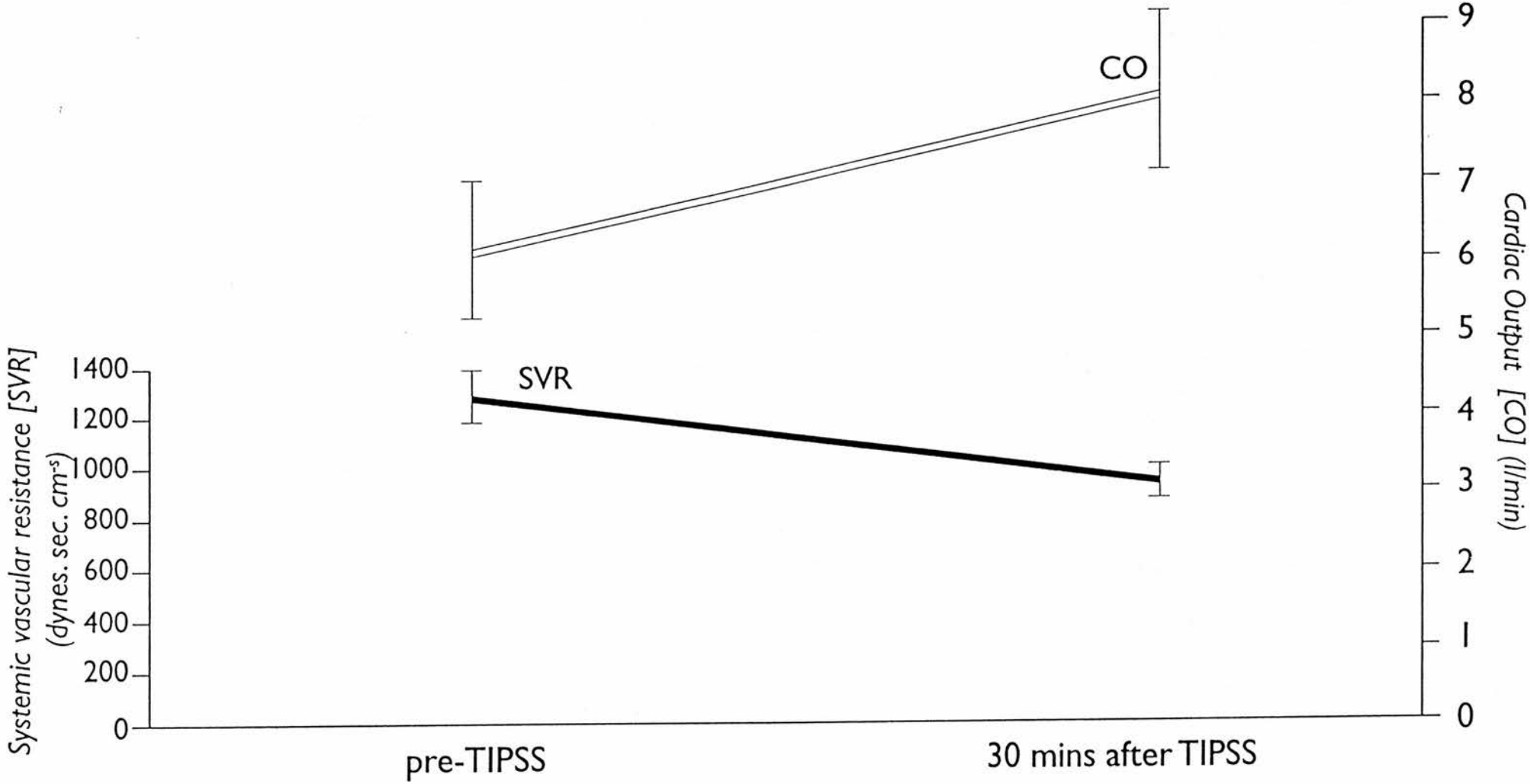
The CO rose from 6.1±0.9 to 8.0±1.0 l/min. ($p=0.001$) and SVR fell from 1283.6±104.4 to 950.2±97.7 dynes.sec/cm^5 ($p=0.003$) thirty minutes after stent placement (figure 16).

The RAP rose from 2.3±1.1 to 7.8±1.0 mmHg ($p<0.001$), PAP from 11.8±2.0 to 24.5±1.9 mmHg ($p<0.001$) and PCWP from 7.8±2.0 to 17.8±1.6 mmHg ($p=0.001$) following TIPSS placement. The fall in PPG correlated only with the fall in SVR ($p<0.05$) and rise in CO ($p<0.05$) (figure 17). TIPSS insertion had no effect on heart rate or MAP. There were no significant differences between the haemodynamic changes observed in patients treated with 10mm or 12mm stents. Full haemodynamic changes are shown in table 15.

Figure 16 (over page)

Graph showing increase in cardiac output ($p=0.001$) and decrease in systemic vascular resistance ($p=0.003$) 30 minutes following TIPSS placement.

Figure 16


CO
SVR
Systemic vascular resistance [SVR]
(dynes. sec. cm-5)
1400
1200
1000
800
600
400
200
0
Cardiac Output [CO] (l/min)
9
8
7
6
5
4
3
2
1
0
pre-TIPSS
30 mins after TIPSS

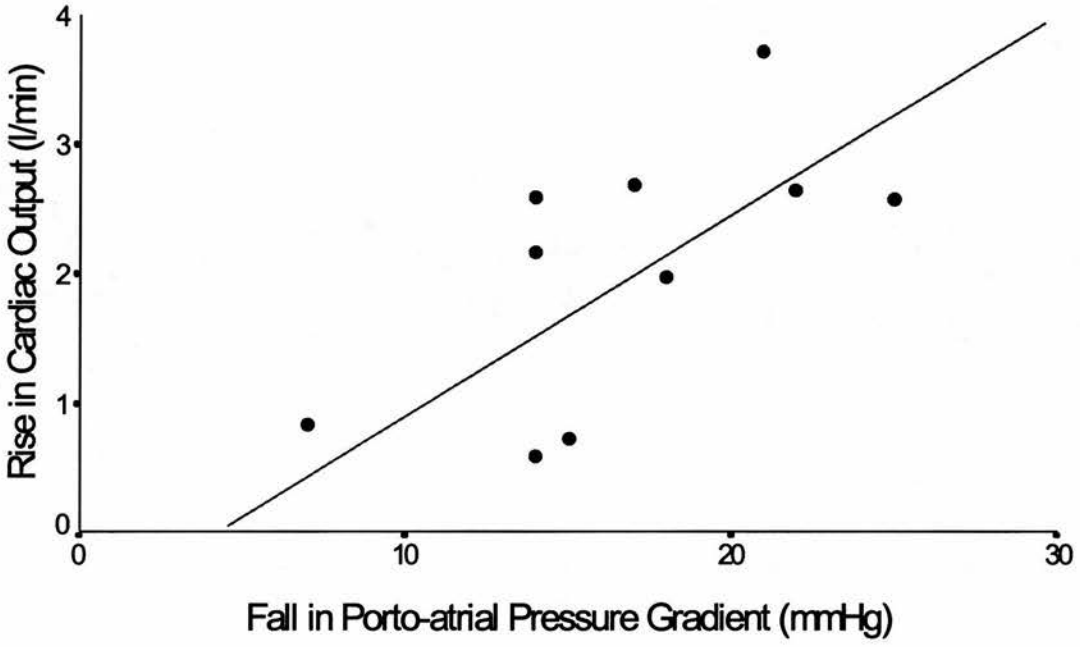


Figure 17. Graph showing correlation between fall in porto-atrial pressure gradient and rise in cardiac output ($p<0.05$) following TIPSS placement.

Table 15.

Haemodynamic changes following TIPSS placement.

	Time following TIPSS placement						
	pre	**+5**	**+15**	**+30**	**+45**	**+60**	**p value**
RBF (ml/min)	252.5±54.2	202.5±34.4	229.5±35.8	272.9±55.9	262.6±46.5	290.7±49.7	NS
PPG (mmHg)	21.7±2.1	-	-	5.5±1.1	-	-	p<0.001
HR (bpm)	86.5±6.4	-	-	88.2±5.3	-	-	NS
MAP (mmHg)	91.7±2.7	-	-	95.3±3.9	-	-	NS
RAP (mmHg)	2.3±1.1	-	-	7.8±1.0	-	-	p<0.001
PAP (mmHg)	11.8±2.0	-	-	24.5±1.9	-	-	p<0.001
PCWP (mmHg)	7.8±2.0	-	-	17.8±1.6	-	-	p=0.001

[RBF=unilateral renal blood flow, PPG= portoatrial pressure gradient, HR=pulse rate, MAP=mean arterial pressure, RAP=right atrial pressure, PAP=mean pulmonary artery pressure, PCWP= pulmonary capillary wedge pressure].

7 d Conclusions

We have shown that following elective TIPSS procedure in cirrhotic patients, there is no acute effect on RBF despite a dramatic reduction in PPG. We also confirm the immediate increases in CO, PAP, PCWP and fall in SVR after shunt placement.

Therefore a suggested hepato-renal reflex does not lead to an immediate rise in RBF following an acute fall in portal pressure. In addition, the reported improvement in renal function following TIPSS procedure does not appear to be due to an acute increase in RBF.

Chapter 8.

LONG-TERM FOLLOW-UP OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT-SHUNT (TIPSS) PROCEDURE FOR THE MANAGEMENT OF COMPLICATIONS OF PORTAL HYPERTENSION

8 a Introduction

Although TIPSS procedure appears effective for acute and recurrent variceal bleeding refractory to endoscopic treatment and may improve ascites, the current literature on this procedure is limited both by short duration of follow-up and small patient numbers. This is important since shunt patency after TIPSS placement may decrease with time, and encephalopathy following surgical shunts was often delayed.

From 1991 until August 1995, we carried out 130 TIPSS procedures in our unit. The aim of this study was to present our results and more importantly the long term follow-up.

8 b Methods

8b i Patients

From 1991 to 1995, TIPSS procedure was attempted in 130 patients, with successful placement of the stent in 119 cases (91.5%). Patient characteristics are shown in tables 16 and 17. Over the same time period, a total of 220 patients were treated for variceal haemorrhage at our institution.

The aetiology of portal hypertension was alcoholic cirrhosis (ALD) in the majority of patients and most patients had Childs-Pugh grade C liver disease at the time of TIPSS procedure (table 16). Four patients were non-cirrhotic (1 each with amyloid, idiopathic portal hypertension, polycystic disease and nodular regenerative hyperplasia).

The most common indication for TIPSS placement was oesophageal variceal bleeding (table 17). These patients had either continued bleeding despite 2 sessions of sclerotherapy or were part of a trial comparing band ligation with TIPSS in the prevention of rebleeding. Five (3.8%) patients had ectopic varices (2 rectal, 2 stomal and 1 duodenal) and the indictation for TIPSS placement was painful splenomegaly, hypersplenism and embolization of a spontaneous shunt in 1 patient each. Thirty-five procedures were carried out as an emergency, with 19 receiving assisted ventilation prior to TIPSS procedure (table 17).

Table 16.

Patient characteristics I

Sex (M/F):	81/49
Age (yr.):	
Mean±SEM:	54.7±1.1
Range:	9-83
Aetiology of Liver Disease (%):	
Alcoholic cirrhosis	84 (64.6%)
Cryptogenic cirrhosis	12 (9.2)
Primary biliary cirrhosis	11 (8.5)
Hepatitis C	5 (3.8)
Hepatitis B	5 (3.8)
Cystic Fibrosis	3 (2.3)
Primary sclerosing cholangitis	2 (1.5)
Autoimmune hepatitis	2 (1.5)
Other	6 (4.6)
Childs-Pugh score (mean±SEM):	9.9±0.2
Childs-Pugh grade (%):	
A	10 (7.9)
B	49 (38.9)
C	67 (53.2)

Table 17.

Patient characteristics II

Indication (%):	
Oesophageal varices	73 (56.2)
Gastric varices	26 (20.0)
Refractory ascites	17 (13.1)
Portal hypertensive gastropathy	6 (4.6)
Ectopic varices	5 (3.8)
Other	3 (2.3)
Emergency procedure (%):	35 (26.9)
Clinical features:	
Artificially ventilated	19 (14.6%)
Haemodynamic compromise	10 (7.7%)
Ascites	86 (66.2%)
Hepatic encephalopathy	44 (33.8%)

8b ii TIPSS procedure

The technique of TIPSS placement was based on the original method described by Richter (Richter *et al* 1990) and is described in detail elsewhere (Chalmers *et al* 1992). Routine pre-procedural mesenteric angiography was undertaken in the first 32 patients to guide portal vein puncture and in 27 subsequent patients, Doppler ultrasonography was used to identify the site of portal vein bifurcation. In the last 71 patients however, no routine imaging was undertaken to localize the portal vein pre-TIPSS, although ultrasonography was used prior to the procedure to exclude portal vein thrombosis. These changes have evolved as a result of ongoing audit at our unit.

Once successful puncture of the portal vein was achieved, 2-3 Palmaz stents (Johnson & Johnson) (24 patients), or 1-2 Wallstents (Schneider U.S. Stent Division) (106 patients) were inserted to reduce the PPG to less than 12mmHg. Three patients subsequently had Angiomed stents (Angiomed, Karlsruhe, Germany) inserted to reduce the shunt size. In 2 patients in whom a thrombus was noted within the portal vein at the end of the procedure, a catheter was left within the shunt for regional infusion of low dose streptokinase for 24 hours.

Prophylactic antibiotics (cefotaxime and amoxycillin) were administered 1 hour prior to procedure and continued for 48 hours thereafter.

8b iii Clinical follow-up

After discharge, patients were reviewed at 6-weeks, then at 3-monthly intervals. Encephalopathy was assessed clinically at each visit, but prophylactic lactulose and protein restriction were not routinely applied. Variceal rebleeding was defined as endoscopically proven variceal haemorrhage occurring more than 24 hours after TIPSS insertion. Non-variceal sources of gastrointestinal bleeding were documented at endoscopy.

Mean follow-up (defined as time to death, most recent clinical review or liver transplantation) for all patients was 10.7±1.0 months, and for survivors (up to October 1995) 18.0±1.3 months.

8b iv Shunt surveillance

Doppler ultrasonography was performed prior to discharge to ensure shunt patency. Routine portography was undertaken at 1-3 months and six-monthly thereafter to assess shunt function, or earlier in the event of rebleeding or reaccumulation of ascites. Early in our experience however, several shunts were left 6-12 months before initial angiographic assessment.

All shunt complications were confirmed angiographically with occlusion defined as absent flow through the shunt. Pseudo-intimal hyperplasia, hepatic vein stenosis, portal vein and shunt thrombosis were defined by the angiographic appearance in conjunction with either a 20% rise in PPG, or an increase in PPG to 12mmHg or more. Primary shunt patency was defined as the (pre-intervention) absence of any of the above shunt complications.

8b v Data analysis

Results are expressed as mean±SEM or range where indicated. Paired students t-test was used to determine statistical significance and Kaplan-Meier method used for rates of variceal rebleeding, primary shunt patency and survival.

8 c Results

8c i Shunt procedure

TIPSS placement was successful in 91.5% patients (table 18). The procedure failed in 11 patients (10 of whom had variceal haemorrhage) because a main branch of the portal vein could not be punctured. Four of these patients subsequently underwent shunt surgery and 5 had further endoscopic therapy. Thirty-day mortality in the failed TIPSS group with variceal haemorrhage was 70%.

Two procedure related deaths occurred from intra-peritoneal haemorrhage due to extrahepatic tear of the portal vein or puncture of the liver capsule. One patient developed an epidural haemorrhage which was diagnosed following the procedure but the exact relationship to TIPSS placement was unclear. Other complications included portal vein thrombosis in 2 patients (successfully treated by local streptokinase infusion), portal vein dissection in 1 (successfully managed by stenting) and shunt dislocation or migration into the splenic vein in 2. There were no clinically significant groin or neck haematomas.

8c ii Shunt dysfunction

A total of 63 episodes of shunt complications were observed in 45 patients (table 18). Twenty-nine of these were clinically significant, associated with variceal rebleeding or reaccumulation of ascites, with the others detected on routine surveillance. Fifty percent of the shunt complications occurring less than 1 month post TIPSS were associated with variceal rebleeding, as were 41.7% of those occurring from 1-3 months, 35% from 3-12 months and 23.5% from 12-24 months. No shunt complications occurring >2 years following TIPSS placement was associated with variceal rebleeding.

Taking follow-up as most recent angiographic TIPSS assessment, pre-intervention shunt patency was 58.1% at 1 year and 21.4% at 2 years (see table 18 and figure 18). The causes of shunt dysfunction are described in table 18. No Palmaz stent had primary patency at 2 years. All shunt complications but one (in a patient who was transferred to an endoscopic banding programme and remains well) were successfully treated by balloon dilatation, local thrombolysis, shunt extension or parallel shunt placement (9 patients).

Table 18.

RESULTS I

Successful TIPSS procedure (%):	119 (91.5)
PPG pre-TIPSS (mmHg):	17.5±0.5
PPG post-TIPSS (mmHg):	8.6 ±0.2
Pre-intervention shunt patency (%):	
6 months	47 (71.2)
1 year	25 (58.1)
2 years	3 (21.4)
Shunt complications	63 episodes in 45 (37.8%) patients:
pseudo-intimal hyperplasia	29
hepatic vein stenosis	13
portal vein/shunt thrombosis	5
occlusion	16

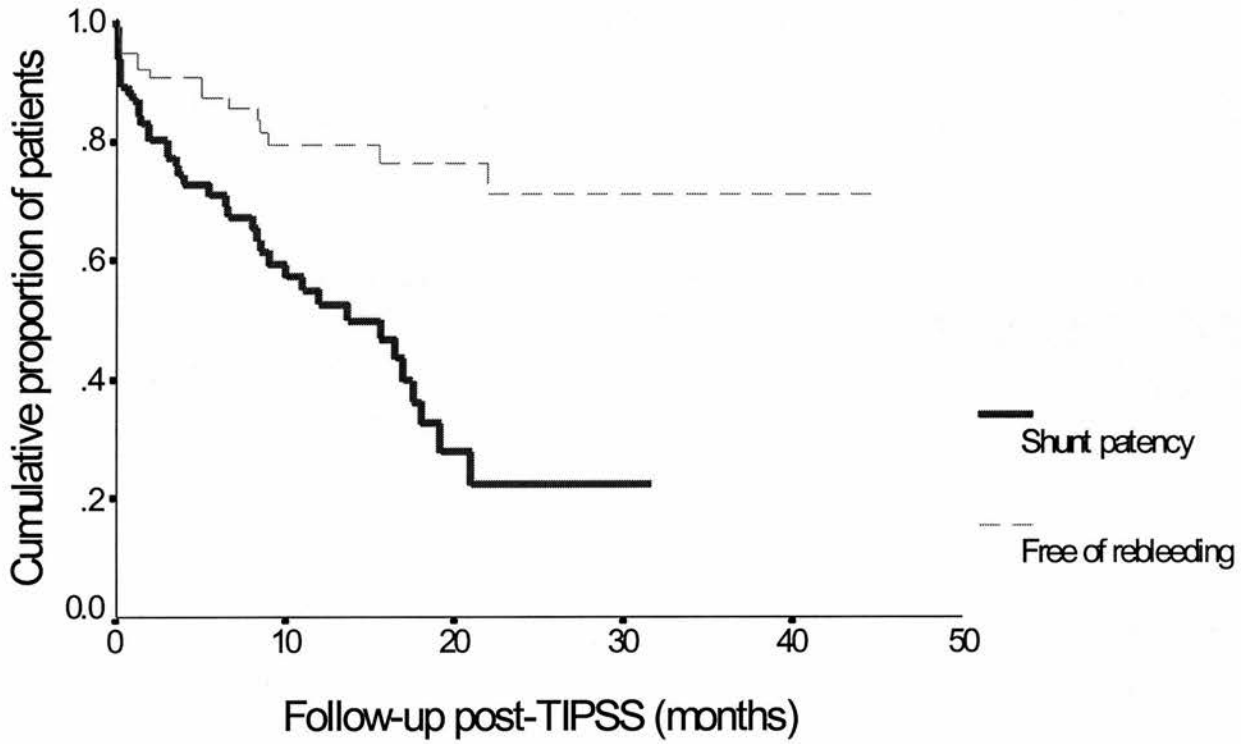


Figure 18.

Kaplan-Meier analysis of patients free of variceal rebleeding and patients with primary shunt patency during follow-up.

8c iii Clinical follow-up

Control of Acute Bleeding

Thirty-five patients had TIPSS procedure for acute variceal haemorrhage uncontrolled despite sclerotherapy with or without balloon tamponade. The procedure was technically successful in 32 of these patients and the other 3 patients died: 2 from massive variceal haemorrhage and 1 shortly after oesophageal transection.

Fourteen of the remaining patients died during the index hospital admission: 3 each from acute on chronic liver failure, sepsis and end stage liver failure, 2 from continued bleeding (1 from an autopsy proven sclerotherapy ulcer and 1 with disseminated intravascular coagulation and acidosis), 2 from cardiac arrests/myocardial infarcts, and one from a procedure related intra-peritoneal bleed. Two further patients had subsequent variceal rebleeds, both related to shunt insufficiency which was successfully treated by angioplasty and shunt extension.

Recurrent Variceal Bleeding

TIPSS procedure was successful in reducing recurrent variceal haemorrhage. There were 24 episodes of variceal re-bleeding in 13.4% patients (see figure 18 and table 19), all of which were associated with shunt insufficiency and responded to dilatation or further stenting. None of the 5 patients who underwent TIPSS placement for ectopic variceal haemorrhage had a recurrent bleed. Non-variceal haemorrhage occurred in 7.6% patients (see table 19).

Ascites

Eighty-six patients had ascites prior to TIPSS placement and this was the primary indication in 17 patients (7 of whom had established hepato-renal syndrome; see table 19). The ascites improved (reduced or no diuretic requirement) in 65.1% of these patients, but reaccumulated in 14. This was associated with shunt insufficiency in 11 patients and spontaneous bacterial peritonitis (SBP) in 2, but was responsive in all cases to shunt revision and antibiotics respectively. Of the 17 patients who underwent TIPSS procedure for refractory ascites, improvement occurred in 11 and 2 have

subsequently undergone successful liver transplantation. Those with biochemical evidence of renal dysfunction tended to respond less well after TIPSS insertion.

Other Indications

TIPSS procedure was performed for intractable bleeding from portal hypertensive gastropathy in 6 patients. Four of these have not required further transfusion and the other two have required one admission each for transfusion. Both of these patients had evidence of shunt dysfunction due to neo-intimal hyperplasia in association with a raised PPG, which was successfully treated by angioplasty or shunt extension. TIPSS placement resulted in an improvement in platelet count from 13000/l to 50000/l in one patient with hypersplenism. Another patient had a large spontaneous shunt successfully embolized via the TIPSS for amelioration of intractable hepatic encephalopathy.

Hepatic Encephalopathy

Forty-four patients were clinically encephalopathic prior to TIPSS procedure and this resolved in 54.5% after the procedure. Twenty (16.8%) patients developed new or worsening spontaneous encephalopathy during follow-up (15 within the first 6 months). A further 12.6% developed encephalopathy secondary to sepsis or bleeding during follow up (see table 19). Reduction in shunt size was performed because of encephalopathy in 4 patients (successful in 3), with all others responding to simple medical therapy.

Sepsis

Fourteen patients developed clinically significant infections in the week following TIPSS placement (7 pulmonary, 2 SBP, 2 related to central venous catheter, 1 cellulitis and 2 of unknown origin). Sepsis was the cause of death in 2 patients during the index admission: 1 with pre-existing staphylococcal and fungal septicaemia and one with cystic fibrosis and pre-existing lung sepsis. All other infective episodes responded to antibiotics.

Table 19.

RESULTS II

Variceal rebleeding:	24 episodes in 16 (13.4%) patients
Non-variceal rebleeding:	9 patients (7.6%):
	7 sclero. ulcers
	1 duodenal ulcer
	1 mallory-weiss tear

Ascites:

Pre- TIPSS	86 (66.2%)
Improved post-TIPSS	56 (65.1%)
Reaccumulation	14 (25.0%)
1° indication for TIPSS	17 (13.1%)

Encephalopathy:

Pre-TIPSS	44 (33.8%)
New/worse spont. enceph.	20 (16.8%)
New/worse enceph. 2° sepsis	9 (7.6%)
New/worse enceph. 2° bleed	6 (5.0%)

Sepsis post TIPSS: 14 (11.8%)

Liver Function

Approximately one third of patients exhibited a transient deterioration in their liver function tests in the first week following TIPSS placement, with rises particularly in bilirubin and alanine aminotransferase levels. Three patients died with clinical features of acute liver failure, characterized by hypotension, renal failure and hypoglycaemia. Two of these patients also had evidence of raised intra-cranial pressure on extra-dural pressure recordings or computed tomography. Childs-Pugh score did however improve at 3-6 months to 7.6±0.3 ($p=0.019$) largely due to a reduction in ascites.

Transplantation

Thirteen patients underwent orthotopic liver transplantation following TIPSS procedure. Transplant was undertaken a mean of 7.1±1.6 months following stent placement, and 11 of these patients remain alive and well.

Mortality

Of the 119 patients with successful TIPSS placement, 52 have died and 13 have been transplanted. Procedure related mortality was 1.5% and mean time to death was 6.0±1.2 months (range 0.03-45.3). Mean follow-up of survivors is 18.0±1.3 months (range 2.0-43.5). Thirty-day mortality was 21.8% (84.6% of whom had Childs C disease) and six month survival 69.2%. One and two year survival is 62.3% and 46.5% respectively. Mortality was dependent on Childs grade at time of TIPSS procedure (see figure 19).

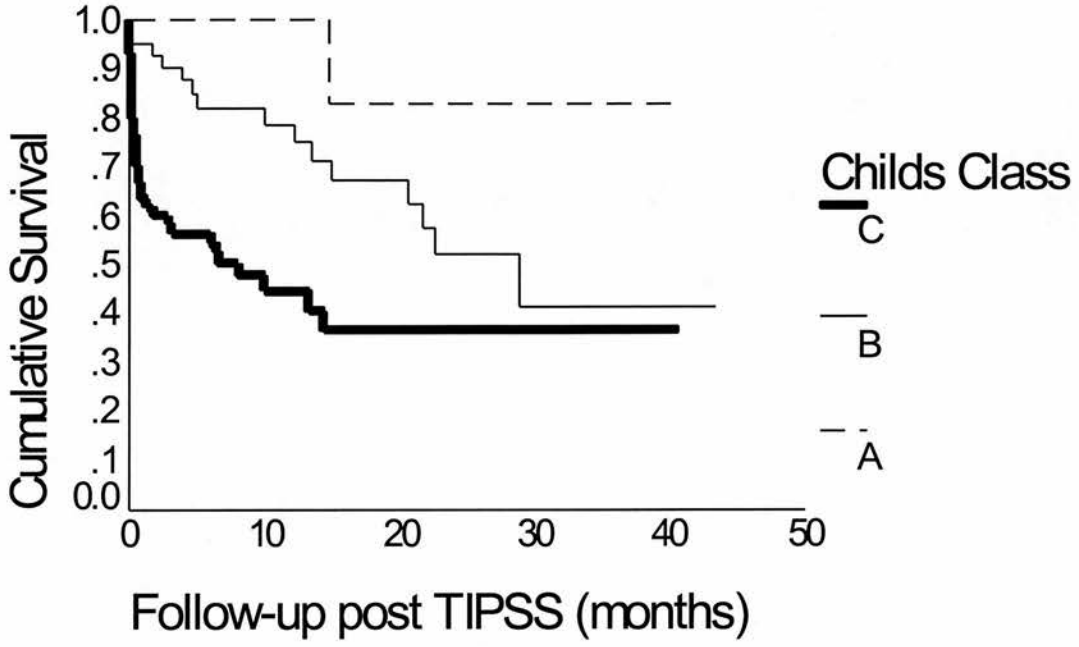


Figure 19.

Kaplan-Meier analysis of patient survival post-TIPSS by Childs grade.

8 d Conclusions.

This large study indicates that following variceal haemorrhage, TIPSS procedure is associated with low rebleeding rates provided shunt patency can be maintained during follow-up. The definitive role of this procedure in the management of variceal bleeding will be determined from randomised trials comparing TIPSS placement with endoscopic and pharmacological therapies.

Shunt dysfunction remains the major limitation of TIPSS procedure, and regular shunt surveillance is required, preferably with direct portography to identify shunt insufficiency and allow therapeutic intervention. Post-TIPSS encephalopathy is significant, but is generally easy to manage with lactulose and protein restriction. Although TIPSS placement reduces ascites, its place in the management of patients with refractory ascites remains unclear, and it should not be performed for this indication outwith clinical trials.

Chapter 9.

DISCUSSION

The questions stimulating this thesis were:

a) what is the relationship between the haemodynamics of cirrhosis and prognosis?

b) what are the haemodynamic, renal and clinical effects of pharmacological and radiological interventions for portal hypertension and ascites?

9 a Haemodynamics of cirrhosis

The haemodynamic changes in cirrhosis have long been recognised, but the relationship between the systemic, renal and portal circulations in these patients remains poorly understood. The splanchnic circulation is thought to be the main site of reduced vascular resistance in cirrhosis (Marato *et al* 1993), and the alterations in systemic haemodynamics are thought to arise secondary to splanchnic vasodilators gaining access to the systemic vasculature via collateral vessels and reduced hepatic clearance (Schrier *et al* 1988). The vasodilated splanchnic and systemic circulations lead to activation of neurohumoral systems causing sodium and water retention and renal vasoconstriction which can lead to ascites formation and functional renal abnormalities (Bosch *et al* 1980, Schrier *et al* 1988).

9a i Relationship between systemic and splanchnic haemodynamics and severity of liver disease

We have shown that the severity of the hyperdynamic circulatory disturbances observed in cirrhosis is related to the degree of hepatic impairment, with heart rate, MAP, CO and SVR all correlating with the CPS. However, perhaps surprisingly RBF was not related to the CPS.

The HVPG is an indirect measurement of portal pressure which accurately reflects the pressure gradient between the portal and hepatic veins in patients with sinusoidal portal hypertension such as alcoholic cirrhosis, but not in those with pre- or post-

sinusoidal portal hypertension (Boyer *et al* 1977). Although we found no relationship between HVPG or collateral flow as measured by AzBF and systemic haemodynamic parameters, we found that both HVPG and AzBF correlate with CPS, which is consistent with earlier reports (Braillon *et al* 1986).

9a ii Prognostic value of haemodynamic parameters for bleeding and survival

Bleeding

Recently, a number of studies have assessed the prognostic value of HVPG measurement in cirrhosis, with some authors suggesting it should be used much more frequently in such patients (Armonis *et al* 1996). In addition, early reports of a "bleeding threshold" of an HVPG of 12mmHg, below which variceal bleeding did not occur, have subsequently been confirmed (Garcia-Tsao *et al* 1985, Groszmann *et al* 1990, Vorbioff *et al* 1996). In our study, only one patient with an HVPG <12mmHg went on to have a variceal bleed. However this patient had their haemodynamic study when abstinent from alcohol, then subsequently returned to drinking prior to their variceal haemorrhage. Active drinking has previously been shown to increase the HVPG and therefore the risk of variceal bleeding (Vorbioff *et al* 1996). Obviously other patients in our study may have returned to or continued drinking during follow-up, but abstinence is difficult to assess in this patient group. Therefore we did not analyse this factor with regard to its effect on patient outcome.

Although a number of patients were on a band ligation surveillance programme and others were on diuretic therapy at the time of study, endoscopic treatment of varices does not appear to affect HVPG (Lo *et al* 1996), and it remains unclear whether diuretics have an effect (Nevens *et al* 1996, Sogni *et al* 1994). There was no difference in the HVPG between patients who were on diuretic therapy and those not on diuretics in our study.

Using Cox's regression, we found that HVPG was the only haemodynamic, laboratory or clinical parameter to predict bleeding on multivariate analysis. In particular, it had

better predictive value than CPS. It is interesting that one measurement of HVPG appears to predict variceal haemorrhage over the next two years, despite the fact that a number of patients subsequently had pharmacological intervention as attempted prophylaxis for variceal bleeding. This study was designed to assess the prognostic value of a "snap-shot" baseline haemodynamic assessment and we did not evaluate the individual benefit of any subsequently administered drugs.

Endoscopic signs such as variceal size and the presence of red spots on the varices have also been shown to predict variceal bleeding (NIEC 1988). However, few of our patients underwent endoscopy around the time of the haemodynamic study, therefore we were unable to include endoscopic signs in the analysis.

Interestingly, we found no relationship between AzBF, which is a marker of collateral flow, and the risk of bleeding. This finding has been previously reported (Cales *et al* 1984), and is probably explained by the fact that the azygos vein also drains mediastinal channels in addition to the oesophageal submucosa. Presumably for similar reasons, AzBF was not related to survival.

Survival

Unlike the findings from our study, Llach and colleagues reported that MAP independently predicts survival on multivariate analysis in cirrhotic patients with ascites (Llach *et al* 1988). However, similar to our results, a number of studies have suggested that the measurement of HVPG predicts survival in cirrhosis above and beyond the information given by the CPS (Merkel *et al* 1992, Vinel *et al* 1986, Gluud *et al* 1988). We have confirmed Merkel and colleagues earlier report of a lower survival in patients with HVPG>16mmHg (Merkel *et al* 1992). HVPG has previously been shown to be an independent predictor of survival on multiple regression analysis (Merkel *et al* 1992, Gluud *et al* 1988, Armonis *et al* 1997).

We found that HVPG and the CPS were the only haemodynamic, laboratory or clinical parameters which predicted survival on multivariate analysis. HVPG retained independent significant predictive value for survival even when patients with a

previous history of variceal bleeding, or those with death due to bleeding were omitted from analysis. The CPS is of course a composite score of five clinical and laboratory parameters. When HVPG was compared with these individual parameters on multivariate analysis with the exclusion of the CPS, only the prothrombin time and the presence of ascites were superior to HVPG in predicting death. Therefore, incorporation of HVPG into a scoring system including some or all of the current CPS parameters is likely to lead to an improved prognostic score.

9a iii Implications for management

Measurement of HVPG is a relatively simple and safe procedure that takes less than twenty minutes to perform. In our group of patients, 5 had self-limiting bruising over the femoral venous site, but no other complications were encountered. Apart from its possible prognostic value for survival, HVPG measurement can help target therapy for patients at high risk of bleeding and perhaps should become part of the routine assessment of patients with cirrhosis, especially those with varices.

Patients with an HVPG >12mmHg who have not previously bled should receive primary prophylaxis with beta-blockers with or without nitrates (D'Amico *et al* 1995). Although band ligation is the most commonly used treatment for patients who have suffered a variceal bleed, trials are currently underway to compare this with drug therapy in the prevention of rebleeding. Ideally, any patient undergoing pharmacological therapy as primary or secondary prophylaxis for variceal haemorrhage should undergo serial measurements of HVPG, which can act as a "splanchnic sphygmomanometer" (Armonis *et al* 1996). This will identify patients not responding to treatment, who can then be offered alternative therapeutic strategies (Groszmann *et al* 1990, Feu *et al* 1995).

9 b Aspects of the pharmacological management of portal hypertesion.

Propranolol and to a lesser extent ISMN are widely used in the pharmacological management of portal hypertension, most commonly in the primary prophylaxis of variceal haemorrhage. However, recent reports have suggested that these drugs may compromise renal function in cirrhosis, and questions remain regarding the tolerability of these agents in this patient population.

9b i Effects of propranolol and isosorbide-5-mononitrate on renal blood flow

There are conflicting data in the literature with regard to the renal effects of beta-blockers and nitrates in cirrhosis, which may be due to differences in the study populations or in the duration of treatment. The concern is greatest for those patients with advanced cirrhosis and ascites who would be least likely to tolerate a fall in renal perfusion and impaired renal function (Henriksen & Ring-Larsen 1993). In our study which assessed the effects of propranolol and ISMN on RBF, although all patients had normal serum creatinine levels, it is possible that some may have had a degree of renal impairment not evident from their serum creatinine. However, when ascitic patients alone were assessed, there was still no effect on RBF.

Generally the autoregulation in the kidney maintains a constant RBF over a wide range of arterial blood pressures (Wilkinson 1982). Henriksen and Ring-Larsen suggest that in cirrhosis, a pharmacologically induced fall in MAP may compromise renal perfusion and GFR, leading to a subsequent reduction in sodium and water excretion, partly due to a shift in this autoregulation (Henriksen & Ring-Larsen 1993). Although we did not assess GFR or sodium and water excretion, we found no change in RBF despite the expected changes in MAP, HVPG and AzBF following administration of propranolol and/or ISMN. This would suggest that renal autoregulation is intact in this patients group.

We assessed only the acute effect of these drugs on RBF, therefore we cannot draw conclusions regarding prolonged therapy. It is possible that administration of these drugs to cirrhotic patients may compromise renal function by mechanisms other than a reduction in RBF, such as neurohumoral or tubular effects. However, the main concern of many studies was the possible reduction in renal perfusion consequent on the systemic haemodynamic changes induced by these drugs.

Beta-blockers

Beta-blockers have been shown to reduce the frusemide-stimulated increase in renal interlobular arterial flow (Ljubicic *et al* 1992), and reduce estimated RBF in cirrhosis as assessed by doppler ultrasonography (Bolognesi *et al* 1994). However, Bataille and colleagues found no effect on RBF of acute propranolol therapy when given to cirrhotic patients (Bataille *et al* 1984), and no difference in creatinine clearance was detected between cirrhotic patients given diuretics alone and those given propranolol and diuretics (Rector & Reynolds 1984).

In addition, propranolol has been reported as having no effect on GFR in cirrhosis despite suppressing renin secretion (Wilkinson *et al* 1977), and Bernardi and colleagues found that propranolol actually increased GFR and natriuresis in ascitic cirrhotics with high sympathetic tone (Bernardi *et al* 1989). Other studies have reported both decreased (Rector & Reynolds 1984) and increased (Hayes *et al* 1984) natriuresis in cirrhotic patients in response to propranolol.

However, despite the anticipated reductions in heart rate, AzBF and HVPG in our study following acute administration of propranolol, no effect on RBF was observed. Indeed, the patients with the lower initial RBF who were given propranolol (whose renal function would be of most concern) actually had a rise in RBF following therapy.

Nitrates

Nitrate therapy has been shown to reduce renal plasma flow, GFR, and sodium and water excretion and increase renin and aldosterone values in cirrhosis (Salmeron *et al* 1993). The fall in GFR and free water clearance was greater in those patients who had ascites. Vorbioff et al found that 57% cirrhotic patients with ascites or a history of ascites developed worsening of ascites when given propranolol and nitrates, compared with no worsening of ascites in any patient given propranolol alone (Vorbioff *et al* 1993). Salerno et al recently reported that acute ISMN therapy in cirrhosis reduced diuresis and natriuresis, and reduced GFR in patients with ascites (Salerno *et al* 1996).

However, the same study also showed that chronic administration of ISMN did not affect renal function if patients did not have ascites, but reduced diuresis and naturesis in ascitic patients. No effect on GFR or renal plasma flow was detected.

However, Morrillos et al recently reported no effect on inulin clearance, free water clearance, plasma renin activity, aldosterone concentration or ascites outcome in cirrhotic patients given long-term propranolol and ISMN, despite a reduction in blood pressure (Morrillos *et al* 1994). In addition, Merkel and colleagues found no deterioration in renal function in cirrhotic patients given 6 months of ISMN and nadolol compared with patients given nadolol alone (Merkel *et al* 1995). Although there was a correlation between the fall in blood pressure and the rise in serum creatinine in the group as a whole, it was only the patients given combination therapy who had a reduction in their ascites.

We observed no change in RBF when patients were given ISMN alone or in combination with propranolol, despite significant effects on MAP, HVPG and AzBF consistent with previous reports in the literature (Navasa *et al* 1989, Garcia-Pagan *et al* 1990).

Different methods of renal blood flow measurement

Apart from the different study populations and treatment durations, the studies described above differed in their method of assessing renal blood flow, with most using doppler ultrasonography or PAH clearance techniques. Ultrasound is insensitive in the assessment of renal blood flow, and accurate PAH clearance requires high renal PAH extraction which does not occur in the presence of hypoxia and shunting of blood which occurs in sepsis or cirrhosis (Brenner *et al* 1990). Therefore, thermodilution methods may be more accurate in pathologiocal states.

For this reason, we used the reverse thermodilution method to measure changes in RBF. Although this has the limitation of only measuring RBF in one kidney and represents flow circulating during a short period of time, it has previously been used

to measure acute RBF changes in cirrhosis in response to drug therapy (Forrest *et al* 1996).

In view of our desire to assess both AzBF and RBF in this study, we had to move the thermodilution catheter out of the renal vein between the two recordings of RBF. The initial position of the catheter in the left renal vein was recorded fluoroscopically and the catheter re-positioned to the exact same position for the 1 hour recording of RBF using fluoroscopic guidance. To ensure validity of these measurements, 3 other cirrhotic patients had multiple RBF recordings made over 1 hour, with the catheter moved in and out of the left renal vein under similar conditions. The coefficient of variation in RBF recordings was <10 %.

In our study, the possibility of a type II error for the RBF results exists, but the numbers studied produced significant results with regard to the other haemodynamic parameters. Although the patients given ISMN had slightly lower baseline RBF compared to those given propranolol or combination therapy, this difference was not significant, and similar to the other therapeutic groups, these patients had no change in RBF following therapy.

In summary, there appears to be no change in RBF following acute administration of propranolol, ISMN or a combination of the two drugs to cirrhotic patients, despite the anticipated changes in MAP, HVPG and AzBF. Therefore any effect of these drugs on renal function in cirrhosis does not appear to be due to an acute reduction in RBF.

9b ii Comparisons between carvedilol and beta-blockers or nitrates in the management of portal hypertension.

We have shown that the vasodilating beta-blocker carvedilol has a portal hypotensive effect after both acute and chronic administration. The haemodynamic effects of carvedilol were studied prior to and 60 minutes following oral administration at which time peak plasma levels have been reported in cirrhosis (Neugebauer *et al* 1988). However a significant minority of patients are intolerant of 4 weeks therapy with this drug. The optimum dose of carvedilol in cirrhosis remains unclear, but a Japanese group recently reported a 15% drop in HVPG following acute administration of 10mg carvedilol to cirrhotic patients (Sekiyama *et al* 1997). It is possible that a lower dose of carvedilol will allow greater long-term tolerability with only a slight reduction in the beneficial effect on HVPG.

Splanchnic haemodynamics

Although beta-blockers remain the "gold standard" for pharmacological treatment of portal hypertension (D'Amico *et al* 1995), haemodynamic studies have shown that combination therapy with beta-blockers plus nitrates has a greater portal hypotensive effect than beta-blockers alone (Garcia-Pagan *et al* 1990).

Following acute propranolol therapy, a reduction in HVPG of 12-18% has been reported with an associated reduction in collateral flow and HBF (Bosch *et al* 1984, Garcia-Tsao G *et al* 1986, Garcia Pagan *et al* 1990). Following acute administration of combined propranolol and ISMN therapy, the HVPG has been shown to fall by a greater degree than propranolol alone (26% vs. 14%), but also lead to a further reduction in HBF (Garcia-Pagan *et al* 1990). In our study, acute administration of carvedilol reduced the baseline HVPG by a mean of 20.8% whilst having no effect on HBF.

We observed an acute reduction in HVPG of >10% in 76.5% patients given carvedilol. This compares with 55% patients given propranolol acutely, although most patients with minimal acute or chronic portal hypotensive response to beta-blokers can

be converted to "responders" by addition of ISMN (Garcia-Pagan *et al* 1990, Merkel *et al* 1997).

Following 4 weeks carvedilol therapy, we observed a mean fall in HVPG of 16.3%, 40% patients having a fall of 20% or more. In a previous report, chronic administration of propranolol led to a mean fall in HVPG of 10%, compared with 19% in patients given chronic combined propranolol and ISMN therapy (Garcia-Pagan *et al* 1991). In that study, HVPG fell by at least 20% in 10% of the propranolol group compared with 50% given combined therapy. Propranolol also reduced HBF.

Therefore, chronic administration of carvedilol appears to reduce HVPG to a greater extent than propranolol alone and similar to combined propranolol and ISMN. However, unlike beta-blocker therapy carvedilol does not appear to compromise liver blood flow.

Systemic haemodynamics

Acute propranolol therapy reduces heart rate and CO, and combination therapy with nitrates leads to a further fall in CO and reduces MAP (Garcia-Pagan *et al* 1990). In our study, heart rate, MAP and CO fell after acute carvedilol therapy, but no effect on CO or SVR was seen after chronic administration. However, a continued reduction in MAP was observed after 4 weeks carvedilol therapy.

Although this drop in MAP was similar to that reported after chronic combined propranolol and ISMN therapy (Garcia-Pagan *et al* 1991), 3 patients had to discontinue carvedilol due to hypotension and another required dose reduction due to dizziness. In total, 41% patients were unable to complete 4 weeks carvedilol therapy, and a further 2 patients had to be changed to a lower dose. Most studies report that 15-40% cirrhotic patients are intolerant of long-term beta-blockers, with a larger proportion unable to tolerate combined beta-blockers and nitrates.

Renal function

As described above, there have been suggestions that propranolol may impair sodium excretion in cirrhosis and nitrates may compromise renal blood flow and GFR (Rector & Reynolds 1984, Salmeron *et al* 1993). Vorbioff and colleagues reported a deterioration in renal function in the majority of ascitic patients given combined propranolol and ISMN therapy (Vorbioff *et al* 1993), but later studies reported no effect on renal function of this combination (Morrillas *et al* 1994, Merkel *et al* 1995).

Although we did not find an acute reduction in RBF following propranolol and ISMN combined therapy, there remains some concern regarding chronic administration of this drug combination in patients with advanced cirrhosis and ascites. The numbers in our study were small, but it is reassuring that no deleterious effects of chronic carvedilol therapy on urine volume, sodium excretion or creatinine clearance were observed.

Therefore carvedilol appears to have a beneficial portal hypotensive effect in cirrhotic patients following both acute and chronic therapy, with no detrimental effect on liver blood flow or renal function. Although a significant minority of patients are unable to tolerate chronic carvedilol therapy, lower doses may have continued beneficial effects.

9 c Role of adenosine-1 antagonism in the management of cirrhotic ascites.

Adenosine-1 antagonists have not been previously studied in patients with cirrhosis. We demonstrated improved renal function and RBF in cirrhotic patients following adenosine-1 antagonism with FK352. There was an immediate isokaliuretic improvement in urine flow rate and a tendency for free water clearance to rise following FK352, and an increase in natriuresis which persisted for at least 2 hours. These effects are of obvious benefit in cirrhotic patients with ascites in whom sodium and water excretion is impaired and diuretic therapy often leads to potassium imbalance (Naranjo *et al* 1979). Although we were only able to repeat right heart catheterisation 2 hours after drug administration and may have missed an earlier effect, minimal effects on systemic haemodynamics were observed which may reflect the renal specificity of adenosine-1 receptors.

9c i Effect on renal sodium and water handling

Water loading and commencement of the supine position may have led to the relatively high baseline urine volumes and RBF, but there were no significant changes in urine flow rate, natriuresis or free water clearance during the 2 hours prior to drug administration. Administration of FK352 was then followed by an immediate increase in urine flow and natriuresis. Any relation of this effect to the fluid load and posture change 4 hours earlier is improbable and inconsistent with previous reports (Bernardi *et al* 1994, Madsen *et al* 1986).

Although the patients in our study all had clinical evidence of ascites, none had biochemical renal impairment or true refractory ascites as defined by Arroyo and colleagues (Arroyo *et al* 1996) and therefore we cannot extend our findings to these patient groups. However, there was a consistent rise in urine flow rate, natriuresis and RBF when only the patients with Childs grade C disease were considered, indicating a continued benefit to patients at the more advanced end of the spectrum of liver disease. Certainly at present, therapeutic options for patients with refractory ascites or

hepato-renal syndrome are limited and we are keen to study the effects of this drug on such patients.

9c ii Effects on renal blood flow and GFR

The standard methods of measuring renal blood flow and GFR are PAH and inulin clearance respectively. However, as previously described, accurate PAH clearance requires high renal PAH extraction, and in cirrhotic patients, this method may be invalid (Brenner *et al* 1990). Therefore we measured renal venous PAH to calculate the PAH extraction, and also used the reverse thermodilution method as a separate indicator of changes in renal flow. The improved RBF we have shown following FK352 is consistent with earlier results from animal studies and the improved RBF seen in cirrhotic patients given xanthines (Milani *et al* 1983, Forrest *et al* 1997).

In normal subjects, PAH extraction should be >0.9, but in the 4 patients in whom we measured this, the pre-FK352 PAH extraction values ranged from 0.21-0.81. However, the number of patients studied was too small to properly assess the effect of FK352 on corrected ERPF. Inulin clearance remains the "gold standard" for GFR measurement and we were surprised that no rise in GFR was detected despite the increase in RBF, diuresis and natriuresis. It is possible that FK352 leads to tubular transport changes and improved RBF via antagonism of adenosine-1 receptors on the tubule cells and renal vasculature respectively, with little effect on GFR which may already be at the maximal achievable level in these patients.

9d iii Effect on RAAS and cAMP

A secondary objective of our study was to assess any hormonal change following FK352 administration. We observed an increase in plasma angiotensin II, PRA and cAMP, but no change in plasma catecholamines or urinary cAMP. Stimulation of adenosine-1 receptors inhibits renin release (Arend *et al* 1986, Deray *et al* 1987) and

suppression of this inhibition by administration of theophylline or an adenosine-1 receptor antagonist has been reported to increase PRA (Van Buren *et al* 1993, Erley *et al* 1994).

It has been suggested that the activity of the RAAS is closely related to the impaired natriuresis in cirrhosis (Wong *et al* 1997). In addition, increased local adenosine levels have been shown to potentiate sodium and water retention and renal vasoconstriction in cirrhotic patients with ascites and overactivity of the RAAS (Llach *et al* 1993). Therefore it is of interest that following administration of FK352 to cirrhotic patients, we observed an improvement in natriuresis and urine flow rate despite an increase in PRA and angiotensin II. This would suggest that adenosine-1 receptor antagonism is unique in being able to counter the detrimental effects on the kidney of overactivity of the RAAS without a deleterious effect on the peripheral vasculature.

Stimulation of adenosine-1 receptors leads to a decrease in cAMP via adenyl cyclase inhibition (Burnatowska & Spielman 1991) and antagonism of these receptors has been shown to inhibit this decrease in human glomeruli (Toya *et al* 1993). Therefore, adenosine-1 antagonism by FK352 may explain the observed rise in plasma cAMP during the study. It is unclear if urinary cAMP reflects local renal production or its excretion via the kidney, making interpretation of urine levels difficult. No effect of FK352 on peripheral catecholamine levels were observed, which may reflect a limited effect on systemic haemodynamics.

In summary, adenosine-1 specific antagonism in the form of FK352 appears safe and effective in cirrhotic patients with ascites. An improvement in diuresis, natriuresis and RBF is seen. Adenosine-1 antagonism offers a novel approach to the management of cirrhotic ascites and the spectrum of renal abnormalities seen in cirrhosis.

9 d TIPSS procedure in the management of complications of portal hypertension.

9d i Haemodynamic and renal effects of TIPSS placement

The dramatic cardiopulmonary and systemic haemodynamic effects of TIPSS procedure have been described in a number of recent studies. However, the relationship of these changes to any effect on renal function remains unclear.

Effects on cardiopulmonary haemodynamics

We have confirmed previous reports of a significant rise in CO, PAP and PCWP and a fall in SVR following TIPSS insertion. Azoulay et al reported an immediate increase in RAP, PAP, PCWP and CO and a decrease in SVR following the procedure, and a further worsening of the CO and SVR after 1 month (Azoulay *et al* 1994). Colombato and colleagues observed an immediate rise in RAP, PAP, PCWP and cardiac index, and a fall in SVR following TIPSS placement (Colombato *et al* 1996). A slight attenuation of the rise in cardiac index was the only further change detected at 2 months.

Van der Linden et al suggested that the increase in pulmonary pressures was the major haemodynamic alteration after TIPSS placement (Van der Linden *et al* 1996). Unlike the results from our study, they found that the drop in PPG correlated with the rise in PAP. It seems likely that the extra blood volume delivered to the right heart, mostly from decompression of the splanchnic circulation, leads to increased pulmonary pressures and CO. However. in addition to this volume load, the delivery of vasodilators from the splanchnic to the systemic circulation may precipitate the haemodynamic changes in the pulmonary, cardiac and systemic circulations.

Effects on renal function

The effect of TIPSS insertion on renal function is currently of great interest. TIPSS procedure has been shown to improve ascites control, with a delayed natriuresis

maximal 1 month after shunt placement (Wong *et al* 1995, Somberg *et al* 1995, Quiroga *et al* 1995, Wong *et al* 1997). TIPSS insertion also reduces the elevated circulating levels of plasma renin activity, aldosterone and noradrenaline over a period of weeks to months following the procedure (Wong *et al* 1995, Somberg *et al* 1995, Quiroga *et al* 1995, Jalan *et al* 1996, Wong *et al* 1997). Variable effects on glomerular filtration rate or creatinine clearance have been reported (Wong *et al* 1995, Somberg *et al* 1995, Quiroga *et al* 1995, Jalan *et al* 1996).

Wong and colleagues have suggested that sodium retention in cirrhosis is critically linked to sinusoidal portal hypertension, and enhanced by increased activity of the RAAS (Wong *et al* 1997). Our results suggest that any improvement in renal funtion after TIPSS placement does not occur secondary to any reflex increase in RBF.

The validity of thermodilution techniques in the assessment of changes in RBF over a period of weeks or months is questionable due to the difficulty in ensuring precise replacement of the catheter in the same position in the renal vein. Therefore we only assessed the acute changes in RBF following TIPSS placement, and may have missed a later improvement in RBF. Other studies have reported no effect on renal plasma flow as estimated by PAH clearance at variable intervals from 1 day to 4 months following TIPSS insertion (Wong *et al* 1995, Lebrec *et al* 1996, Wong *et al* 1997).

Possibility of a hepato-renal reflex

Studies by Lang and Jalan have suggested the presence of an hepato-renal reflex (Lang *et al* 1991, Jalan *et al* 1997). In an animal model, Lang and colleagues infused glutamine into the portal vein, thereby causing acute hepatocyte swelling. This was associated with an acute reduction in RBF, which was abolished by renal denervation or section of the hepatic vagal fibres. Stimulation of the sympathetic nerves innervating the kidney has also been shown to reduce RBF (DiBona & Sawin 1985), and effective renal plasma flow has improved following sympathectomy (Solis-Herruzo *et al* 1987).

Jalan and colleagues reported that occlusion of a TIPSS in cirrhotic patients was accompanied by an immediate reduction in RBF which correlated with the rise in PPG (Jalan *et al* 1997). There was a smaller but significant reduction in CO which did not account for the reduction in RBF, and a rise in SVR. TIPSS occlusion had no effect on renal venous or right atrial levels of angiotensin II, plasma renin activity, atrial natriuretic peptide, adrenaline or noradrenaline.

Although we did not observe a rise in RBF following the acute reduction in portal pressure achieved by TIPSS insertion, this does not disprove the presence of an hepato-renal reflex. A rise in portal pressure may be only one of a variety of mechanisms that may trigger such a reflex arc, and a fall in portal pressure may not necessarily activate the reflex.

Renal blood flow can be affected by neural factors, the RAAS, circulating noradrenaline, vasopressin and natriuretic peptides and intrarenal prostaglandins, leukotrienes, kinins, endothelin, nitic oxide and adenosine (Bernardi *et al* 1985, Moore *et al* 1992, Wong *et al* 1993, Llach *et al* 1993, Forrest *et al* 1996). Therefore full assessment of the changes in RBF caused by altering portal pressure would ideally require measurement of these parameters. However, the reported improvement in renal function following TIPSS procedure does not appear to involve an acute increase in RBF.

9d ii Long-term outcome following TIPSS procedure.

Variceal bleeding

TIPSS insertion has established a position as a "rescue procedure" for uncontrolled variceal bleeding. In our long-term study, shunt creation was successful in the vast majority (91.4%) of the 35 patients who had TIPSS procedure for continued variceal haemorrhage despite sclerotherapy with or without balloon tamponade. Most of these patients had Childs C cirrhosis. Although only 2 patients had continued bleeding, the in-patient mortality in this high risk group was 43.7%.

The options of a surgical portosystemic shunt or transection in this situation have higher procedure-related and early mortality (Franco & Smadja 1985). In addition transection has higher rebleeding rates and surgical shunting has higher rates of encephalopathy whilst also compromising a subsequent liver transplant (Matory *et al* 1980, Grace 1994). Although a recent report suggested benefits from a small diameter H-graft portocaval shunt compared with TIPSS placement (Rosemurgy *et al* 1996), it should be noted that in many cases TIPSS procedure is performed in critically ill patients who would not be considered fit for surgery.

It remains unclear whether patients who have suffered a first variceal bleed should be treated with band ligation to obliteration, pharmacological therapy, TIPSS insertion or some combination of these modalities. Cost analysis, patient compliance with various treatments and the availability of TIPSS procedure will help determine the optimum therapy for such patients. In our study, nine (7.6%) patients developed non-variceal bleeding during follow-up, mostly as a result of sclerotherapy ulcers and these were the cause of death in 2 patients. Sclerotherapy ulcers have been recognised as a major problem by many investigators and remain a major potential cause of morbidity and mortality no matter how effective the shunt is. The more widespread use of band ligation should reduce the frequency of this complication (Laine *et al* 1995).

Refractory ascites

Treatment of patients with refractory ascites remains a major clinical problem. Apart from liver transplantation, the main therapeutic options are repeated large volume paracentesis and peritoneovenous shunting. However, these are associated with significant morbidity and prolonged in-patient management and may aggravate functional renal failure. Although early reports described benefits of TIPSS procedure for refractory ascites (Quiroga *et al* 1995, Ochs *et al* 1995), the only published randomised trial comparing it with paracentesis for this indication reported a higher mortality in the TIPSS group (Lebrec *et al* 1996). Results from further trials which should include quality of life data are awaited.

The role of TIPSS procedure in the management of hepato-renal syndrome also remains controversial. Several authors have reported improvement in functional renal failure following the procedure (Lake *et al* 1993, Ochs *et al* 1995, Brensing *et al* 1996), and a preliminary study demonstrated a post-TIPSS decrease in the levels of endothelin-1 which is thought to have a major role in the syndrome (Martinet *et al* 1994). However as we found in our study, results of TIPSS placement in this patient group are generally disappointing, and they have a very poor prognosis without liver transplantation.

Shunt dysfunction

Our recurrent variceal rebleeding rate (13.4% patients) compares favourably with most other series (Helton *et al* 1993, Rossle *et al* 1994, Coldwell *et al* 1995, LaBerge *et al* 1995). Similar to other investigators, we found shunt dysfunction in all patients with variceal rebleeding (LaBerge *et al* 1995). There appears to be a steady attrition rate in shunt patency with time with a primary (pre-intervention) patency of 21.4% at 2 years. Although we have previously shown that shunt dysfunction is more common with Palmaz stents than Wallstents (Jalan *et al* 1994), it should be noted that our early (often Palmaz-stented) patients were left longer than 3 months prior to initial angiographic assessment. Therefore it is difficult to be sure of the exact timing of shunt dysfunction in this patient group.

Accepting this limitation, if it is believed important to assess the stent prior to a 20% risk of dysfunction, it would be necessary to check the shunt at 2 months and then approximately 6 monthly thereafter. It would appear that early shunt dysfunction is more likely to be associated with variceal rebleeding than that occurring later post TIPSS, therefore even closer shunt assessment in the first few months after placement may be neccessary.

When shunt insufficiency was detected, intervention maintained shunt patency in all but one patient, although the majority of stents treated with balloon dilatation required repeat dilatation on follow-up. This procedure would appear to have only a temporary effect and the long-term benefits of and exact indications for dilatation remain unclear. The current limitations of ultrasonographic methods of shunt assessment mean that direct portography remains the "gold standard" for surveillance (Ferguson *et al* 1995, Bartolone *et al* 1996). This is a major limitation of TIPSS procedure but as stated above, the development of new covered stents may address this problem.

Encephalopathy

In our study, new or worsening spontaneous encephalopathy was seen in 16.8% of our patients and a further 12.6% had new or worsening encephalopathy secondary to sepsis or bleeding following TIPSS placement. However, considering that 33.6% patients were encephalopathic prior to the procedure (often because of a recent bleed), it is difficult to determine the exact role of the shunt in the development of encephalopathy in this group. In all but 4 patients (who went on to shunt reduction), the encephalopathy responded to simple medical therapy such as lactulose and protein restriction. This contrasts with the often debilitating encephalopathy seen in around one third of patients after non-selective surgical shunts and is likely due to the small stent diameter and intrahepatic position which encourages continued portal flow into the liver (Franco & Smadja 1985, Lacy *et al* 1992).

A reduced incidence of encephalopathy has been reported in narrow portocaval H-grafts and selective splenorenal shunts although the associated risks of surgery and subsequent problems with transplantation must be considered (Langer *et al* 1985, Johansen 1992). Risk factors for post-TIPSS encephalopathy include a previous history of encephalopathy, advanced age, female gender, hypoalbuminaemia, non-alcohol aetiology of cirrhosis, and low post-procedural PPG. These must be carefully assessed prior to and following TIPSS procedure, and consideration should be given to smaller stent placement and prophylactic use of lactulose and protein restriction in such patients.

Liver function

Similar to other investigators, we found a transient deterioration in liver function tests in a third of patients, probably secondary to reduced hepatic perfusion (Rossle *et al* 1993). Three patients died soon after TIPSS procedure with clinical features of acute liver failure, two of whom also had evidence of raised intra-cranial pressure. This is unusual in patients with chronic liver disease but has been previously reported (Crippen *et al* 1992). However, all three of these patients were extremely ill at the time of TIPSS procedure, with periods of prolonged hypotension and requiring

ventilation. The role of the shunt in their clinical deterioration is therefore difficult to define, although any reduction in liver perfusion in such patients may be critical. However, overall there was a significant improvement in Childs-Pugh score at 3-6 months largely due to improvement in ascites.

Mortality

Procedure related mortality in our study was 1.5% which is similar to most reported series and compares favourably with the 10% operative mortality associated with surgical portosystemic shunts (Henderson *et al* 1984). We observed a relatively high 30-day mortality of 21.8% compared with some groups (Rossle *et al* 1994). However, mortality has been consistently shown to depend on Childs grade at time of TIPSS placement and our high percentage of Childs B and C patients (38.9% and 53.2% respectively) and high numbers of emergency procedures (26.9%) would account for this. Our one and two year survival of 62.3% and 46.5% respectively are similar to the recently reported series from San Francisco (LaBerge *et al,* 1995).

Long term survival following TIPSS procedure will depend on the underlying severity of liver disease and improved survival due to reduced rebleeding will be difficult to detect. However the benefits of reduced morbidity due to less variceal rebleeding and improved control of ascites should not be underestimated. Apart from the severity of liver disease, hyponatraemia and encephalopathy prior to TIPSS placement have been shown to independently determine long-term survival (Jalan *et al* 1995). Thirteen of our patients subsequently underwent liver transplantation and the benefits of TIPSS procedure as a "bridge to transplantation" have previously been reported (John *et al* 1996). In particular, when managing variceal bleeding prior to transplantation, the avoidance of surgery is advantageous.

In summary, TIPSS insertion is a relatively simple procedure that can be successfully performed even on critically ill patients. It is effective in controlling both acute and recurrent variceal haemorrhage and problematic portal hypertensive gastropathy, and may improve ascites contol. Unlike most surgical portosystemic shunts, TIPSS procedure does not compromise subsequent liver transplantation.

However, shunt dysfunction is common and appears to increase linearly with time. Both variceal rebleeding and reaccumulation of ascites usually occur in the presence of shunt dysfunction. Therefore regular surveillance by portography is required, and this probably represents the major limitation of this procedure. Post-TIPSS encephalopathy is significant but is generally easy to manage. Trials are underway to compare TIPSS placement with pharmacological or endoscopic therapy in the prevention of variceal rebleeding and with paracentesis for refractory ascites. Such trials must include data on quality of life and costs to help define the role of TIPSS procedure in these situations.

EPILOGUE:

Thoughts for future research.

The work presented in this thesis answers some questions but poses others. It is my aim to continue to be involved in studies arising from this research, and I outline some potential projects below.

Haemodynamics of cirrhosis:

It is clear that there is a close relationship between the severity of liver disease and HVPG in cirrhosis, and this measurement also predicts subsequent variceal bleeeding and death. Serial measurements of HVPG will allow accurate assessment of bleeding risk in patients undergoing drug therapy for portal hypertension, and the effect of abstinence in patients with alcohol related liver disease. The evolution of a scoring system containing CPS parameters, HVPG and possibly other measurements may provide a more accurate indication of prognosis in cirrhotic patients.

Drug therapy for portal hypertension:

Although propranolol remains the drug of choice in the management of portal hypertension, recent studies have shown the haemodynamic and clinical benefits of combined beta-blocker and nitrate therapy. However, we have shown that new therapies such as carvedilol provide similar portal hypotensive effects. We are now assessing the chronic haemodynamic effects of lower doses of carvedilol in cirrhotic patients. We then hope to compare carvedilol with propranolol ± ISMN in a clinical trial to assess its value in the primary prophylaxis of variceal haemorrhage.

Adenosine-antagonism in cirrhosis:

Acute administration of an adenosine-1 antagonist improves natriuresis and diuresis in cirrhotic patients with ascites. Future studies with such agents must assess their long-term efficacy and tolerability. However, spironolactone remains a cheap and effective first line diuretic for cirrhotic patients with ascites, therefore we hope to study the

effects of adenosine-1 antagonists in patients with refractory ascites or hepatorenal syndrome, where current therapy is limited.

TIPSS:

The role of TIPSS procedure in the prevention of variceal rebleeding remains unclear. Further trials are required to define the exact role of TIPSS, endoscopic therapy and pharmacological agents in the prevention of variceal rebleeding. TIPSS procedure does not appear beneficial in the treatment of refractory ascites. However further studies may identify a subset of patients who may benefit from this procedure in comparison with paracentesis or peritoneo-venous shunts. Quality of life and cost issues and must also be taken into account in such studies.

The dramatic haemodynamic changes and alterations in sodium and water homeostasis observed after TIPSS procedure provide a useful model to investigate the pathophysiology and treatment of the circulatory and renal changes of cirrhosis. In addition, the measurement of humeral factors and vasoactive substances in the splanchnic, renal and systemic vascular beds will also help elucidate the mechanisms behind the haemodynamic abnormalities seen in cirrhosis.

References

Agmon Y, Dinour D, Brezis M. Disparate effects of adenosine A1 and A2 receptor agonists on intrarenal blood flow. Am J Physiol 1993;265:F802-6.

Albillos A, Banares R, Barrios C, et al. Oral administration of clonidine in patients with alcoholic cirrhosis. Hemodynamic and liver function effects. Gastroenterology 1992;102:248-54.

Albillos A, Lledo JL, Rossi I, et al. Continuous prazosin administration in cirrhotic patients: Effects on portal hemodynamics and on liver and renal function. Gastroenterology 1995;109:1257-65.

Altman C, Grange JD, Amiot X et al. Survival after a first episode of spontaneous bacterial peritonitis: prognosis of potential candidates for orthotopic liver transplantation. J Gastroenterol Hepatol 1995;10:47-50.

Alvarez D, Golombek D, Lopez P et al (1994). Diurnal fluctuations of portal and systemic haemodynamic parameters in patients with cirrhosis. Hepatology 20:1198-1203.

Andreani T, Poupon RE, Balkau BJ, et al. Preventative therapy of first gastrointestinal bleeding in patients with cirrhosis: Results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. Hepatology 1990;12:1413-19.

Angelico M, Carli L, Piat C, Gentile S, Rinaldi V, Bologna E, Capocaccia L. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. Gastroenterology 1993;104:1460-1465.

Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of Isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. Gastroenterology 1997;113:1632-39.

Arend LJ, Thompson CI, Brandt MA, Speilman WS. Elevation of intrarenal adenosine by maleic acid decreases GFR and renin release. Kidney Int 1986;30:656-661.

Armonis A, Patch D, Burroughs AK. Hepatic venous pressure measurement: An old test as a new prognostic marker in cirrhosis? Hepatology 1996;25;245-248.

Armonis A, Patch D, McCormick PA, et al. Prognostic significance of hepatic venous pressure measurements in cirrhosis. J Hepatol 1997(Suppl 1);26:76.

Arroyo V, Bosch J, Mauri M et al. Renin, aldosterone and renal haemodynamics in cirrhosis with ascites. Eur J Clin Invest 1979;9:69-73.

Arroyo V, Gines P. Renal function abnormalities in cirrhosis. Eur J Gastroenterol Hepatol 1991;3:714-20.

Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;164-176.

Arroyo V, Gines P, Planas R, et al. Management of patients with cirrhosis and ascites. Sem Liv Dis 1986;6:353-363.

Arroyo V, Planas R, Gaya J, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis. Relationship to functional renal failure and sodium and water excretion. Eur J Clin Invest 1983;13:271-278.

Azoulay D, Castaing D, Dennison A, Martino W, Eyraud D, Bismuth H .Transjugular intrahepatic portosystemic shunt worsens the hyperdynamic circulatory state of the cirrhotic patient: Preliminary report of a prospective study. Hepatology 1994;19:129-32.

Balakrishnan VS, Coles GA, Williams JD. Effects of intravenous adenosine on renal function in healthy human subjects. Am J Physiol 1996;271:F374-381.

Banares R, Garcia-Pagan JC, Piqueras B, Casado M, Moitinho E, Diego A, Escorsell A, Bandi J, Cos E, Bosch J. Carvedilol, a new non-selective Beta-blocker with intrinsic anti-alpha adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology 1997;26:133A(abstract).

Barrett RJ, Wright KF. A selective adenosine A1 receptor antagonist attenuates renal dysfunction during controlled hypotension with adenosine in rats. Anaes Analg 1994;79:460-465.

Bartolone CJ, Owens C, Warner D et al. Assessment of patency in transjugular intrahepatic portosystemic shunts (TIPS): a prospective double-blind study comparing ultrasound (US) assessment with direct portal venography. Gastroenterology 1996;110:A1147(abstract)

Bataille C, Bercoff E, Pariente EA, Valla D, Lebrec D. Effects of propranolol on renal blood flow and renal function in patients with cirrhosis. Gastroenterology 1984;86:129-33.

Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. J Hepatol 1997;26:312-324.

Bernardi M, De Palma R, Trevisani F, Tame MR, Ciancaglini GC, Pesa O, Ligabue A, Baraldini M, Gasbarrini G. Renal function and effective B-blockade in cirrhosis with ascites. J Hepatol 1989; 8:279-286.

Bernardi M, Treviasini F, Fornale L, Di Marco C, Gasbarrini A, Baraldini M, Ligabue A, Gasbarrini G. Renal sodium handling in cirrhosis with ascites: Mechanisms of impaired naturetic response to reclining. J Hepatol 1994;21:1116-1122.

Bertoni G, Sassatelli R, Fornaciari G, Briglia R, Tansini P, Grisendi A, et al. Oral isosorbide-5-mononitrate reduces the rebleeding rate during the course of injection sclerotherapy for esophageal varices. Scand J Gastroenterol 1994;29:363-370.

Best JH, Halter JB. Blood pressure and norepinephrine spillover during propranolol infusions in humans. Am J Physiol 1985;248:R400-406.

Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol 1985;1:325-337.

Binmoeller KF, Soehendra N. Nonsurgical Treatment of Variceal Bleeding: New Modalities. Am. J. Gastroenterol.. 1995;90:1923-30.

Bolognesi M, Sacerdoti D, Merkel C, Gatta A. Duplex Doppler sonographic evaluation of splanchnic and renal effects of single agent and combined therapy with nadolol and isosorbide-5-mononitrate in cirrhotic patients. J Ultrasound Med 1994;13:945-952.

Bosch J, Mastai R, Krvetz D, et al. Effects of propranolol on azygos blood flow and hepatic and systemic hemodynamics in cirrhosis. Hepatology 1984;4:1200-5.

Bosch J, Arroyo V, Betriu A, et al. Hepatic hemodynamics and the renin-angiotensin-aldosterone system in cirrhosis. Gastroenterology 1980;78:92-9.

Boyer TD, Triger DR, Horisawa M, Redeker AG, Reynolds TB. Direct transhepatic measurement of portal vein pressure using a thin needle. Comparison with wedge hepatic vein pressure. Gastroenterology 1977;72:584-589.

Braillon A, Cales P, Valla D et al. Influence of the degree of liver failure on systemic and splanchnic haemodynamics and on response to propranolol in patients with cirrhosis. Gut 1986;27:1204-1209.

Brenner M, Schaer GL, Mallory DL, Suffredinin AF, Parillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. Chest 1990;98:170-79.

Brensing KA, Textor J, Raab P et al. Sustained improvement of Hepatorenal syndrome after TIPS-insertion in patients with terminal liver cirrhosis not eligible for transplantation. Gastroenterology 1996;110:A1158(abstract).

Burnatowska MA, Spielman WS. Effects of adenosine on cAMP production and cytosolic Ca2+ in cultured rabbit medullary thick limb cells. Am J Physiol 1991;260:C143-150.

Burroughs AK, D'Heygere F, McIntyre N. Pitfalls in studies of prophylactic therapy for variceal bleeding in cirrhotics. Hepatology 1986;6:4107-4113.

Cabrera J, Maynar M, Granados R et al. Transjugular Intrahepatic Portosystemic Shunt vs. Sclerotherapy in the elective treatment of variceal haemorrhage. Gastroenterology 1996;110:832-839.

Cales P, Braillon A, Jiton MI, Lebrec D. Superior portosystemic collateral circulation estimated by azygos blood flow in patients with cirrhosis. Lack of correlation with oesophageal varices and gastrointestinal bleeding. Effect of propranolol. J Hepatol 1984;1:34-46.

Cello JP, Ring EJ, Olcott E et al. Endoscopic sclerotherapy compared with percutaneous Transjugular Intrahepatic Portosystemic Shunt after initial sclerotherapy in patients with acute variceal hemorrhage. Ann Intern Med 1997;126:858-865.

Chalmers N, Redhead DN, Simpson KJ, Hayes PC. Transjugular intrahepatic portosystemic stent-shunt (TIPSS): Early clinical experience. Clin Radiol 1992;46:166-169.

Chong WK, Malisch TA, Mazer MJ, Lind CD, Worrell JA, Richards WO. Transjugular intrahepatic portosystemic shunt: US assessment with maximal flow velocity. Radiology 1993;189:789-93.

Christensen R, Gaverholdt I, Schlicting P, et al. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisolone. Gastroenterology 1981;81:944-52.

Coldwell DM, Ring EJ, Rees CR et al. Multicenter investigation of the role of transjugular intrahepatic portosystemic shunt in management of portal hypertension. Radiology 1995;196:335-340.

Colombato LA, Spahr L, Martinet JP, Dufresne MP, Lafortune M, Fenyves D, Pomier-Layrargues G. Haemodynamic adaptation two months after transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients. Gut 1996;39:600-604.

Conn HO, Grace N, Bosch J, Groszmann RJ, Rodes J, Wright SC, et al and members of the Boston-New Haven-Barcelona portal hypertension study group. Propranolol in the prevention of the first variceal haemorrhage from oesophageal varices: results of a randomized double-blind cooperative clinical trial. Hepatology 1991;13:902-912.

Crenshaw WB, Gordon FD, McEniff NJ et al. Severe ascites: Efficacy of the transjugular intrahepatic portosystemic shunt in treatment. Radiology 1996;200:185-192.

Crippin JS, Gross JB, Lindor KD. Increased intracranial pressure and hepatic encephalopathy in chronic liver disease. Am. J. Gastroenterol 1992;87:879-882.

D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22:332-354.

Deray G, Branch RA, Herzer WA, et al. Adenosine inhibits beta-adrenoceptor but not DBcAMP-induced renin release. AM J Physiol 1987;252:F46-52.

DiBona GF, Sawin LL. Renal nerve activity in conscious rats during volume expansion and depletion. Am J Physiol 1985;248:F15-23.

Dodd GD III, Zajko AB, Orons PD, Martin MS, Eichner LS, Santaguida LA. Detection of transjugular intrahepatic portosystemic shunt dysfunction: Value of duplex Doppler sonography. Am J Roenterol 1995;164:1119-24.

Dupont AG, Neipen P vd, Taeymans Y, et al. Effect of carvedilol on ambulatory blood pressure, renal hemaodynamics and cardiac function in essential hypertension. J Cardiovasc Pharm 1987;10 (Suppl 11):130-136.

Edlund A, Ohlsen H, Sollevi A. Renal effects of local infusion of adenosine in man. Clin Sci 1994;87:143-9.

Epstein M, ed. The kidney in liver disease. Baltimore: Williams & Wilkins. 1988:3-72.

Erley CM, Duda SH, Schlepckow S, Koehler J, Huppert PE, Strohmaier WL, Bohle A, Risler T, Osswald H. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int 1994;45:1425-1431.

Eustace S, Buff B, Kruskal J et al. Magnetic reonance angiography in transjugular intrahepatic portosystemic stenting: Comparison with contrast hepatic and portal venography. Eur J Radiol 1994;19:43-9.

Ferguson J, Jalan R, Redhead DN, Hayes PC, Allan PL. The role of duplex and colour doppler ultrasound in the follow-up evaluation of transjugular intrahepatic portosystemic stent-shunt. Brit J Radiol 1995;68:587-589.

Ferral H, Bjarnason H, Wegryn Saet al. Refractory ascites: Early experience in treatment with transjugular intrahepatic portosystemic shunt. Radiology 1993;189:795-801.

Ferral H, Foshager MC, Bjarnson H et al. Early sonographic evaluation of the transjugular intrahepatic portosystemic shunt (TIPS). Cardiovasc Intervent Radiol 1993;16:275-9.

Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, Rodes J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056-59.

Forrest EH, Bouchier IAD, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. J Hepatol 1996;26:909-915.

Forrest EH, Bouchier IADB, Hayes PC. Acute effect of low dose theophylline on the circulatory disturbances of cirrhosis. Gut 1997;40:139-144.

Forrest EH, Stanley AJ, Finlayson NDC, McGilchrist AJ, Hayes PC. Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) as a treatment for refractory ascites. Aliment Pharmacol Ther 1996;10:801-806.

Forrest EH. Jalan RJ, Hayes PC. Review article: renal circulatory changes in cirrhosis-pathogenesis and therapeutic prospects. Aliment Pharmacol Ther 1996;10:219-231.

Foshager MC, Ferral H, Nazarian GK, CastanedaZuniga WR, Letourneau JG. Duplex sonography after transjugular intrahepatic portosystemic shunts (TIPS): Normal hemodynamic findings and efficacy in predicting shunt patency and stenosis. Am J Roenterol 1995;165:1-7.

Franco D, Smadja C. Prevention of recurrent variceal bleeding: Surgical procedures. Clin. Gastroenterol. 1985;12:233-57.

Fredholm BB. Are methylxanthine effects due to antagonism of endogenous adenosine? Trends Pharmacol Sci 1980;129-32.

Friedman SL. Seminars in medicine of the Beth Israel Hospital, Boston. The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. N Engl J Med 1993;328:1828-1835.

Gandhi CR, Sproat LA, Subbotin VM. Increased hepatic endothelin-1 levels and endothelin receptor density in cirrhotic rats. Life Sci 1996;58:55-62.

Garcia-Pagan JC, Escorsell A, Feu F, et al. Propranolol plus molsidomine vs propranolol alone in the treatment of portal hypertension in patients with cirrhosis. J Hepatol 1996;24:430-35.

Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared to propranolol plus isosorbide-5-mononitrate for portal hypertension: a randomised controlled study. Ann Intern Med 1991;114:869-873.

Garcia-Pagan JC, Feu F, Castells A, Luca A, Hermida RC, Rivera F, Bosch J, Rodes J. Exercise and Circadian Variations of Portal Pressure and Variceal Hemorrhage in Patients with Cirrhosis. Gastroenterology 1996;111:1300-1306.

Garcia-Pagan JC, Navasa M, Bosch J et al. Enhancement of portal pressure reduction by the association of isosorbide-5-mononitrate to propranolol administration in patients with cirrhosis. Hepatology 1990;11:230-238.

Garcia-Pagan JC, Feu F, Navasa M, Bru C, Ruiz de Arbol L, Bosch J, Rodes J. Long-term hemodynamic effects of isosorbide-5-mononitrate in patients with cirrhosis and portal hypertension. J Hepatol 1990;11:189-195.

Garcia-Tsao G, Grace ND, Groszman RJ, Conn HO, Bormann MM, Patrick MJC, et al. Short-term effects of propranolol on portal pressure. Hepatology 1986;6:101-106.

Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M: Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5:419-424.

Garcia-Villarreal L, Martinez-Lagares F, Sierra A et al. TIPS vs Sclerotherapy for the prevention of variceal rebleeding. Preliminary results of a randomised study. Hepatology 1996;24:A326(abstract).

Gerbes AL. Medical treatment of ascites in cirrhosis. J Hepatol 1993; 17:S4-9.

Gines P, Tito LI, Arroyo V et al. Randomised comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493-1502.

Gluud C, Henriksen JH, Nielsen G and the Copenhagen Study Group for Liver Disease. Prognostic indicators in alcoholic cirrhotic men. Hepatology 1988;8:222-227.

Grace ND. The side-to-side shunt revisited. N. Engl. J. Med. 1994;330:208-209.

Graham D, Smith J. The course of patients after variceal haemorrhage. Gastroenterology 1981;80:800-809.

Groszmann RJ, Bosch J, Grace ND et al. Haemodynamic events in a prospective randomised trial of propranolol versus placebo in the prevention of a first variceal haemorrhage. Gastroenterology 1990;99:1401-7.

Groszmann RJ. Hyperdynamic circulation in cirrhosis: A Historical Perspective. Hepatology 1994;20:1356-1358.

Groupe d'Etude des Anastomoses Intra-Hepatiques (Toulouse, Bondy, Lille, Nice, Creteil, Paris) France. TIPS vs Sclerotherapy + Propranolol in the prevention of variceal rebleeding: preliminary results of a multicenter randomised trial. Hepatology 1995;22:299A(abstract).

Hadoke PWK, Hayes PC. In vitro evidence for vascular hyporesponsiveness in clinical and experimental cirrhosis. Pharmacol Ther 1997;75:1-18.

Hall JE, Granger JP. Adenosine alters glomerular filtration control by angiotensin II. Am J Physiol 1986;250:F917-923.

Hasegawa M, Yamada S, Hirayama C. Fasting plasma caffeine level in cirrhotic patients: relationship to plasma levels of catecholamines and renin activity. Hepatology 1989;10:973-977.

Haskal ZJ, Cope C, Soulen MC, Shlansky-Golberg RD, Baum RA, Redd DC. Intentional reversible thrombosis of transjugular intrahepatic portosystemic shunts. Radiology 1995;195:485-488.

Haskal ZJ, Pentecost MJ, Soulen MC, SchlanskyGoldberg RD, Baum RA, Cope C. Transjugular intrahepatic portosystemic shunt stenosis and revision: Early and midterm results. Am J Roenterol 1994;163:439-44.

Hauenstein KH, Haag K, Ochs A, Langer M, Rossle M. The reducing stent: Treatment for transjugular intrahepatic portosystemic shunt-induced refractory hepatic encephalopathy and liver filure. Radiology 1995;194:175-9.

Hausegger KA, Sternthal HM, Klein GE, Karaic R, Stauber R, Zenker G. Transjugular intrahepatic portosystemic shunt: Angiographic follow-up and secondary intervention. Radiology 1994;191:177-81.

Hayes PC, Davis JM, Lewis JA Bouchier IAD. Meta-analysis of the value of propranolol in prevention of variceal haemorrhage Lancet 1990;1:153-6.

Hayes PC, Stewart WW, Bouchier IAD. Influence of propranolol on weight and salt and water homeostasis in chronic liver disease. Lancet 1984;10:1064-106

Hayes PC, Terrace D, Peaston I, Bouchier IAD, Redhead DN, Brash HM. Computerised system for the continuous measurement of azygos venous blood flow. Gut 1992;33:372-374.

Hayes PC, Westaby D, Williams R. Effects and mechanisms of action of isosorbide-5-mononitrate. Gut 1988;29:757-765.

Helton WS, Belshaw A, Althaus S, et al. Critical appraisal of the angiographic portacaval shunt (TIPS). Am J Surg 1993;165:566-71.

Henderson JM, Millikan WJ, Warren WD. The distal splenorenal shunt: an update. World J. Surg. 1984;8:722-32.

Henriksen JH, Bendtsen F, Gerbes AL, Christensen NJ, Ring-Larsen H, Sorensen TIA. Estimated central blood volume in cirrhosis: relationship to sympathetic nervous activity, beta-adrenergic blockade and atrial natriuretic factor. Hepatology 1992;16:1163-1170.

Henriksen JH, Ring-Larsen H. Renal effects of drugs used in the treatment of portal hypertension. Hepatology 1993;18:688-695.

Henriksen JH. Cirrhosis: Ascites and hepatorenal syndrome. Recent advances in pathogenesis. J Hepatol 1995;23(Suppl 1):25-30.

Henriksen JH, Ring-Larsen H, Christensen NJ. Sympathetic nervous activity in cirrhosis: a survey of plasma catecholamine studies. J Hepatol 1984;1:55-65.

Holz FG, Steinhausen M. Renovascular effects of adenosine receptor agonists. Renal Physiol 1987;10:272-282.

Hornych A, Brod J, Slechta V. The measurement of renal venous outflow in man by the local thermodilution method. Nephron 1971;8:17-32.

Ibarra FR, Afione C, Garzon D, et al. Portal pressure, renal function and hormonal profile after acute and chronic captopril treatment in cirrhosis. Eur J Clin Pharmacol 1992;43:477-82.

Jalan R, Elton RA, Redhead DN, Finlayson NDC, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol 1995;23:123-8.

Jalan R, Forrest EH, Redhead DN, Dillon JF, Hayes PC. Reduction in renal blood flow following acute increase in the portal presure: evidence for the existence of a hepatorenal reflex in man? Gut 1997;40:664-670.

Jalan R, Forrest EH, Stanley AJ et al. A randomized trial comparing Transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. Hepatology 1997;26:1115-1122.

Jalan R, Harrison DJ, Redhead DN, Hayes PC. Transjugular intrahepatic portosystemic stent-shunt (TIPSS) and the role of biliary venous fistulae. J Hepatol 1996;24:169-76.

Jalan R, John TG, Redhead DN et al. A comparative study of emergency transjugular intrahepatic portosystemic stent-shunt and esophageal transection in the management of uncontrolled variceal hemorrhage. Am J Gastroenterol 1995;90:1932-1937.

Jalan R, Redhead DN, Ferguson J, Simpson KJ, Elton RA, Hayes PC. Wallstents or Palmaz stents for the transjugular intrahepatic portosystemic stent-shunt (TIPSS). J Intervent. Radiol. 1994;9:147-52.

Jalan R, Redhead DN, Thomas H, Henderson N, O'Rourke K, Dillon JF, Williams BC, Hayes PC. Mechanisms of changes in renal handling of sodium following transjugular intrahepatic portal systemic stent-shunt (TIPSS). Eur J Gastroenterol Hepatol 1996;8:1111-1116.

Jimenez W, Martinez-Pardo A, Arroyo V et al. Temoral relationship between hyperaldosteronism, sodium retention and ascites formation in rats with experimental cirrhosis. Effect of spironolactone. Hepatology 1985;5:245-50.

Johansen K. Prospective comparison of portal versus total portal decompression for bleeding oesophageal varices. Surg. Gynaecol. Obstet. 1992;175:528-534.

John TG, Jalan R, Stanley AJ, Redhead DN, Hayes PC, Sanfey HA, Garden OJ. insertion as a prelude to orthotopic liver transplantation in patients with severe portal hypertension. Eur J Gastroenterol Hepatol 1996;8:1145-49.

Kawada N, Tran-Thi TA, Klein H, Decker K. The contraction of hepatic stellate cells stimulated with vasoactive substances. Possible involvement of endothelin-I and nitric oxide in the regulation of the sinusoid tonus. Eur J Biochem 1993;213:815-823.

Kellet R, Bowmer CJ, Collis MG, Yates MS. Amelioration of glycerol-induced acute renal failure in the rat with 8-cyclopentyl-1, 3-dipropylxanthine. Br J Pharmacol 1989;98:1066-74.

Knight RJ, Bowmer CJ, Yates MS. The effects of 8-cyclopentyl-1, 3-dipropylxanthine on E-coli endotoxin-induced renal dysfunction (Abstract). Br J Pharmacol 1992;106:18P(Abstract)

Knight RJ, Collis MG, Yates MS, Bowmer CJ. Amelioration of cisplatin-induced acute renal failure with 8-cyclopentyl-1, 3-dipropylxanthine. Br J Pharmacol 1991;104:1062-1068.

Koshy A, Sekiyama A, Hadengue A, et al. Effects of alpha-1 and beta-adrenergic antagonists and 5-hydroxytryptamine receptor antagonist on portal-systemic collateral vascular resistance in conscious rats with portal hypertension. J Gastroenterol Hepatol 1992;7:449-454.

Krause T, Siegerstetter V, Haag K, Hauenstein KH, Rossle M. Evaluation of thrombogenicity of metallic stents in patients with TIPS using technetium-99m labelled platelets. Eur J Nucl Med 1994;21:741A.

Kuan CJ, Herzer WA, Jackson EK. Cardiovascular and renal effects of blocking A1 adenosine receptors. J Cardiovasc Pharmacol 1993;21:822-828.

Kuradusenge P, Rousseau H, Vinel J et al. Traitment des hemorragies par rupture de varices cardio-tuberositaires par anastomose porto-systemique intra-hepatique par voie trans-jugulaire. Gastroenterol. Clin. Biol. 1993;17:431-34.

LaBerge JM, Ferrell LD, Ring EJ, Gordon RL. Histopathological study of stenotic and occluded transjugular intrahepatic portosystemic shunts. J Vasc Intervent Radiol 1993;4:779-786.

LaBerge JM, Somberg KA, Lake JR et al. Two-year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: Results in 90 patients. Gastroenterology 1995;108:1143-1151.

Lacy AM, Nevasa M, Gilabert R et al. Long-term effects of distal splenorenal shunt on hepatic haemodynamics and liver function in patients with cirrhosis: importance of reversal of portal blood flow. Hepatology 1992;15:616-22.

Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Int Med 1995;123:180-187.

Lake JR, Ring EJ, LaBerge J, Gordon R, Roberts J, Ascher N. Transjugular intrahepatic portocaval stent shunts in patients with renal insufficiency. Transplant Proc. 1993;25:1766-7.

Lang F, Tschernko E, Schulze E, Ottl I, Ritter M, Hallbruker HC, Haussinger D. Hepatorenal reflex regulating kidney function. Hepatology 1991;14:590-594.

Langer B, Taylor BR, Mackenzie DR. et al. Further report of a prospective randomised trial comparing distal splenorenal shunt with end-to-side portacaval shunt. Gastroenterology 1985;88:424-9.

Lebrec D, Poynard T, Capron JP, et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis. A randomised trial. J Hepatol 1988;7:118-125.

Lebrec D, Giuily N, Hadengue A et al. Transjugular Intrahepatic Portosystemic Shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatol 1996;25:135-144.

Lebrec D. Pharmacotherapeutic agents in the treatment of portal hypertension. J Gastroenterol Hepatol 1997;12:159-166.

Li Kam Wa TC, Freestone S, Samson RR, Jonhston NR, Lee MR. A comparison of the renal and neuroendocrine effects of two 5-hydroxytryptamine renal prodrugs in normal man. Clin Sci 1993;85:607-14.

Lind CD, Malisch TW, Chong WK et al. Incidence of shunt occlusion or stenosis following transjugular intrahepatic portosystemic shunt placement. Gastroenterology 1994;106:1277-83.

Ljubicic N, Bilic A, Plavsic V. Effect of propranolol on urinary prostaglandin E2 excretion and renal interlobar arterial blood flow after furosemide administration in patients with hepatic cirrhosis. Eur J Clin Pharmacol 1992;43:555-558.

Llach J, Gines P, Arroyo V et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482-487.

Llach J, Gines P, Arroyo V, Salmeron JM, Gines A, Jimenez W, Gaya J et al. Effect of dipyridamole on kidney function in cirrhosis. Hepatology 1993;17:59-64.

Lo GH, Liang HL, Lai KH, et al. The impact of endoscopic variceal ligation on the pressure of the portal venous system. J Hepatol 1996;24:74-80.

Madsen M, Pedersen EB, Danielsen H, et al. Impaired renal water excretion in early hepatic cirrhosis. Lack of relationship between renal water excretion and plasma levels of arginine vasopressin, angiotensin II and aldosterone after water loading. Scand J Gastroenterol 1986;21:749-755.

Marato A, Gines P, Arroyo V, Gines A, Salo J, Claria J, Jimenez W et al. Brachial and femoral artery flow in cirrhosis: relationship to kidney dysfunction. Hepatology 1993;17:788-793.

Martinet JP, Legault L, Cernacek P et al. Effect of TIPS on splanchnic and renal production of endothelins. Hepatology 1994;20:113A,abstract.

Martini GA, Baltzer G, Arndt H. Some aspects of circulatory disturbances in cirrhosis of the liver. Prog Liver Dis 1972;4:231-250.

Matory WE Jr, Sedgwick CE, Rossi RL. Non-shunting procedures in management of bleeding oesophageal varices. Surg. Clin. North Am. 1980;60:281-95.

McCormick PA, Dick R, Panagou EB et al. Emergency transjugular intrahepatic portasystemic stent-shunting as salvage treatment for uncontrolled variceal bleeding. Br J Surg 1994;81:1324-27.

McIndoe AH. Vascular lesions of portal cirrhosis. Arch Path. 1928;5:23

McMathuna P, Vlavianos P, Wendon J, Westaby D, Williams R. Role of adenosine in the haemodynamic disturbances of cirrhosis and portal hypertension (Abstract) Hepatology 1990;12:852A.

Merkel C, Bolognesi M, Bellon S, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology 1992;102:973-979.

Merkel C, Finucci G, Zuin R. Effects of isosorbide dinitrate on portal hypertension in alcoholic cirrhosis. J Hepatol 1987;4:174-180.

Merkel C, Gatta A, Donada C, Enzo E, Marin R, Amodio P, et al & the GTIP. Long-term effect of nadolol or nadolol plus isosorbide-5-mononitrate on renal function and ascites formation in patients with cirrhosis. Hepatology 1995;22:808-813.

Merkel C, Marin R, Donada C, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Lancet 1996;348:1677-81.

Merkel C, Sacerdoti D, Bolognesi M, et al. Hemodynamic evaluation of the addition of isosorbide-5-mononitrate to nadolol in cirrhotic patients with insufficient response to the *B*-blocker alone. Hepatology 1997;26:34-39.

Merli M, Salerno F, Riggio O, et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: A ransomized multicenter trial. Hepatology 1998;27:40-45.

Milani L, Merkel C, Gatta A. Renal effect of aminophylline in hepatic cirrhosis. Eur J Clin Pharmacol 1983;24:757-760.

Mills PR, Rae AP, Farah DA, Russell RI, Lorimer AR, Carter DC. Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension. Gut 1984;25:73-8.

Moore K, Wendon J, Frazer M, et al. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. New Engl J Med 1992;327:1774-8.

Moreau R, Champigneulle B, Gaudin C, Poo JL, Kleber G, Bacq Y, Lebrec D. Effects of theophylline on hemodynamics and tissue oxygenation in patients with cirrhosis. J Hepatol 1992;15:323-329.

Moreau R, Lee SS. Soupison T, Roche-Sicot J, Sicot C. Abnormal tissue oxygenation in patients with cirrhosis and liver failure. J Hepatol 1988;7:98-105.

Moreau R, Cailmail C, Hamon G, Lebrec D. Renal and hemodynamic responses to a novel kappa opiod receptor agonist, iravoline (RU 51599) in rats with cirrhosis. J Gastroenterol Hepatol 1996;11:857-63.

Morrillos RM, Planas R, Cabre E, Galan A, Quer JC, Feu F, et al. Propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: Long-term hemodynamic and renal effects. Hepatology 1994;20:1502-1508.

Naranjo CA, Pontigo E, Valdenegro C, et al. Furosemide-induced adverse reactions in cirrhosis of the liver. Clin Pharmacol Ther 1979;25:154-60.

Navasa M, Chesta J, Bosch J, Rodes J. Reduction of portal pressure by isosorbide-5-mononitrate in patients with cirrhosis: effects on splanchnic and systemic hemodynamics and liver function. Gastroenterology 1989;96:1110-1118.

Neugebauer G, Gabor M, Reiff K. Disposition of carvedilol enantiomers in patients with liver cirrhosis: evidence for disappearance of stereoselective first-pass extraction. J Cardiovasc Pharm 1992;19(suppl 1):S142-146.

Neugebauer G, Gabor M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with cirrhosis. Drugs 1988;36(suppl 6):148-54.

Nevens F, Lijnen P, VanBilloen H, Fevery J. The effect of long-term treatment with spironolactone on variceal pressure in patients with portal hypertension without ascites. Hepatology 1996;23:1047-1052.

Nishimine K, Saxon RR, Kichikawa K et al. Improved transjugular intrahepatic portosystemic shunt patency with PTFE-covered stent grafts: Experimental results in swine. Radiology 1995;196:341-7.

North Italian Endoscopic Club (NIEC) for the study and treatment of esophageal varices. Prediction of the first variceal haemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-9.

Ochs A, Gerbes AL, Haag K et al. TIPS and paracentesis for the treatment of refractory ascites (RA): Interim analysis of a randomized controlled trial. Hepatology 1995;22:297A(abstract).

Ochs A, Rossle M, Haag K et al. TIPS for hepatorenal syndrome. Hepatology 1994;20:114A(abstract).

Ochs A, Rossle M, Haag K, Hauenstein KH, Deibert P, Siegersteter V, Hounker M, Langer M, Blum HE. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. N Engl J Med 1995;332:1192-1197.

Ohisalo JJ, Regulatory functions of adenosine. Med Biol 1987;65:181-191.

Okumura H, Aramaki T, Katsuta Y, et al. Reduction in hepatic venous pressure gradient as a consequence of volume contraction due to chronic administration of spironolactone in patients with cirrhosis and no ascites. Am J Gastroenterol 1991;86:46-52.

Olsson RA, Pearson JD. Cardiovascular purinoceptors. Phyiol Rev 1990;70:761-845.

Panes J, Teres J, Bosch J. Efficacy of balloon tamponade in treatment of bleeding gastric and oesophageal varices. Dig. Dis. Sci. 1988;33: 454-9.

Pascal JP, Cales P. Multicenter Study Group. Propranolol in the prevention of first upper gastrointestinal tract haemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med 1987;317:856-861.

Pagliaro L, Burroughs AK, Sorensen TIA, et al. Therapeutic controversies and randomised controlled trials (RCT's): Prevention of bleeding and rebleeding in cirrhosis. Gastroenterol Int 1989;2:71-84.

Pagliaro L, D'Amico G, Sorensen TIA et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomised trials of non-surgical treatment. Ann Intern Med 1992;117:59-70.

Pagliaro L, D'Amico G, Pasta L, et al. Bosch J, Groszmann RJ, editors. Portal hypertension. Pathophysiology and treatment. Oxford:Blackwell Scientific, 1994;5, Portal hypertension in cirrhosis: Natural history; 72-92.

Pariente EA, Bataille C, Bercoff E, Lebrec D. Acute effects of captopril on systemic and renal hemodynamics and renal function in cirrhotic patients with ascites. Gastroenterology 1985;88:1255-59.

Patch D, Dick R, McCormick PA, Armonis A, Burroughs AK. Emergency TIPS for Gastric Fundal Varices: Effective treatment? Gut 1996;38(suppl.1)W22(abstract).

Paul S, Kurunwana B, Biaggioni I. Caffeine withdrawal: apparent heterologous sensitization to adenosine and prostacyclin actions in human platelets. J Pharmacol Exp Ther 1993;267:838-43.

Poynard T, Cales P, Pasta L, Ideo G, Pascal JP, Pagliaro L, Lebrec D and the Franco-Italian Multicenter study group. B-adrenergic-antagonists in the prevention of first gastrointestinal bleeding in patients with cirrhosis and oesophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. N Engl J Med 1991;324:1532-1538.

PROVA Study Group. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: A randomized multicenter trial. Hepatology 1991;14:1016-24.

Quiroga J, Sangro B, Nunez M, Bilbao I, Longo J, Garcia-Villarreal L, Zozaya JM, Betes M, Herrero JI, Prieto J. Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: Effect on clinical, renal, humoral and hemodynamic parameters. Hepatology 1995;21:986-994.

Ramond MJ, Valla D, Mosnier JF, et al. Successful endoscopic obturation of gastric varices with butyl cyano-acrylate. Hepatology 1989;10:488-93.

Rector WG Jr, Reynolds TB. Propranolol in the treatment on cirrhotic ascites. Arch Int Med 1984;144:1761-1763.

Richter GM, Noeledge G, Palmaz JC. The transjugular intrahepatic portosystemic stent-shunt (TIPSS): experience and results of a pilot study. Cardiovasc. Intervent. Radiol. 1990;13:200-7.

Riggio O, Merli M, Pendretti G, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Incidence and risk factors. Dig Dis Sci 1996;41:578-584.

Ring EJ, Lake JR, Roberts JP, et al. Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. Ann Intern Med 1992;116:304-309.

Rockey DC, Chung JJ. Inducible nitric oxide synthetase in rat hepatic lipocytes and the effect of nitric oxide production on lipocyte contractility. J Clin Invest 1995;95:1199-1206.

Rockey DC, Weisiger RA. Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: Implication for regulation of portal pressure and resistance. Hepatology 1996;24:233-40.

Rockey D. The cellular pathogenesis of portal hypertension: Stellate cell contractility, endothelin, and nitric oxide. Hepatology 1997;25:2-5.

Rose SE, Katz MD. Intentional occlusion of a transjugular intrahepatic portosystemic shunt. Cardiovasc Intervent Radiol 1995;18:109-11.

Rosemurgy AS, Goode SE, Zwiebel BR, Black TJ, Brady PG. A prospective trial of transjugular intrahepatic portosystemic stent shunts versus small diameter prostheteic

H-graft portocaval shunts in the treatment of bleeding varices. Ann Surg 1996;224:378-384.

Rossle M, Richter GM, Noldge G et al. Peformance of an intrahepatic portacaval shunt (PCS) using a catheter technique: a case report. Hepatology 1988;8:1348A.

Rossle M, Deibert P, Haag K, Ochs A, Siegerstetter V, Langer M. Randomised trial of transjugular intrahepatic portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. Lancet 1997;349:1043-49.

Rossle M, Haag K, Ochs A, Sellinger M, Noldge G, Perarnau JM, Berger E, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. N Engl J of Med 1994;330:165-171.

Rossle M, Sellinger M, Ochs A, Haag K. Liver function and blood flow before and after TIPSS. Hepatology 1993;18:285A (abstract.)

Roulot D, Moureau R, Gaudin C, et al. Long-term sympathetic and hemodynamic responses to clonidine in patients with cirrhosis and ascites. Gastroenterology 1992;102:1309-18.

Ruiz del Arbol L, Garcia-Pagan JC, Feu F, et al. Effects of molsidomine, a long acting venous dilator, on portal hypertension: a hemodynamic study in patients with cirrhosis. J Hepatol 1991;13:179-86.

Salerno F, Borroni G, Lorenzano E, Solenghi D, Cassaniga M, Bissoli F, et al. Long-term administration of isosorbide-5-mononitrate does not impair renal function in cirrhotic patients. Hepatology 1996;23:1135-1140.

Salmeron JM, Ruiz del Arbol L, Gines A, Garcia-Pagan JC, Gines P, Feu F, et al. Renal effects of acute isosorbide-5-mononitrate administration in cirrhosis. Hepatology 1993;17:800-806.

Sanyal AJ, Freedman AM, Luketic VA et al. Transjugular Intrahepatic Portosystemic Shunts for Patients With Active Variceal Haemorrhage Unresponsive to Sclerotherapy. Gastroenterology 1996;111:138-46.

Sanyal AJ, Freedman AM, Purdum PP et al. Transjugular Intrahepatic Portosystemic Shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal haemorrhage: A randomised, controlled trial. Ann Intern Med 1997;126:849-857.

Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP III, Luketic VA, Cheatham AK. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: Results of a prospective controlled study. Hepatology 1994;20:46-55.

Sanyal AJ, Freedman AM, Luketic VA, et al. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. Gastroenterology 1997;112:889-898.

Sarin SK, Lamba GS, Kumar M. Randomised trial of propranolol vs. endoscopic variceal ligation (EVL) in the primary prophylaxis of bleeding from high risk varices in cirrhosis: an interim analysis. Hepatology 1997;360A9(abstract).

Sauer P, Theilmann L, Stremmel W, Benz C, Richter GM, Stiehl A. Transjugular intrahepatic portosystemic stent-shunt versus Sclerotherapy plus propranolol for variceal rebleeding. Gastroenterology 1997;113:1623-1631.

Sauer P, Theilmann L, Benz C, Richter GM, Stremmel W, Stiehl A. Transjugular intrahepatic portosystemic stent-shunt (TIPS) vs. endoscopic banding in the prevention of variceal rebleeding: interim analysis of a randomized study. Gastroenterology 1997;112:A1374 (abstract).

Sauer P, Theilmann L, Roren D, Richter G, Stremmel W, Steihl A. Phenprocoumon for prevention of early shunt occlusion after transjugular intrahepatic portosystemic stent-shunt (TIPS): results of a randomized trial. Gastroenterology 1995;108:A1164(abstract).

Schedl HP, Bartter FC. An explanation for and experimental correction of the abnormal water diuresis in cirrhosis. J Clin Invest 1960;39:248-61.

Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151-7.

Sekiyama T, Komeichi H, Nagano T, Ohsuga M, Terada H, Katsuta Y, Satomura K, Aramaki T. Effects of the alpha/beta-blocking agent carvedilol on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension. Arzneim.-Forsch./Drug Res 1997;47:353-355.

Shiffman ML, Jeffers L, Hoofnagle JH, Tralka TS. The role of transjugular intrahepatic portosystemic shunt for treatment of portal hypertension and its complications: A conference sponsored by the National Digestive Diseases Advisory Board. Hepatology 1995;22:1591-7.

Silvain C, Chauvin C, Verneau A, Carretler M, Beauchant M. How many cirrhotics may receive propranolol after gastrointestinal bleeding? Gastroenterol Clin Biol 1985;9:670-673.

Simpson, KJ, Chalmers N, Rehead DN, et al. Transjugular intrahepatic portosystemic stent shunting for control of acute and recurrent upper gastrointestinal haemorrhage related to portal hypertension. Gut 1993;34:968-73.

Sogni P, Soupison T, Moreau R, LeMoine O, Bacq Y, Hadengue A, Lebrec D. Hemodynamic effects of acute administration of furosemide in patients with cirrhosis receiving B-adrenergic antagonists. J Hepatol 1994;20:548-552.

Solis-Herruzo JA, Duran A, Favela V, Castellano G, Madrid JL, Munoz-Yague MT, et al. Effects of lumbar sympathetic block on kidney function in cirrhotic patients with hepatorenal syndrome. J Hepatol 1987;5:167-73.

Somberg KA, Lake JR, Tomlanovich SJ, LaBerge JM, Feldstein V, Bass NM. Transjugular Intrahepatic Portosystemic Shunts for refractory ascites: Assessment of clinical and hormonal response and renal function. Hepatology 1995;21:709-716.

Somberg KA, Riegler JL, LaBerge JM et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: incidence and risk factors. Am J Gastroenterol 1995;90:549-555.

Spahr L, Dufresne MP, Bui BT et al. Efficacy of TIPS in the prevention of rebleeding from esophageal and fundal varices: a comparitive study. Hepatology 1995;22:296A(abstract).

Spahr L, Fenyves D, NGuyen VV, Roy L, Legault L, Dufresne MP, Pomier Layrargues G. Improvement of hepatorenal syndrome by transjugular intrahepatic portosystemic shunt. Am J Gastroenterol 1995; 90:1169-1171.

Spielman WS, Thompson CI. A proposed role for adenosine in the regulation of renal haemodynamics and renin release. Am J Physiol 1982;242:F423-425.

Sponer G, Strein K, Bartsch W, Muller-Beckmann B. Vasodilatory action of carvedilol. J Cardiovasc Pharm 1992;19:(suppl 1):S5-11.

Stanley AJ, Jalan R, Ireland HM, Redhead DN, Bouchier IAD, Hayes PC. A comparison between gastric and oesophageal variceal haemorrhage treated with

Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS). Aliment Pharmacol Ther 1997;11:171-176.

Stiles GL, Adenosine receptors. J Biol Chem 1992;267:6451-6454.

Sturgis TM. Hepatorenal syndrome: Resolution after transjugular intrahepatic portosystemic shunt. J Clin Gastroenterol 1995;20:241-3.

Sugano S, Kawafune T, Suzuki T, et al. Oral administration of nipradilol and the acute and chronic splanchnic hemodynamic effects of a new beta-blocker with nitovasodilating properties in patients with liver cirrhosis. Am J Gastroenterol 1995;90:788-793.

Takeda M, Yoshitomi K, Imai M. Regulation of sodium bicarbonate cotransport in rabbit proximal convoluted tubule via adenosine A-1 receptor. Am J Physiol 1993;265:F511-519.

Tincani E, Cioni G, D'Alimonte P, et al. Effects of propranolol compared with clonidine on portal haemodynamics: a double-blind cross-over study using duplex-Doppler ultrasosnography. Eur J Gastroenterol Hepatol 1995;7:893-97.

Tobe SW, Blendis LM, Morali GA, Warner LC, Logan AG, Skorecki KL. Angiotensin II modulates atrial natriuretic factor-induced natriuresis in cirrhosis with ascites. Am J Kidney Dis 1993;21:472-79.

Toya Y, Umemura S, Iwamoto T, Hirawa N, Kihara M, Takagi N, Ishii M. Identification and characterization of adenosine A1 receptor cAMP system in human glomeruli. Kidney Int 1993;43:928-932.

Tsai YT, Lin HC, Lee SD. Recent advances in the pathophysiology of portal hypertension. J Gastroenterol Hepatol 1997;12(Suppl.) S283-287.

Van Buren M, Bijlisma JA, Boer P, Van Rijn HJM, Koomans HA. Naturetic and hypotensive effect of adenosine-1 blockade in essential hypertension. Hypertension 1993;22:728-734.

Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Deviere J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: Effects on right ventricular function. Hepatology 1996;23:1003-11.

Villanueva C, Balanzo J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. N Engl J Med 1996;334:1642-9.

Villarreal LG, Urmeneta JMZ, Vila JQ et al. Portosystemic intrahepatic prosthesis; PIP (TIPS) in the treatment of refractory ascites. A pilot study. Gastroenterol Hepatol 1993;16:18-22.

Vinel JP, Cassigneul J, Levade M, Voigt JJ, Pascal JP. Assessment of short term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of portohepatic gradient. Hepatology 1986;6:116-117.

Vinel JP, Monnin JL, Combis JM, et al. Hemodynamic evaluation of molsidomine: a vasodilator with antianginal properties in patients with alcoholic cirrhosis. Hepatology 1990;11:239-42.

Vorbioff J, Garcia-Tsao G, Groszmann RJ, et al. Long-term hemodynamic effects of ketanserin, a 5-hydroxytryptamine blocker in portal hypertensive patients. Hepatology 1989;8:88-91.

Vorbioff J, Groszmann RJ, Picabea E, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: A 10-year prospective study. Gastroenterology 1996;111:701-709.

Vorobioff J, Picabea E, Gamen M, Villavicencio R, Bordato J, Bessone F, et al. Propranolol compared with propranolol plus isosorbide dinitrate in portal-hypertensive patients: Long-term hemodynamic and renal effects. Hepatology 1993;18:477-484.

Whittle, BJR, Moncada S. Nitric Oxide: The elusive mediator of the hyperdynamic circulation of cirrhosis. Hepatology 1992;16:1089-1092.

Wilkinson R. B-Blockers and renal function. Drugs 1982; 23;195-206.

Wilkinson SR, Bernardi M, Smith IK, Jowet TP, Slater JDH, Williams R. Effect of B-adrenergic blockade on the renin-angiotensin system, sodium excretion, and renal hemodynamics in cirrhosis with ascites. Gastroenterology 1977;73:659-663.

Williams SGJ, Peters RA, Westaby D. Thrombin - an effective treatment for gastric variceal haemorrhage. Gut 1994; 35:1287-89.

Willett IR, Esler M, Burke F, et al. Total and renal sympathetic nervous system activity in alcoholic cirrhosis. J Hepatol 1985;1:639-648.

Willett IR, Esler M, Jennings G, Dudley FJ. Sympathetic tone modulates portal venous pressure in alcoholic cirrhosis. Lancet 1986;ii:939-943.

Wong F, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: Effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. Ann Int Med 1995;122:816-822.

Wong F, Sniderman K, Liu P, Blendis L. The mechanism of the initial natriuresis after transjugual intrahepatic portosystemic shunt. Gastroenterology 1997;112:899-907.

Zemel G, Katzen BT, Becker GJ, et al. Percutaneous transjugular portosystemic shunt. JAMA 1991;266:390-3.

Zervos EE, Goode SE, Wright T, Rosemurgy AS. A prospective randomized trial comparing TIPS and peritoneovenous shunt in the treatment of intractable ascites. Gastroenterology 1996;110:A1368(abstract).

Zhang JX, Pegoli W, Clemens MG. Endothelin-1 induces direct constriction of hepatic sinusoids. Am J Physiol 1994;266:G624-32.

Zweiten PA. Pharmacodynamic profile of carvedilol. Cardiology 1993;2(suppl 3):19-23.

Appendix.

Publications arising from the work presented in this thesis:

AJ Stanley, R Jalan, EH Forrest, DN Redhead, PC Hayes. Long Term Follow-up of Transjugular Intrahepatic Portosystemic Stent-shunts for the Treatment of Portal Hypertension: Results in 130 Patients.
Gut 1996;39:479-485.

AJ Stanley, DN Redhead, PC Hayes. Update on the role of transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of complications of portal hypertension.
Alimentary Pharmacology and Therapeutics 1997;11:261-272.

AJ Stanley, PC Hayes. Seminar: Variceal Haemorrhage.
Lancet 1997;350:1235-39.

AJ Stanley, I Robinson, EH Forrest, AL Jones, PC Hayes. Haemodynamic parameters predicting variceal haemorrhage and survival in alcoholic cirrhosis.
Quarterly Journal of Medicine 1998;91:19-25.

AJ Stanley, IAD Bouchier, PC Hayes. Effect of propranolol and isosorbide mononitrate on renal blood flow in cirrhotic patients.
Gut 1998;42:283-287.

AJ Stanley, EH Forrest, K Dabos, IAD Bouchier, PC Hayes. Natriuretic effect of an adenosine-1 receptor antagonist in cirrhotic patients with ascites.
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Manuscripts submitted for publication:

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AJ Stanley, G Therapondos, A Salem, PC Hayes. Acute and chronic effects of the vasodilating beta-blocker carvedilol, on hepatic and systemic haemodynamics and renal function in patients with cirrhosis.
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AJ Stanley, DN Redhead, PC Hayes. Post-TIPSS Encephalopathy: Is it a major problem? Caledonian Society of Gastroenterology (Edinburgh 1995).

AJ Stanley, IAD Bouchier, PC Hayes. Do Pharmacological Agents For Portal Hypertension Compromise Renal Flow? BSG Spring Meeting (Brighton 1996), *Gut* 1996;38:227A.

AJ Stanley, IAD Bouchier, PC Hayes. Do Pharmacological Agents For Portal Hypertension Compromise Renal Flow? AGA (San Francisco, May 1996), *Gastroenterology* 1996;50:197A.

AJ Stanley, EH Forrest, AL Jones, PC Hayes. Analysis of portal, systemic and renal haemodynamics in 100 cirrhotic patients. AGA (San Francisco, May 1996), *Gastroenterology* 1996;49:195A.

AJ Stanley, EH Forrest, K Dabos, PC Hayes. Pilot study into the effects of FK 352 (a novel adenosine-1 antagonist) in cirrhotic patients with ascites. Caledonian Society of Gastroenterology, (Glasgow 1996).

AJ Stanley, EH Forrest, K Dabos, PC Hayes. Investigation into the effects of FK 352 (a novel adenosine-1 antagonist) in cirrhotic patients with ascites: a pilot study. BSG Autumn meeting (Manchester1996), *Gut* 1996;39(Suppl 1)T85.

AJ Stanley, EH Forrest, K Dabos, PC Hayes. Assessment of the effects of FK 352 (a novel adenosine-1 antagonist) in cirrhotic patients with ascites: a pilot study. AASLD (Chicago 1996), *Hepatology* 1996;24:1284A.

AJ Stanley, DN Redhead, IAD Bouchier, PC Hayes. Effect of TIPSS on Renal Blood Flow in Cirrhosis. BSG (Brighton 1997),
Gut 1997;40(Suppl 1):W57.

AJ Stanley, IAD Bouchier, PC Hayes. Effect of Propranolol and Isosorbide Mononitrate on Renal Blood Flow in Patients with Cirrhosis. EASL (London 1997), *J Hepatology*1997;26:96A.

AJ Stanley, DN Redhead, IAD Bouchier, PC Hayes. Effect of TIPSS on Renal Blood Flow in Cirrhosis. AGA (Washington 1997), *Gastroenterology* 1997;112:1388A

AJ Stanley, G Therapondos, A Salem, PC Hayes. Acute and chronic haemodynamic and renal effects of carvedilol in cirrhosis. BSG (Harrogate 1998), *Gut* 1998;42(suppl 1):A28.

AJ Stanley, G Therapondos, A Salem, PC Hayes. Acute and chronic haemodynamic and renal effects of carvedilol in cirrhosis. AGA (New Orleans 1998), *Gastroenterology* 1998;114:1345A.

Longterm follow up of transjugular intrahepatic portosystemic stent shunt (TIPSS) for the treatment of portal hypertension: results in 130 patients

A J Stanley, R Jalan, E H Forrest, D N Redhead, P C Hayes

Abstract

***Background*—Transjugular intrahepatic portosystemic stent shunts (TIPSS) are increasingly being used to manage the complications of portal hypertension. This study reports on the follow up on 130 patients who have undergone TIPSS.**

***Patients and Methods*—One hundred and thirty patients (81 male), mean (SD) age 54·7 (12·5) years underwent TIPSS. The majority (64·6%) had alcoholic cirrhosis and 53·2% had Childs C disease. Indications were: variceal haemorrhage (76·2%), refractory ascites (13·1%), portal hypertensive gastropathy (4·6%), others (6·1%). Shunt function was assessed by Doppler ultrasonography and two then six monthly portography and mean follow up for survivors was 18·0 months (range 2–43·5).**

***Results*—The procedure was successful in 119 (91·5%). Sixty three episodes of shunt dysfunction were observed in 45 (37·8%) patients. Variceal rebleeding occurred in 16 (13·4%) patients and was always associated with shunt dysfunction. Twenty (16·8%) patients had new or worse spontaneous encephalopathy after TIPSS and 11 (64·7%) patients had an improvement in resistant ascites. Thirty day mortality was 21·8% and one year survival 62·5%.**

***Conclusion*—TIPSS is an effective treatment for variceal bleeding, resistant ascites, and portal hypertensive gastropathy. Rebleeding is invariably associated with shunt dysfunction, the frequency of which increases with time, therefore regular and longterm shunt surveillance is required.**

(*Gut* 1996; **39:** 479–485)

Keywords: transjugular intrahepatic portosystemic stent shunt, portal hypertension, varices, ascites.

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Since their introduction into clinical practice in 1989,[1] transjugular intrahepatic portosystemic stent shunts (TIPSS) are being increasingly used in the management of both variceal haemorrhage and refractory ascites.

Variceal haemorrhage is the most dramatic complication of portal hypertension, occurring in 30% patients with cirrhosis during their lifetime.[2] Mortality from the first bleed approaches 50%[3] and 70–100% patients have recurrent bleeding. Immediate control of bleeding can be achieved in 90% of patients by balloon tamponade,[4] vasoactive drug therapy,[5] sclerotherapy,[6] variceal band ligation[7] or surgery,[8 9] with the greatest reduction in rebleeding rates achieved by surgical shunts.[10] The main limitations of shunt surgery are its high perioperative mortality and frequency of debilitating postoperative encephalopathy, which approaches 30% in some series.[11] TIPSS has been shown to control active variceal haemorrhage and reduce rebleeding rates while having lower procedure related complications and probably less post-treatment encephalopathy[12] compared with surgical shunts. Follow up of patients with TIPSS is however limited, which is important as encephalopathy following surgical shunts commonly was delayed and shunt patency after TIPSS may decrease with time.

Refractory ascites is associated with advanced liver disease and a poor prognosis.[13] The current therapeutic options of repeated paracentesis and a peritoneovenous shunt are far from ideal and associated with significant morbidity and prolonged hospital stay and do not affect survival.[14] TIPSS permits better control of ascites and improves renal sodium excretion[15] although the mortality seems unchanged in the limited reported data. TIPSS has also been used and found to be effective in the control of other conditions such as portal hypertensive gastropathy, splenomegaly,[16] Budd-Chiari syndrome,[17] and hepatic hydrothorax.[18] The present available literature is limited both by short duration of follow up and small patient numbers. Up until August 1995, we had carried out 130 TIPSS procedures in our unit and the aim of this paper is to present our results and more importantly the longterm follow up.

Methods

PATIENTS

From 1991 to 1995, TIPSS insertion was attempted in 130 patients, with successful placement of the stent in 119 cases (91·5%). Table I shows the details of the patients. Eighty one patients were male with mean (SD) age of 54·7 (12·5) years (range 9 to 83 years). Over the same period, a total of 220 patients were treated for variceal haemorrhage at our institution.

TABLE I *Patient characteristics (n=130) before TIPSS*

Sex (M/F)	*81/49*
Age (y)	
mean (SD)	54·7 (12·5)
range	9–83
Aetiology of liver disease (%)	
alcoholic cirrhosis	84 (64·6)
cryptogenic cirrhosis	12 (9·2)
primary biliary cirrhosis	11 (8·5)
hepatitis C	5 (3·8)
hepatitis B	5 (3·8)
cystic fibrosis	3 (2·3)
primary sclerosing cholangitis	2 (1·5)
autoimmune hepatitis	2 (1·5)
other	6 (4·6)
Childs-Pugh score (mean (SD))	9·9 (2·7)
Childs-Pugh grade (%)	
A	10 (7·9)
B	49 (38·9)
C	67 (53·2)
Indication (%)	
oesophageal varices	73 (56·2)
gastric varices	26 (20·0)
refractory ascites	17 (13·1)
portal hypertensive gastropathy	6 (4·6)
ectopic varices	5 (3·8)
other	3 (2·3)
Emergency procedure (%)	35 (26·9)
Clinical features (%)	
artificially ventilated	19 (14·6)
haemodynamic compromise	10 (7·7)
ascites	86 (66·2)
hepatic encephalopathy	44 (33·8)

The aetiology of portal hypertension was alcoholic cirrhosis (ALD) in 84 (64·6%) patients, with other aetiologies shown in Table I. One patient had α_1 antitrypsin deficiency and one Budd-Chiari syndrome. Four patients were non-cirrhotic (one each with amyloid, idiopathic portal hypertension, polycystic disease, and nodular regenerative hyperplasia). Most cirrhotic patients (53·2%) had Childs-Pugh grade C disease at time of TIPSS with a mean (SD) overall Childs-Pugh score of 9·9 (2·7).

The indication for TIPSS was oesophageal variceal bleeding in 73 (56·2%) patients who had either continued bleeding despite two sessions of sclerotherapy or were part of a trial comparing band ligation with TIPSS in the prevention of rebleeding (see Table I). The indication was ectopic varices in five (3·8%) patients (two rectal, two stomal, and one duodenal) and painful splenomegaly, hypersplenism and embolisation of a spontaneous shunt in one patient each. Thirty five procedures (26·9%) were carried out as an emergency with 19 (14·6%) patients receiving assisted ventilation and 23 (17·7%) patients treated with balloon tamponade prior to TIPSS.

STUDY DESIGN

The technique of TIPSS placement was based on the original method described by Richter[19] and is described in detail elsewhere.[20] Routine pre-procedural mesenteric angiography was undertaken in the first 32 patients to guide portal vein puncture and in 27 subsequent patients, Doppler ultrasonography was used to identify the site of portal vein bifurcation. In the last 71 patients however, no routine imaging was undertaken to localise the portal vein pre-TIPSS, although ultrasonography was used prior to the procedure to exclude portal vein thrombosis. These changes have evolved as a result of ongoing audit at our unit.

Once successful puncture of the portal vein was achieved, 2–3 Palmaz stents (Johnson and Johnson) (20 patients), or 1–2 Wallstents (Schneider US Stent Division) (99 patients) were inserted to reduce the portal pressure gradient (defined as: (portal pressure) – (inferior vena-caval pressure)) to less than 12 mm Hg. Three patients subsequently had Angiomed stents (Angiomed, Karlsruhe, Germany) inserted to reduce the shunt size. In two patients in whom a thrombus was noted within the portal vein at the end of the procedure, a catheter was left within the shunt for regional infusion of low dose streptokinase for 24 hours. Prophylactic antibiotics (cefotaxime and amoxycillin) were given one hour before the procedure and continued for 48 hours thereafter and Doppler ultrasonography was performed prior to discharge to ensure shunt patency. Routine portography was undertaken at one to three months and six monthly thereafter to assess shunt function, or earlier in the event of rebleeding or reaccumulation of ascites. Early in our experience however, several shunts were left six to 12 months before initial angiographic assessment.

Encephalopathy was assessed clinically after six weeks then at three monthly intervals during outpatient review. Prophylactic lactulose and protein restriction were not routinely applied. Variceal rebleeding was defined as endoscopically confirmed variceal haemorrhage occurring more than 24 hours after TIPSS insertion. All shunt complications were confirmed angiographically with occlusion defined as absent flow through the shunt. Pseudo-intimal hyperplasia, hepatic vein stenosis, portal vein and shunt thrombosis were defined by the angiographic appearance in conjunction with either a 20% rise in portal pressure gradient or an increase in portal pressure gradient to 12 mm Hg or more. Primary shunt patency was defined as the (pre-intervention) absence of any of the above shunt complications. Mean (SD) follow up (defined as time to death, most recent clinical review or liver transplantation) for all patients was 10·7 (11·0) months and for survivors (patients alive up to October 1995) 18·0 (11·9) months.

STATISTICAL ANALYSIS

Results are expressed as mean (SD) or range where indicated. Paired Student's *t* test was used to determine statistical significance and Kaplan-Meier method used for rates of variceal rebleeding, primary shunt patency, and survival.

Results

Tables II and III summarise the results.

SHUNT PROCEDURE

TIPSS placement was successful in 119 (91·5%) patients. The procedure failed in 11 patients (10 of whom had variceal haemorrhage) because a main branch of the portal vein could not be punctured: four of these patients subsequently underwent shunt surgery and five

TABLE II *Results of TIPSS procedure and shunt complications*

Successful TIPSS procedure (%)	119 (91·5)
PPG before TIPSS mean (SD) (mm Hg)	17·5 (5·9)
PPG after TIPSS (mm Hg)	8·6 (3·4)
Pre-intervention shunt patency (%):	
6 months	47 (71·2)
1 year	25 (58·1)
2 years	3 (21·4)
Shunt complications:	63 episodes in 45 (37·8) patients:
pseudo-intimal hyperplasia	29
hepatic vein stenosis	13
portal vein/shunt thrombosis	5
occlusion	16

PPG=portal pressure gradient.

had further endoscopic therapy. Thirty day mortality in the failed TIPSS group with variceal haemorrhage was 70·0%.

Two procedure related deaths occurred from intraperitoneal haemorrhage because of an extrahepatic tear of the portal vein in one and puncture of the liver capsule in the other. One patient developed an epidural haemorrhage, which was diagnosed after the procedure but the exact relation to TIPSS placement was unclear. Other complications included portal vein thrombosis in two patients (successfully treated by local streptokinase infusion), portal vein dissection in one (successfully managed by stenting), and shunt dislocation or migration into the splenic vein in two. There were no clinically significant groin or neck haematomas. Mean (SD) portal pressure gradient was reduced from 17·5 (5·9) mm Hg pre-TIPSS to 8·6 (3·4) mm Hg ($p<0·001$) after successful stent placement.

A total of 63 episodes of shunt complications were seen in 45 patients (see table II). Twenty nine of these were clinically significant (associated with variceal rebleeding or reaccumulation of ascites), with the others detected on routine surveillance. Fifty per cent of the shunt complications occurring less than one month after TIPSS were associated with variceal rebleeding, as were 41·7% of those occurring from one to three months, 35% from three to 12 months, and 23·5% from 12–24 months. None of the shunt complications occurring more than two years after TIPSS were associated with variceal rebleeding. Taking follow up as most recent angiographic TIPSS assessment, pre-intervention shunt patency was 71·2% at six months, 58·1% at one year, and 21·4% at two years (see Table II and Fig 1). No Palmaz stent had primary patency at two years. All shunt complications but one (in a patient who was transferred to an endoscopic banding programme and remains well) were successfully treated by balloon dilatation, local thrombolysis, shunt extension or parallel shunt placement (nine patients). The causes of shunt dysfunction are described in Table II.

TABLE III *Results of rebleeding, encephalopathy, ascites, and sepsis after TIPSS*

Variceal rebleeding	24 episodes in 16 patients (13·4%)
Non-variceal rebleeding	9 patients (7·6%)
	7 sclerotherapy ulcers
	1 duodenal ulcer
	1 Mallory-Weiss tear
Encephalopathy (%)	
before TIPSS	44 (33·8)
new/worse spontaneous encephalopathy	20 (16·8)
new/worse encephalopathy, secondary to sepsis	9 (7·6)
new/worse encephalopathy, secondary to bleeding	6 (5·0)
Ascites (%)	
before TIPSS	86 (66·2)
improved after TIPSS	56 (65·1)
reaccumulation	14 (25·0)
primary indication for TIPSS	17 (13·1)
Sepsis after TIPSS (%)	14 (11·8)

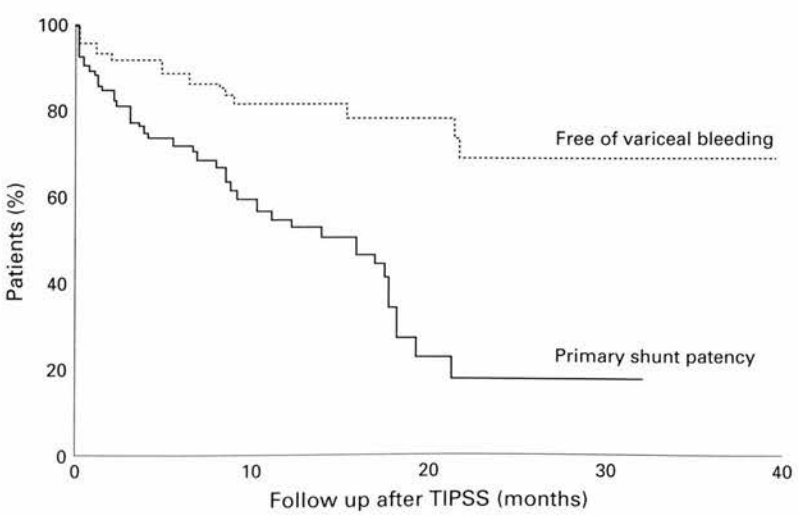

Figure 1: Kaplan-Meier analysis of patients free of variceal rebleeding and with primary shunt patency during follow up.

CLINICAL FOLLOW UP

Control of acute bleeding

Thirty five patients had TIPSS for acute variceal haemorrhage uncontrolled despite sclerotherapy with or without tamponade. Eighteen of these patients were mechanically ventilated and 10 were haemodynamically unstable at time of TIPSS. The procedure was technically successful in 32 of these patients and the other three patients died: two from massive haemorrhage and one shortly after oesophageal transection. Fourteen of the remaining patients died during the index hospital admission: three each from acute on chronic liver failure, sepsis, and end stage liver failure, two from continued bleeding (one from a sclerotherapy ulcer confirmed at necropsy and one with disseminated intravascular coagulation and acidosis), two from cardiac arrests/myocardial infarct, and one from a procedure related intraperitoneal bleed. Two further patients had subsequent variceal rebleeds, both related to shunt insufficiency and successfully treated by angioplasty and shunt extension.

Recurrent variceal bleeding

TIPSS was successful in reducing recurrent variceal haemorrhage. There were 24 episodes of variceal re-bleeding in 16 (13·4%) patients (see Fig 1), all of which were associated with shunt insufficiency and responded to dilatation or further stenting. Five patients underwent TIPSS for ectopic variceal haemorrhage (two rectal, two stomal, and one duodenal) and none of these patients have had a recurrent bleed. Non-variceal haemorrhage occurred in nine (7·6%) patients (see Table III).

Ascites
Eighty six patients (66·2%) had ascites prior to TIPSS and this was the primary indication in 17 patients (seven of whom had established hepatorenal syndrome) (see Table III). The ascites improved (reduced or no diuretic requirement) in 56 (65·1%) of the 86 patients, but reaccumulated in 14. This was associated with shunt insufficiency in 11 patients and spontaneous bacterial peritonitis in two, but was responsive in all cases to shunt revision and antibiotics respectively. Of the 17 patients who had TIPSS performed for refractory ascites, improvement occurred in 11 and two have subsequently undergone successful liver transplantation. Those with biochemical evidence of renal dysfunction tended to respond less well after TIPSS insertion.

Other indications
TIPSS was performed for intractable bleeding from portal hypertensive gastropathy in six patients. Four of these have not required further transfusion and the other two have required one admission each for transfusion. Both of these patients had evidence of shunt dysfunction due to pseudo-intimal hyperplasia in association with a raised portal pressure gradient, which was successfully treated by angioplasty or shunt extension. TIPSS resulted in an improvement in platelet count from 13 000/l to 50 000/l in one patient with hypersplenism. Another patient had a large spontaneous shunt successfully embolised via the TIPSS for amelioration of intractable hepatic encephalopathy.

Hepatic encephalopathy
Forty four (33·8%) patients were clinically encephalopathic prior to TIPSS and this resolved in 24 (54·5%) after the procedure. Twenty (16·8%) patients developed new or worsening spontaneous encephalopathy during follow up (15 within the first six months). A further 15 (12·6%) patients developed encephalopathy secondary to sepsis or bleeding during follow up (see Table III). Reduction in shunt size was performed because of encephalopathy in four patients (successful in three), with all others responding to simple medical treatment.

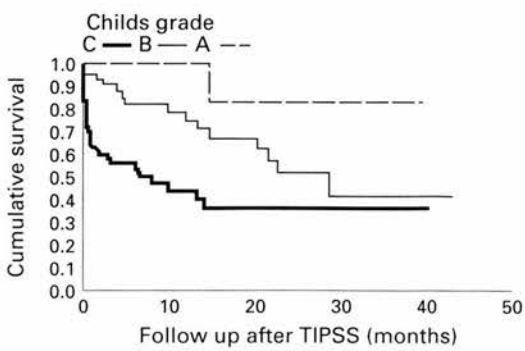

Figure 2: Kaplan-Meier analysis of patient survival after TIPSS by Childs grade. (Childs A, n=12; Childs B, n=44; Childs C, n=61. At 12 months, n=9, 23, and 14 respectively.)

Sepsis
Fourteen (11·8%) patients developed clinically significant infections in the week after TIPSS (seven pulmonary, two spontaneous bacterial peritonitis, two related to central venous catheter, one cellulitis, and two of unknown origin). Sepsis was the cause of death in two patients during the index admission: one with pre-existing staphylococcal and fungal septicaemia and one with cystic fibrosis and pre-existing lung sepsis. All other infective episodes responded to antibiotics.

Liver function
Approximately one third of patients exhibited a transient deterioration in their liver function tests in the first week after TIPSS, usually with doubling of bilirubin and alanine aminotransferase values. Three patients died with clinical features of acute liver failure, characterised by hypotension, renal failure, and hypoglycaemia. Two of these patients also had evidence of raised intracranial pressure on extradural pressure recordings or computed tomography. Childs-Pugh score did however improve at three to six months to 7·6 (2·1) (p=0·019) largely because of a reduction in ascites.

Transplantation
Thirteen patients have undergone orthotopic liver transplantation after TIPSS. Transplant was undertaken a mean of 7·1 (5·4) months after TIPSS and 11 of these patients remain alive and well.

Mortality
Of the 119 patients with successful TIPSS placement, 52 have died and 13 have undergone transplantation. Procedure related mortality was 1·5% and mean time to death was 6·0 (8·9) months (range 0·03–45·3). Mean follow up of survivors is 18·0 (11·9) months (range 2·0–43·5). Thirty day mortality was 21·8% (84·6% of whom had Childs C disease) and six months survival 69·2%. One and two year survival is 62·3% and 46·5% respectively. Mortality was dependent on Childs grade at time of TIPSS (see Fig 2).

Discussion

This is only the second study with large numbers of patients and longterm follow up and our results are similar to the two year follow up of 90 patients reported by Laberge *et al.*[21] Shunt insertion was achieved with a reduction in the portal pressure gradient to below 12 mm Hg in 91·5% patients. Our recurrent variceal rebleeding rate (13·4% patients) and rate of new or worsening spontaneous encephalopathy (16·8% patients) compares favourably with most other series.[12 21–23]

TIPSS has established a position as a 'rescue procedure' for uncontrolled variceal bleeding. Of the 35 patients who had TIPSS for

continued variceal haemorrhage despite sclerotherapy with or without balloon tamponade, shunt creation was successful in the vast majority (91·4%). Most (77·1%) of these patients had Childs C cirrhosis. Although only two patients had continued bleeding the inpatient mortality in this high risk group was 43·7%. The options of a surgical portosystemic shunt or transection in this situation have higher procedure related and early mortality.[24] In addition transection has higher rebleeding rates[25] and surgical shunting has higher rates of encephalopathy[26] while also compromising a subsequent liver transplant. It should be noted that in many cases TIPSS is performed in critically ill patients who would not be considered fit for surgery.

Similar to other investigators,[21] we found shunt dysfunction in all patients with variceal rebleeding. There seems to be a steady attrition rate in shunt patency with time (Table II and Fig 1) with a primary (pre-intervention) patency of 21·4% at two years. We have previously shown that shunt dysfunction is more common with Palmaz stents than Wallstents,[27] although it should be noted that our early (often Palmaz stented) patients were left longer than three months prior to initial angiographic assessment, therefore especially in this group it is difficult to be sure of the exact timing of shunt dysfunction. Accepting this limitation, if it is believed important to assess the TIPSS prior to a 20% risk of dysfunction, it is necessary to check the shunt at two months and then approximately six monthly thereafter. It would seem that early shunt dysfunction is more likely to be associated with variceal rebleeding than that occurring later after TIPSS, therefore even closer shunt assessment in the first few months after placement may be neccessary.

Although intervention maintained shunt patency in all but one patient when insufficiency was detected, most stents treated with balloon dilatation required repeat dilatation on follow up. This procedure would seem to have only a temporary effect and the longterm benefits of and exact indications for dilatation remain unclear. The current limitations of ultrasonographic methods of shunt assessment[28] mean that direct portography remains the 'gold standard' for surveillance. This is an important limitation of TIPSS but hopefully the development of new covered stents will tackle this problem.

An ability to identify early shunt dysfunction and minimise encephalopathy together with a low incidence of rebleeding makes TIPSS an alternative to sclerotherapy in the treatment of recurrent variceal bleeding. Trials are currently underway to compare these two treatments in this situation. In the case of gastric variceal haemorrhage where current endoscopic treatments are unsatisfactory, we believe TIPSS to be the treatment of choice, as indicated by the comparatively large proportion of patients in our series with gastric varices.

Nine (7·6%) patients developed non-variceal bleeding during follow up, mostly as a result of sclerotherapy ulcers and these were the cause of death in two patients. Sclerotherapy ulcers have been recognised as a major problem by many investigators and remain a major potential cause of morbidity and mortality no matter how effective the shunt is. The alternative of band ligation should reduce the frequency of this complication.[29]

New or worsening spontaneous encephalopathy was seen in 16·8% patients and a further 12·6% had new or worsening encephalopathy secondary to sepsis or bleeding after TIPSS. Considering however that 33·6% patients were encephalopathic prior to TIPSS, it is difficult to determine the exact role of the shunt in the development of encephalopathy in this group. In all but four patients (who went on to shunt reduction), the encephalopathy responded to simple medical treatment such as lactulose and protein restriction. This contrasts with the often debilitating encephalopathy seen in around one third of patients after non-selective surgical shunts[11] and is probably because of the small stent diameter and intrahepatic position that encourages continued portal flow into the liver.[30] A reduced incidence of encephalopathy has been reported in narrow portocaval H-grafts[31] and selective splenorenal shunts[32] however the associated risks of surgery and subsequent problems with transplantation must again be considered. Recent reports indicate that increasing age and a previous history of encephalopathy are the main predictors of encephalopathy after TIPSS[33] and perhaps these patients should have narrower stents placed.

Treatment of patients with refractory ascites remains a major clinical problem. Apart from liver transplantation, the main therapeutic options are repeated large volume paracentesis and peritoneovenous shunting, both of which are associated with significant morbidity and prolonged inpatient management and may aggravate functional renal failure. Recent reports[14 15] describe the benefits of TIPSS for refractory ascites although data are limited. The mechanism of action seems to be a combination of reduced portal pressure gradient and increased natriuresis, probably secondary to increased effective circulating plasma volume and neurohumeral factors. Survival is poor in patients with refractory ascites and any trial assessing TIPSS in this situation would need to assess quality of life and cost-benefit factors.

The place of TIPSS in the treatment of hepatorenal syndrome also remains controversial. Several authors have reported improvement in functional renal failure[15 34] and a preliminary study[35] showed a decrease after TIPSS in the levels of endothelin 1, which is thought to have an important role in the syndrome. However as we found in this study, results are generally disappointing in this group of patients and they have a very poor prognosis without liver transplantation.

Similar to other investigators,[36] we found a transient deterioration in liver function tests in a third of patients probably secondary to reduced hepatic perfusion. Three patients died soon after TIPSS with clinical features of acute liver failure, two of whom had evidence of raised intracranial pressure. This is unusual in patients with chronic liver disease but has been

reported.[37] All three of these patients were extremely ill at the time of TIPSS, however, with prolonged hypotension and requiring ventilation. The role of TIPSS in their clinical deterioration is therefore difficult to define, although any reduction in liver perfusion in such patients may be critical. Overall however there was a significant improvement in Childs-Pugh score at three to six months largely due to improvement in ascites.

Procedure related mortality was 1·5%, which is similar to most reported series and compares favourably with the operative mortality associated with surgical portosystemic shunts of around 10%.[38] We found a relatively high 30 day mortality of 21·8% compared with some groups,[22] however mortality has been consistently shown to depend on Childs grade at time of TIPSS and our higher percentage of Childs B and C patients (38·9% and 53·2% respectively) and higher numbers of emergency procedures (26·9%) would account for this. Our one and two year survival of 62·3% and 46·5% respectively are similar to the recently reported series from San Francisco.[21]

Longterm survival after TIPSS will depend on the underlying severity of liver disease and improved survival due to reduced rebleeding will be difficult to detect. However the benefits of reduced morbidity, as a result of improved control of ascites and less variceal rebleeding should not be underestimated. We have previously shown that besides severity of liver disease, hyponatraemia and encephalopathy prior to TIPSS independently determine long-term survival.[39] Thirteen of our patients subsequently underwent liver transplantation and the benefits of TIPSS as a 'bridge to transplantation' have been previously reported.[40] In particular the ability to avoid surgery in the treatment of variceal bleeding before transplant is important.

In conclusion, TIPSS is a comparatively simple procedure that can be successfully performed even on critically ill patients. It is effective in the treatment of both acute and recurrent variceal haemorrhage (especially where they are not amenable to sclerotherapy), refractory ascites, and portal hypertensive gastropathy. Unlike surgical portosystemic shunts, it has the advantage of not compromising subsequent liver transplantation. Shunt dysfunction however is common and seems to increase linearly with time and variceal rebleeding and reaccumulation of ascites usually occur in the presence of shunt stenosis or occlusion. Regular surveillance by portography is therefore necessary and this represents an important limitation of TIPSS. Post-procedure encephalopathy is significant but generally easily treated and bleeding from sclerotherapy ulcers remains an important cause of morbidity and mortality. Trials are currently underway to compare TIPSS with sclerotherapy or banding in the treatment of first variceal haemorrhage and with paracentesis for refractory ascites, which will help define its exact role in these situations.

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1 Richter GM, Noeldge G, Palmaz JC. The transjugular intrahepatic portosystemic stent-shunt (TIPSS): experience of results of a pilot study. *Cardiovasc Intervent Radiol* 1990; **13:** 200–7.
2 Cales P, Pascal JP, Histoire naturelle des varices oesophagiennes au cours de la cirrhose (de la naissance a la rupture). *Gastroenterol Clin Biol* 1988; **12:** 245–54.
3 Graham D, Smith J. The course of patients after variceal haemorrhage. *Gastroenterology* 1981; **80:** 800–9.
4 Panes J, Teres J, Bosch J. Efficacy of balloon tamponade in treatment of bleeding gastric and oesophageal varices. *Dig Dis Sci* 1988; **33:** 454–9.
5 Burroughs AK, McCormick PA, Hughes MD, Sprengers D, D'Heygere F, McIntyre R. Randomised double-blind controlled trial of somatostatin for variceal bleeding. Emergency control and prevention of early variceal rebleeding. *Gastroenterology* 1990; **99:** 1388–95.
6 Westaby D, Hayes PC, Gimson AES, Polson RJ, Williams R. Controlled trial of ejection sclerotherapy for active variceal bleeding. *Hepatology* 1989; **9:** 274–7.
7 Stiegman GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, *et al.* Endoscopic sclerotherapy as compared with band ligation for bleeding oesophageal varices. *N Engl J Med* 1992; **326:** 1527–32.
8 Burroughs AK, Hamilton G, Philips A, Mezzanotte G, McIntyre N, Hobbs KEF. A comparison of sclerotherapy with staple transection of the oesophagus for the emergency control of bleeding from oesophageal varices. *N Engl J Med* 1989; **321:** 857–62.
9 Editorial. Emergency portocaval shunts. (Anonymous). *Lancet* 1991; **337:** 952.
10 Cello J, Grendall J, Crass R, Weber T, Trunkey D. Endoscopic sclerotherapy versus portocaval shunt in patients with severe cirrhosis and acute variceal haemorrhage: long term follow up. *N Engl J Med* 1987; **316:** 11–5.
11 Franco D, Smadja C. Prevention of recurrent variceal bleeding: surgical procedures. In: Benhamou JP, Lebrec D, eds. *Clinics in gastroenterology: portal hypertension.* London: WB Saunders, 1985: 233–57.
12 LaBerge JM, Ring EJ, Gordon RL, Lake JR, Docherty MM, Somberg KA, *et al.* Creation of transjugular intrahepatic portosystemic shunts with Wallstent endoprosthesis: results in 100 patients. *Radiology* 1993; **187:** 413–20.
13 Moore K, Wilkinson S, Williams R. Ascites and renal dysfunction in liver disease. In: Millward-Sadler GH, Wright R, Arthur NJP, eds. *Wright's liver and biliary disease.* London: Saunders, 1992: 1346–71.
14 Quiroga J, Sangro B, Nunez M, *et al.* Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: Effect on clinical, renal, humeral and haemodynamic parameters. *Hepatology* 1995; **21:** 986–94.
15 Ochs A, Rossle M, Haag MD, *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. *N Engl J Med* 1995; **332:** 1192–7.
16 Jalan R, Redhead DN, Simpson KJ, Elton RA, Hayes PC. Transjugular intrahepatic portosystemic stent-shunt (TIPSS): long-term follow up. *Q J Med* 1994; **87:** 565–73.
17 Peltzer NY, Ring EJ, LaBerge JM, Haskal ZJ, Radosevich PM, Gordon RL. Treatment of Budd-Chiari syndrome with transjugular intrahepatic portosystemic shunt. *J Vasc Intervent Radiol* 1993; **4:** 263–7.
18 Strauss RM, Martin LG, Kaufman SL, Boyer TD. Transjugular intrahepatic portal systemic shunt for the management of symptomatic cirrhotic hydrothorax. *Am J Gastroenterol* 1994; **89:** 1520–2.
19 Richter GM, Noeledge G, Palmaz JC. The transjugular intrahepatic portosystemic stent-shunt (TIPSS): experience and results of a pilot study. *Cardiovasc Intervent Radiol* 1990; **13:** 200–7.
20 Chalmers N, Redhead DN, Simpson KJ, Hayes PC. Transjugular intrahepatic portosystemic stent shunt (TIPSS): Early clinical experience. *Clin Radiol* 1992; **46:** 166–9.
21 LaBerge JM, Somberg KA, Lake JR, *et al.* Two-year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: results in 90 patients. *Gastroenterology* 1995; **108:** 1143–51.
22 Rossle M, Haag K, Ochs A, *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N Engl J Med* 1994; **330:** 165–71.
23 Coldwell DM, Ring EJ, Rees CR, *et al.* Multicenter Investigation of the role of transjugular intrahepatic portosystemic shunt in management of portal hypertension. *Intervent Radiology* 1995; **196:** 335–40.
24 Franco D, Smadja C. Prevention of recurrent variceal bleeding: Surgical procedures. *Clin Gastroenterol* 1985; **12:** 233–57.
25 Matory WE Jr, Sedgwick CE, Rossi RL. Non-shunting procedures in management of bleeding oesophageal varices. *Surg Clin North Am* 1980; **60:** 281–95.
26 Grace ND. The side-to-side shunt revisisted. *N Engl J Med* 1994; **330:** 208–9.
27 Jalan R, Redhead DN, Ferguson J, Simpson KJ, Elton RA, Hayes PC. Wallstents or Palmaz stents for the transjugular intrahepatic portosystemic stent-shunt (TIPSS). *J Intervent Radiol* 1994; **9:** 147–52.
28 Jalan R, Ferguson J, Allan PL, Redhead DN, Hayes PC. The role of duplex and colour flow doppler utrasonography in the assessment of TIPSS shunt function. *Gut* 1995; **36** (suppl 1): A20.
29 Hou MC, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal

variceal hemorrhage: a prospective randomized trial. *Hepatology* 1995; **21:** 1517–22.
30 Lacy AM, Nevasa M, Gilabert R, *et al.* Long-term affects of distal splenorenal shunt on hepatic haemodynamics and liver function in patients with cirrhosis: importance of reversal of portal blood flow. *Hepatology* 1992; **15:** 616–22.
31 Johansen K. Prospective comparison of portal versus total portal decompression for bleeding oesophageal varices. *Surg Gynaecol obstet* 1992; **175:** 528–34.
32 Langer B, Taylor BR, Mackenzie DR, *et al.* Further report of a prospective randomised trial comparing distal splenorenal shunt with end-to-side portacaval shunt. *Gastroenterology* 1985; **88:** 424–9.
33 Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP, Leketic VA, Cheatham AK. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology* 1994; **20:** 46–55.
34 Lake JR, Ring EJ, LaBerge J, Gordon R, Roberts J, Ascher N. Transjugular intrahepatic portocaval stent shunts in patients with renal insufficiency. *Transplant Proc* 1993; **25:** 1766–7.
35 Martinet JP, Legault L, Cernacek P, *et al.* Effect of TIPSS on splanchnic and renal production of endothelins. *Hepatology* 1994; **20:** 113A.
36 Rossle M, Sellinger M, Ochs A, Haag K. Liver function and blood flow before and after TIPSS. *Hepatology* 1993; **18:** 285A.
37 Crippin JS, Gross JB, Lindor KD. Increased intracranial pressure and hepatic encephalopathy in chronic liver disease. *Am J Gastroenterol* 1992; **87:** 879–82.
38 Henderson JM, Millikan WJ, Warren WD. The distal splenorenal shunt: an update. *World J Surg* 1984; **8:** 722–32.
39 Jalan R, Elton R, Redhead DN, Finlayson NDC, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol* 1995; **23:** 123–8.
40 John TG, Jalan R, Redhead DN, Hayes PC, Sanfey HA, Garden OJ. Transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion as a preclude to orthotopic liver transplantation (OLT) in patients with severe portal hypertension. *Gut* 1994; **35** (suppl 5): S24.

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Review article: update on the role of transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of complications of portal hypertension

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SUMMARY

In the 8 years since its introduction into clinical practice, initial enthusiasm for the transjugular intrahepatic portosystemic stent-shunt (TIPSS) has been tempered by a more critical appraisal of its role in the management of portal hypertension. TIPSS has established its role as a rescue procedure for variceal haemorrhage uncontrolled by endoscopic means and as a treatment for ectopic or recurrent variceal bleeding. Randomized trials comparing TIPSS with endoscopic methods in the secondary prophylaxis of oesophageal variceal haemorrhage have shown reduced rebleeding after TIPSS but no effect on survival. Its exact role in this situation awaits further assessment, including quality of life and cost analyses, and consideration of the current limited availability of the technique.

Experience of TIPSS in patients with refractory ascites or hepatorenal syndrome has been disappointing. Little data currently exist, but results of further randomized studies comparing TIPSS with paracentesis for refractory ascites are awaited. Ideally these should be multicentre studies, and should include quality of life data for this poor prognostic group.

Development of shunt insufficiency remains a major problem and occurs in $\approx$ 50% patients at 1 year. The need for continued shunt surveillance by Doppler sonography and direct portography is the major limitation of TIPSS, but hopefully the development of covered stents will address this problem.

INTRODUCTION

Following the introduction of the transjugular intrahepatic portosystemic stent-shunt procedure (TIPSS) into clinical practice in 1989,[1] there have been numerous reports describing its use in the management of the complications of portal hypertension. Much of this literature involves assessment in small numbers of patients and therefore it has been difficult to determine the exact role of TIPSS. However, several recent randomized studies have compared TIPSS with established treatments for both variceal haemorrhage and refractory ascites. These provide valuable data with which to critically judge the role of TIPSS in these settings. In the light of these and other recently published studies, this review seeks to examine the current role of TIPSS in the management of portal hypertension and to assess its complications and limitations.

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TIPSS PROCEDURE

The techniques of TIPSS placement are generally based on the original method described by Richter *et al.*[1] Many centres use pre-procedural Doppler ultrasonography to exclude portal vein thrombosis (see below) and in some cases to localize the portal vein bifurcation.

Following midazolam and pethidine premedication, a sheath is introduced over a guidewire into the inferior vena cava via a right internal jugular approach. Using a stiff hydrophilic guidewire, the middle or right hepatic

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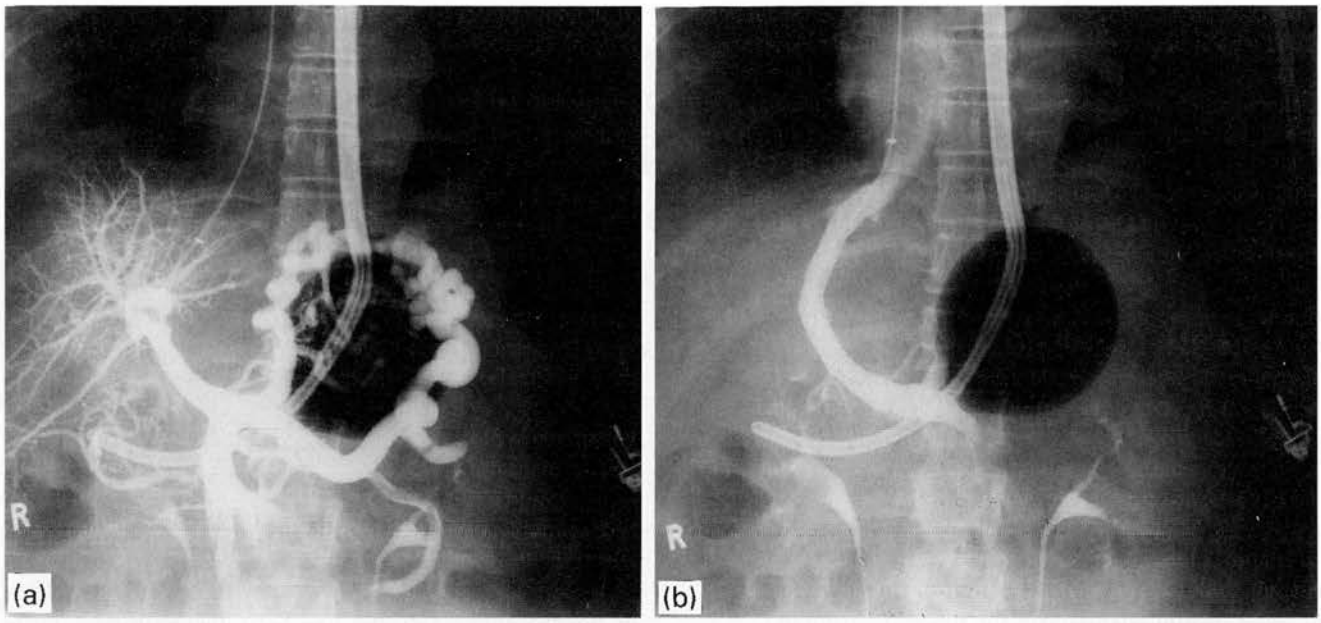

Figure 1. (a) Initial portogram prior to emergency TIPSS insertion showing oesophageal varices and Sengstaken balloon *in situ*. (b) Portogram of same patient just following TIPSS placement with shunting of portal blood through TIPSS and resolution of varices.

vein is selected under fluoroscopic guidance and the sheath is advanced into the selected vein. A transjugular needle is then passed down the sheath and used to direct the puncture of the portal vein. Following this, the guidewire is passed into the portal system and the whole sheath is then advanced and portal venography carried out (Figure 1A).

Following measurement of the portal pressure gradient (PPG, defined as the difference between portal venous pressure and inferior vena caval pressure), the track is dilated with an angioplasty balloon. A self-expanding metal stent (8–12 mm diameter) is then inserted into the parenchymal channel, portography is repeated and the final PPG measured (Figure 1B). The most commonly used stents are the Wallstents (Schneider, US Stent Division) or the Palmaz stents (Johnson & Johnson). The PPG should be reduced to below 12 mmHg,[2] although in the rare occurrence of a low initial PPG, the aim should be a reduction in baseline PPG by 20%.

When the procedure is being undertaken for uncontrolled variceal haemorrhage, varices can be embolized with steel coils or particulate matter and indeed this is routinely done in some centres. Some units also inject intravenous heparin at the time of stent insertion, but the benefits of these interventions are unclear.

As with any technique, TIPSS is operator-dependent and a learning curve exists, which is the main reason why TIPSS is likely to remain limited to specialist units. In experienced hands, the procedure can be completed successfully in 90% patients, usually within 2 h.

VARICEAL HAEMORRHAGE

The first reports of TIPSS were in the management of oesophageal variceal haemorrhage.[1, 3] The treatment of uncontrolled variceal haemorrhage or recurrent oesophageal variceal haemorrhage remain the main indications for TIPSS procedure (Table 1). TIPSS placement appears preferable to shunt surgery or oesophageal transection as a rescue procedure for uncontrolled variceal haemorrhage refractory to endoscopic therapy, in view of the less invasive technique and lower reported complications and mortality,[4] although no prospective randomized studies have been performed. Indeed, successful TIPSS placement leads to immediate haemostasis in up to 100% patients with uncontrolled variceal haemorrhage.[4–6]

Recurrent variceal haemorrhage despite adequate endoscopic therapy is also an accepted indication for TIPSS placement, especially for patients with Childs B or C disease in whom shunt surgery is poorly tolerated.[7] Several large cohort studies have reported variceal rebleeding rates of 13–18% during a follow-up period of

Table 1. Four major series reporting TIPSS insertion

	Rossle[7]	Coldwell[8]	La Berge[9]	Stanley[10]
Number of patients	100	96	90	130
Childs C patients (%)	22	35	47	53
Emergency procedure (%)	10	–	33	27
Mean follow-up (months)	12	> 6	14	11
Rebleeding (%)	18	15	18	13
Encephalopathy (%)	15	29	–	17
Shunt dysfunction (%)	33	33	29	45
Mortality–30 day(%)	3	14	16	22
Mortality–overall (%)	10	23	38	44

Table 2. Nine randomized trials comparing TIPSS with endoscopic methods to prevent oesophageal variceal rebleeding

	No. TIPSS/ sclero.	Follow-up (months)	Rebleeding (%)*	H. enceph. (%)*	Survival (%)*
Rossle *et al.*†[12]	26/28	8	8 vs. 26‡	19 vs. 4	92 vs. 96
Sanyal *et al.*[13]	40/39	–	22 vs. 15	22 vs. ?	73 vs. 90‡
G d'EAIH†[14]	32/33	12	41 vs. 61	–	50 vs. 48
Cello *et al.*[15]	21/19	12	0 vs. 37§	52 vs. 42	81 vs. 84 (30 day)
Jalan *et al.*¶[16]	31/27	16	10 vs. 50**	22 vs. 8	81 vs. 89 (30 day)
Riggio *et al.*[17]	38/43	19	21 vs. 51‡ (1 yr)	50 vs. 16§	83 vs. 85 (1 yr)
Sauer *et al.*†[18]	42/41	18	9 vs. 44‡ (1 yr)	29 vs. 10‡	77 vs. 85 (1 yr)
Garcia-Villarreal *et al.*[19]	18/19	15	11 vs. 47§	26 vs. 22	94 vs. 56§
Cabrera *et al.*[20]	31/32	15	23 vs. 52‡	33 vs. 13‡	80 vs. 84

* results expressed as TIPSS group vs. endoscopy group.
† used concomitant propranolol in sclerotherapy arm.
¶ used band ligation as endoscopic therapy.
‡ $P < 0.05$
§ $P < 0.01$
** $P < 0.001$

5–14 months after TIPSS placement for variceal haemorrhage[8–11] (Table 2).

However, it is only in the past 2–3 years that randomized trials comparing TIPSS procedure with endoscopic therapy for the secondary prophylaxis of oesophageal variceal haemorrhage (i.e. to reduce rebleeding) have been reported, eight in abstract form[12–19] and one as a full paper.[20] In these studies, patients were randomized to receive TIPSS or definitive endoscopic therapy a variable time (up to 1 week) following control of the initial bleed by endoscopic or pharmacological means. All except one study[16] (which used band ligation), used sclerotherapy as the endoscopic treatment and three studies[12, 14, 18] added propranolol to the endoscopic treatment arm. These studies are summarized in Table 2.

Seven of these studies found a significant reduction in rebleeding following TIPSS compared with endoscopic therapy, with the other two showing no difference between the groups. There were no differences in mortality in seven of the nine trials, with one finding an increased mortality in the TIPSS group[13] and another an increased mortality in the sclerotherapy group.[19] In some trials, patients who rebled in the endoscopy group were 'rescued' by TIPSS insertion, thereby reducing the chance of demonstrating a difference in survival. Encephalopathy occurred more often in the TIPSS group in most studies, but was generally easy to manage.

Shunt insufficiency and the subsequent need for surveillance of the stent remains a major limitation of TIPSS (see below) and must be taken into account when comparing TIPSS with other treatment modalities, although long-term surveillance is also necessary in endoscopic treatment. In addition, little information exists regarding the cost-effectiveness of the various treatments for variceal haemorrhage, although one abstract concluded that preventing variceal bleeding by TIPSS placement is about one-third more expensive than by endoscopic sclerotherapy.[21] Although TIPSS

Table 3. Indications for TIPSS

Definite indications:
Acute oesophageal variceal bleeding refractory to endoscopic therapy
Recurrent oesophageal variceal bleeding
Gastric or ectopic variceal haemorrhage
Bleeding from portal hypertensive gastropathy
Unproven indications:
Refractory ascites or hepatic hydrothorax
First oesophageal variceal haemorrhage
Budd–Chiari syndrome
Hepatorenal syndrome
Hepatopulmonary syndrome
Hypersplenism
Veno-occlusive disease

procedure appears promising in this situation, further information on its cost-effectiveness and advances in shunt patency and surveillance methods will help clarify its role in preventing oesophageal variceal rebleeding.

Gastric and ectopic varices

Endoscopic methods for treating bleeding gastric varices remain unsatisfactory. In view of the perceived benefits of TIPSS over shunt surgery, TIPSS placement has been advocated by some as the treatment of choice for gastric variceal haemorrhage.[22, 23] Although one study suggested TIPSS was less successful for gastric than oesophageal variceal haemorrhage,[24] other studies have confirmed its efficacy in this group of patients.[25, 26] However, no randomized trials have been carried out to compare TIPSS with surgery or endoscopic treatments such as bovine thrombin sclerotherapy in the management of gastric variceal haemorrhage; ideally these should be undertaken.

The situation is similar with regard to ectopic varices. TIPSS has been shown to be effective for the management of bleeding rectal, intestinal and stomal varices[27–30] and recurrent urinary conduit bleeding.[31]

REFRACTORY ASCITES

In most series, refractory ascites is the second most common indication for TIPSS placement after variceal haemorrhage. Over the past 3 years, numerous abstracts and eight published papers[32–39] have assessed the efficacy of TIPSS for refractory ascites. The findings are broadly similar and indicate that TIPSS improves renal function and urinary sodium excretion, and most patients have at least a partial improvement in their ascites, with reduced diuretic requirements. However, most studies report a high incidence of hepatic encephalopathy and high mortality, due largely to the advanced liver disease present in these patients. Several studies therefore recommended TIPSS for patients with refractory ascites and Childs grade B but not grade C disease. In view of their poor prognosis, patients with refractory ascites should also be considered for orthotopic liver transplantation.

Two studies,[40, 41] (one in abstract form[41]), have reported results of randomized trials comparing TIPSS with paracentesis. Lebrec *et al.*[40] found that TIPSS procedure was effective in the control of refractory ascites, but only in patients with Childs C disease. Survival was actually lower in patients treated with TIPSS, possibly due to a reduction in hepatic perfusion. They concluded that the improvement in ascites following TIPSS placement was due to neurohumeral factors controlling naturesis, which depended on hepatic sinusoidal pressure. Ochs *et al.*[41] found that TIPSS was more effective than paracentesis in the control of refractory ascites, with a reduction in the period of hospitalization. They found no difference in survival between the two groups.

In addition, one study, presented in abstract form, randomized patients with refractory ascites to receive either TIPSS or a peritoneovenous shunt.[42] The authors found that both treatments were equally effective in palliating ascites but no difference in survival was detected. Patients treated with peritoneovenous shunts had fewer days in intensive care.

Currently TIPSS procedure should not be considered a routine treatment for refractory ascites. In view of the high mortality in these patients, future studies assessing the role of TIPSS in this condition should measure quality of life and in-patient stay. These studies will probably

need to be multicentre and prospectively randomize patients to compare TIPSS placement with paracentesis or peritoneovenous shunt insertion for the management of refractory ascites.

HEPATORENAL SYNDROME

Patients with hepatorenal syndrome (HRS) have a poor prognosis without orthotopic liver transplantation. Several abstracts and case reports,[43–48] describing the use of TIPSS in a small number of patients with HRS, have suggested it may improve renal function, reduce the need for haemodialysis and prolong the waiting time to liver transplantation. However, mortality remained very high in this patient group due to their advanced liver disease, and the use of TIPSS can only provide at best a temporary reprieve.

OTHER INDICATIONS

Budd–Chiari syndrome can be treated by thrombolysis of the occluded vein, the creation of a surgical shunt, stent insertion in the hepatic vein or inferior vena cava, or by liver transplantation.[49] Recently, several reports have described successful treatment of Budd–Chiari syndrome by TIPSS placement.[50–52] These reports confirm that in this condition, TIPSS procedure reduces ascites, collateral blood flow and intestinal congestion. In addition, unlike shunt surgery, TIPSS is not compromised by an enlarged caudate lobe and is less invasive.

Although portal vein thrombosis was initially considered a relative contraindication to TIPSS insertion, two recent reports indicate that this procedure can be successfully undertaken in such patients.[53, 54] However, one of these reports included patients with non-cavernous portal vein thrombosis only and used concomitant local thrombolysis.[54] Data remains scarce on the use of TIPSS for this indication and the exact nature and site of the portal vein occlusion, together with local expertise, must be taken into account before considering it as a treatment for portal vein thrombosis.

In addition, TIPSS has been shown to be of benefit in the management of patients with bleeding secondary to portal hypertensive gastropathy.[55] TIPSS has also been used effectively in the management of cirrhotic hydrothorax,[56–58] hypersplenism[59] (see below), veno-occlusive disease[60] and the hepatopulmonary syndrome.[61]

The presence of TIPSS in patients who have had this procedure as treatment for their portal hypertension allows relatively easy access to the portal vein by transjugular puncture via the stent. Portal venous blood sampling and portal haemodynamic assessment can therefore be undertaken for research purposes, particularly at the time of portographic shunt surveillance.

'BRIDGE TO TRANSPLANTATION'

Insertion of TIPSS has been shown to have less associated morbidity and mortality than portocaval shunt surgery and has less potential to compromise subsequent orthotopic liver transplantation.[62] A number of studies have assessed the possible benefits of TIPSS insertion on subsequent transplantation.[63–65] Most authors agree that although prior TIPSS insertion for variceal bleeding or refractory ascites does not compromise surgery at the time of transplantation, elective TIPSS procedure prior to operation does not facilitate surgery and should not be undertaken unless indicated to treat a defined complication such as variceal haemorrhage.

CONTRAINDICATIONS TO TIPSS PROCEDURE

Absolute contraindications to TIPSS placement (Table 4) include severe right heart failure or pulmonary hypertension, since the procedure exacerbates these conditions and may lead to clinical decompensation (see below). Due to the reduction in sinusoidal perfusion following TIPSS placement, which may result in a temporary deterioration in liver function, TIPSS should not be used in patients with acute or severe progressive liver disease unless essential for the control of life-threatening variceal bleeding.[7] The procedure should also be avoided in the presence of polycystic liver disease due to the risks of severe haemorrhage. In addition, occlusion of the jugular or caval veins precludes stent placement.

Relative contraindications include active systemic or intrahepatic sepsis, severe hepatic encephalopathy not related to bleeding, portal vein thrombosis (see above) and hepatocellular carcinoma.

PROCEDURE-RELATED COMPLICATIONS AND MORTALITY

A 1–2% procedure-related mortality has been reported in the large TIPSS series.[8–11] This compares favourably with perioperative mortality for shunt surgery, especially when it is considered that many patients undergoing

Table 4. Contraindications to TIPSS

Absolute:
Severe right heart failure or pulmonary hypertension
Severe acute or progressive liver failure
Polycystic liver disease
Supra-hepatic inferior vena-caval or bilateral internal and external jugular venous occlusion
Relative:
Systemic or hepatic sepsis
Severe hepatic encephalopathy (not related to bleeding)
Portal vein thrombosis
Hepatocellular carcinoma

TIPSS as a rescue procedure for refractory variceal bleeding would not be fit for surgery.[5]

Most series report procedure-related complications of around 10%. These include intraperitoneal haemorrhage, hepatic arterial puncture, biliary leaks or haemorrhage, liver capsule haematoma, stent dislocation or migration into the splenic vein or pulmonary artery, portal vein dissection, portal vein or hepatic arterial thrombosis and endocarditis.[66–69] Due to the risks of hypoxaemia and dysrhythmias during the procedure, continuous oxygen saturation and ECG monitoring is essential during TIPSS placement. Many studies describe a transient worsening of liver function in approximately one-third of patients in the weeks following TIPSS procedure. This may further compromise liver function, as discussed above.

Several studies have assessed prognostic markers for TIPSS placement.[70–74] These have shown that poor outcome following the procedure has been can be predicted by a high Childs–Pugh and APACHE II score, raised serum creatinine and low serum sodium, prior encephalopathy, non-viral aetiology, advanced age and female gender.

HEPATIC ENCEPHALOPATHY

One of the major concerns that was anticipated about TIPSS placement is the increased risk of hepatic encephalopathy due to the portosystemic shunting of blood and reduced hepatic sinusoidal perfusion. New or worsening encephalopathy has been reported in 15–29% patients in the large TIPSS cohort studies[8–11] (Table 1). Unlike the chronic debilitating encephalopathy reported by the early shunt surgery series, post-TIPSS encephalopathy has been generally easily managed by medical measures such as protein restriction and lactulose. However, for the minority of patients who develop refractory encephalopathy, successful treatment by shunt reduction or occlusion has been reported.[75–77]

Studies that have prospectively assessed the development of encephalopathy following TIPSS placement have suggested that the incidence is highest in the first 3 months after shunt placement, thereafter improving, presumably due to gradual narrowing of the stent.[78, 79]

Using multivariate analysis, encephalopathy following TIPSS procedure has been shown to be predicted by its presence prior to the procedure, hypoalbuminaemia, non-alcohol aetiology of cirrhosis and female gender.[70, 80] A recent prospective study also identified advanced age and low post-procedural PPG as predictors of encephalopathy following TIPSS insertion.[78] Such patients must be carefully assessed prior to and following TIPSS procedure, and should perhaps have narrower stents placed and be given prophylactic lactulose and protein restriction.

It remains difficult to achieve the optimal balance between the reduction in portal pressure required to minimize the risk of variceal bleeding and that pressure required to maintain hepatic perfusion and lessen the risk of post-procedural encephalopathy.

SHUNT INSUFFICIENCY

The frequent occurrence of shunt insufficiency and therefore the need for repeated assessment of shunt patency during follow-up is probably the major limitation of TIPSS. The major cohort studies describe shunt insufficiency in 29–45% patients during follow-up, with the consequent risks of variceal rebleeding or ascites reaccumulation.[8–11] A prospective study assessing shunt patency during follow-up revealed a 1 year shunt insufficiency rate of 53%.[81] Patency can be maintained in the vast majority of patients by a combination of balloon angioplasty, shunt extension or parallel TIPSS

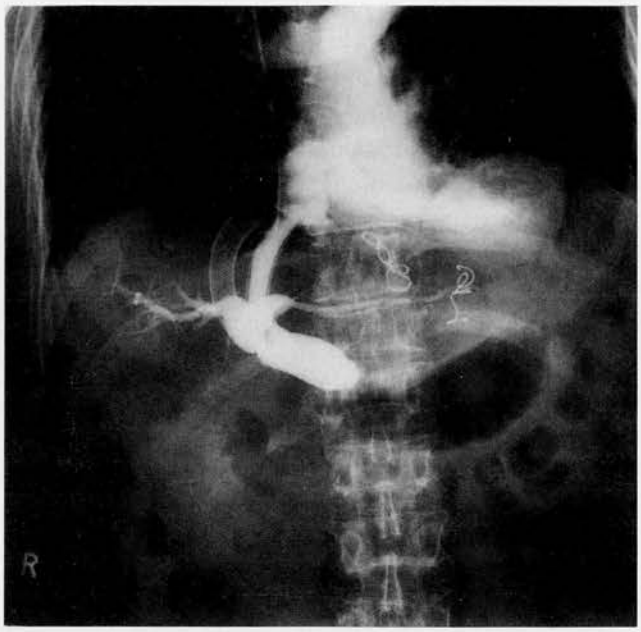

Figure 2. Portogram showing patent parallel TIPSS and initial blocked TIPSS lateral to it with metal coils used to embolize oesophago-gastric varices.

placement (Figure 2),[10] but the challenge is to detect the shunt insufficiency before clinical consequences occur.

It must be remembered that any report of shunt insufficiency following TIPSS procedure depends to a large extent on both the frequency and method of assessing shunt patency and the definition of 'shunt insufficiency' used. A variety of different definitions have been used in the literature, but the most clinically appropriate appears to be: any narrowing of the shunt leading to a rise in the PPG to 12 mmHg (above which the risk of variceal bleeding increases[2]) or a 20% rise in immediate post-TIPSS PPG (for those patients with a low initial portal pressure).

The pathogenesis of shunt dysfunction remains poorly understood. Early shunt occlusion is usually due to thrombosis within the stent, but longer-term shunt insufficiency is usually related to the development of pseudo-intimal hyperplasia causing stenosis within the stent or the hepatic vein.[82] It has been suggested that the creation of a transient biliary venous fistula by transection of a bile duct at the time of the TIPSS procedure may lead to shunt stenosis or occlusion due to the thrombogenic nature of bile.[83, 84]

There is debate as to whether duplex sonography is as effective as the 'gold standard' direct portography in the assessment of shunt patency following TIPSS procedure. Several studies have suggested that duplex sonography is highly sensitive and specific at detecting shunt stenosis, with maximum flow velocity within the shunt being the best parameter of shunt function.[85–89] However, other authors found poor detection of shunt insufficiency by ultrasonography as compared with portography and therefore suggest that intermittent direct portography is essential to assess shunt function during follow-up.[90–92] A recent report highlighted the possible benefits of magnetic resonance angiography in the assessment of TIPSS patency,[93] but currently this has limited availability.

A number of studies have suggested benefit from heparin or phenprocoumon in the reduction of early shunt occlusion following TIPSS placement.[94, 95] However, the best hope of reducing the need for continual shunt assessment is probably the development of covered stents, which have improved shunt patency in swine.[96] Until such stents are available, the cost, time and invasive nature of direct portography must be weighed against the possible deficiencies of ultrasonography in detecting shunt dysfunction.

HAEMODYNAMIC EFFECTS

Following TIPSS placement, there is an immediate worsening of the hyperdynamic cirrhotic circulation, with increased cardiac output and associated decreased systemic vascular resistance.[97, 98] How permanent these haemodynamic changes are remains unclear. Initially at least, this is thought to occur secondary to the increased venous return to the right heart, largely from the splanchnic circulation.

However, a recent study suggested that the major haemodynamic alteration after TIPSS placement is the development of pulmonary hypertension, since this correlated with the decreased porto-atrial gradient.[99] In this study, transient shunt occlusion also returned all haemodynamic parameters except pulmonary artery pressure to baseline. The authors postulated that both mechanical and neurohumeral factors were involved in these changes.

In addition to the volume load, the delivery of vasodilators from the splanchnic to the systemic circulation may precipitate the haemodynamic changes in the pulmonary, cardiac and systemic circulations. The clinical implication is that TIPSS should be used with caution in patients with known right heart failure or pulmonary hypertension (see above).

HAEMATOLOGICAL EFFECTS

Several case reports and two prospective studies[100, 101] have assessed the incidence of haemolysis following TIPSS placement. These indicated that up to 30% of patients develop haemolysis after stent insertion. This is usually mild and transient, but can cause clinically significant anaemia in 5–13% of cases. Post-TIPSS haemolysis appears similar to the traumatic haemolysis following prosthetic cardiac valve replacement or dacron aorto-femoral bypass grafts. In such cases, turbulent flow in contact with a foreign surface leads to shear, producing stress and fragmentation haemolysis.

Conn has alluded to the 'naked stent syndrome', in which naked steel wires of the TIPSS can protrude into the portal or hepatic veins leading to fragmentation haemolysis.[102] The transient nature of such haemolysis may be explained by the gradual covering of the stent by pseudointimal hyperplasia, protecting against further haemolysis.

There is some conflict in the literature about the effect of TIPSS on the peripheral platelet count, with the above two prospective studies reaching differing conclusions. Jalan *et al.*[101] found a significant increase in platelet count and reduction in spleen size 3 months after TIPSS placement, whilst Sanyal *et al.*[100] found no consistent improvement in platelet count during 1 year follow-up after TIPSS insertion. A recent retrospective report described an increase in the platelet count from 1 week to 1 year following TIPSS placement in 11 patients with hypersplenism.[103] A further study of 21 patients described a significant improvement in the platelet count within 1 week of TIPSS procedure in those patients with a post-procedural PPG 12 mmHg.[85]

More data are required on this subject, but thrombocytopenia caused by hypersplenism associated with portal hypertension remains an unproven indication for TIPSS placement. No authors have found a significant change in the white cell count following TIPSS procedure.

CONCLUSION

Following the initial enthusiasm with which the introduction of TIPSS procedure was met, there has been a more recent critical and hopefully evidence-based appraisal of its role. It has established its place in the treatment of uncontrolled variceal haemorrhage, recurrent variceal haemorrhage and gastric or ectopic variceal haemorrhage not responsive to endoscopic therapy. Although TIPSS appears promising for secondary prophylaxis following a first variceal haemorrhage, further data are required to assess its role in this situation and additional factors such as cost and availability must be considered.

There is currently no proven advantage for the use of TIPSS as compared with paracentesis for the management of refractory ascites, and TIPSS should not be used for this indication outwith clinical trials. Improved identification of patients at risk of post-procedural encephalopathy and haemodynamic complications will aid patient selection. Covered stents may improve shunt patency, which is currently the major limitation of the procedure.

REFERENCES

1 Richter GM, Noeldge G, Palmaz JC, Rossle M. The transjugular intrahepatic portosystemic stent-shunt (TIPSS): results of a pilot study. Cardiovasc Intervent Radiol 1990; 13: 200–7.
2 Groszmann RJ, Bosch J, Grace ND, *et al.* Haemodynamic events in a prospective randomised trial of propranolol vs. placebo in the prevention of a first variceal haemorrhage. Gastroenterology 1990; 99: 1401–7.
3 Richter GM, Noeldge G, Palmaz JC, *et al.* Transjugular intrahepatic portocaval stent-shunt: Preliminary clinical results. Radiology 1990; 174: 1027–30.
4 Jalan R, John TG, Redhead DN, *et al.* A comparative study of emergency transjugular intrahepatic portosystemic stent-shunt and esophageal transection in the management of uncontrolled variceal hemorrhage. Am J Gastroenterol 1995; 90: 1932–7.
5 Sanyal AJ, Freedman AM, Luketic VA, *et al.* Transjugular intrahepatic portosystemic shunts for patients with active variceal haemorrhage unresponsive to sclerotherapy. Gastroenterology 1996; 111: 138–46.
6 McCormick PA, Dick R, Panagou EB, *et al.* Emergency transjugular intrahepatic portasystemic stent-shunting as salvage treatment for uncontrolled variceal bleeding. Br J Surg 1994; 81: 1324–7.
7 Shiffman ML, Jeffers L, Hoofnagle JH, Tralka TS. The role of transjugular intrahepatic portosystemic shunt for treatment of portal hypertension and its complications: A conference sponsored by the National Digestive Diseases Advisory Board. Hepatology 1995; 22: 1591–7.
8 Rossle M, Haag K, Ochs A, *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. N Engl J Med 1994; 330: 165–71.
9 Coldwell DM, Ring EJ, Rees CR, *et al.* Multicenter investigation of the role of transjugular intrahepatic portosystemic shunt in management of portal hypertension. Radiology 1995; 196: 335–40.

10 La Berge JM, Somberg KA, Lake JR, *et al.* Two-year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: Results in 90 patients. Gastroenterology 1995; 108: 1143–51.
11 Stanley AJ, Jalan R, Forrest EH, Redhead DN, Hayes PC. Long term follow-up of Transjugular Intrahepatic Portosystemic Stent-shunt (TIPSS) for the treatment of portal hypertension: Results in 130 patients. Gut 1996; 39: 479–85.
12 Rossle M, Deibert P, Haag K, Ochs A, Siegerstetter V, Langer M. TIPS vs. sclerotherapy and B-blockade: Preliminary results of a randomised study in patients with variceal haemorrhage. Hepatology 1994; 20: 107A(Abstract).
13 Sanyal AJ, Freedman AM, Purdum PP, *et al.* Transjugular Intrahepatic Portosystemic Shunt (TIPS) vs. sclerotherapy for prevention of recurrent variceal haemorrhage: A randomised prospective trial. Gastroenterology 1994; 106: A975(Abstract).
14 Groupe d'Etude des Anastomoses Intra-Hepatiques (Toulouse, Bondy, Lille, Nice, Creteil, Paris) France. TIPS vs. sclerotherapy + propranolol in the prevention of variceal rebleeding: preliminary results of a multicenter randomised trial. Hepatology 1995; 22: 299A(Abstract).
15 Cello JP, Ring EJ, Olcott E, *et al.* Transjugular Intrahepatic Portosystemic Shunt (TIPS) vs. Sclerotherapy (ES) for variceal hemorrhage (VH). Gastroenterology 1995; 108: A1045(Abstract).
16 Jalan R, Forrest EH, Stanley AJ, *et al.* TIPSS vs. variceal band ligation for the prevention of variceal rebleeding in cirrhosis: a randomised, controlled study. Hepatology 1996; 24: A483(Abstract).
17 Riggio O, Merli M, Capocaccia L, *et al.* TIPS vs. endoscopic sclerotherapy (ES) for prevention of variceal rebleeding: a randomised controlled trial. J Hepatol 1996; 25: A65(Abstract).
18 Sauer P, Theilmann L, Benz C, *et al.* Transjugular intrahepatic portosystemic shunt (TIPS) vs. Sclerotherapy in the prevention of variceal rebleeding: A randomized study. Gastroenterology 1996; 110: A1113(Abstract).
19 Garcia-Villarreal L, Martinez-Lagares F, Sierra A, *et al.* TIPS vs. Sclerotherapy for the prevention of variceal rebleeding. Preliminary results of a randomised study. Hepatology 1996; 24: A326(Abstract).
20 Cabrera J, Maynar M, Granados R, *et al.* Transjugular Intrahepatic Portosystemic Shunt vs. Sclerotherapy in the elective treatment of variceal haemorrhage. Gastroenterology 1996; 110: 832–9.
21 Riggio O, Lionetti R, Rossi P, *et al.* TIPS vs. Sclerotherapy (ES) in the prevention of variceal rebleeding: a cost analysis. J Hepatol 1995; 1: A200(Abstract).
22 Kuradusenge P, Rousseau H, Vinel J, *et al.* Traitment des hemorragies par rupture de varices cardio-tuberositaires par anastomose porto-systemique intra-hepatique par voie transjugulaire. Gastroenterol Clin Biol 1993; 17: 431–4.
23 Binmoeller KF, Soehendra N. Nonsurgical treatment of variceal bleeding: New modalities. Am J Gastroenterol 1995; 90: 1923–30.
24 Spahr L, Dufresne MP, Bui BT, *et al.* Efficacy of TIPS in the prevention of rebleeding from esophageal and fundal varices: a comparative study. Hepatology 1995; 22: 296A(Abstract).
25 Patch D, Dick R, McCormick PA, Armonis A, Burroughs AK. Emergency TIPS for gastric fundal varices: Effective treatment? Gut 1996; 38(Suppl. 1): W22(Abstract).
26 Stanley AJ, Jalan R, Ireland HM, Redhead DN, Bouchier IAD, Hayes PC. A comparison between gastric and oesophageal variceal haemorrhage treated with Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS). Aliment Pharmacol Ther 1997; 11: 171–6.
27 Katz JA, Rubin RA, Cope C, Holland G, Brass CA. Recurrent bleeding from anorectal varices: Successful treatment with a transjugular intrahepatic portosystemic shunt. Am J Gastroenterol 1993; 88: 1104–7.
28 Haskal ZJ, Scott M, Rubin RA, Cope C. Intestinal varices: Treatment with the transjugular intrahepatic portosystemic shunt. Radiology 1994; 191: 183–7.
29 Fantin AC, Zala G, Risti B, Debatin JF, Schopke W, Meyenberger C. Bleeding anorectal varices: Successful treatment with transjugular intrahepatic portosystemic shunting (TIPS). Gut 1996; 38: 932–5.
30 Lagier E, Rousseau H, Maquin P, Olives JP, Le Tallec C, Vinel JP. Treatment of bleeding stomal varices using transjugular intrahepatic portosystemic shunt. J Ped Gastroenterol Nutrit 1994; 18: 501–3.
31 Zimmerman G, Smith DC, Taylor FC, Hadley HR. Recurrent urinary conduit bleeding in a patient with portal hypertension: Management with a transjugular intrahepatic portosystemic shunt. Urology 1994; 43: 748–51.
32 Ferral H, Bjarnason H, Wegryn SA, *et al.* Refractory ascites: Early experience in treatment with transjugular intrahepatic portosystemic shunt. Radiology 1993; 189: 795–801.
33 Ochs A, Rossle M, Haag K, *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. N Engl J Med 1995; 332: 1192–7.
34 Wong F, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: Effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. Ann Int Med 1995; 122: 816–22.
35 Somberg KA, Lake JR, Tomlanovich SJ, La Berge JM, Feldstein V, Bass NM. Transjugular Intrahepatic Portosystemic Shunts for refractory ascites: Assessment of clinical and hormonal response and renal function. Hepatology 1995; 21: 709–16.
36 Quiroga J, Sangro B, Nunez M, *et al.* Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: Effect on clinical, renal, humeral and hemodynamic parameters. Hepatology 1995; 21: 986–94.
37 Crenshaw WB, Gordon FD, McEniff NJ, *et al.* Severe ascites: Efficacy of the transjugular intrahepatic portosystemic shunt in treatment. Radiology 1996; 200: 185–92.
38 Villarreal LG, Urmeneta JMZ, Vila JQ, *et al.* Portosystemic intrahepatic prosthesis; PIP (TIPS) in the treatment of refractory ascites. A pilot study. Gastroenterol Hepatol 1993; 16: 18–22.
39 Forrest EH, Stanley AJ, Finlayson NDC, McGilchrist AJ, Hayes PC. Transjugular Intrahepatic Portosystemic Stent-Shunt

(TIPSS) as a treatment for refractory ascites. Aliment Pharmacol Ther 1996; 10: 801–6.
40 Lebrec D, Giuily N, Hadengue A, *et al.* Transjugular Intrahepatic Portosystemic Shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatol 1996; 25: 135–44.
41 Ochs A, Gerbes AL, Haag K, *et al.* TIPS and paracentesis for the treatment of refractory ascites (RA): Interim analysis of a randomized controlled trial. Hepatology 1995; 22: 297A(Abstract).
42 Zervos EE, Goode SE, Wright T, Rosemurgy AS. A prospective randomized trial comparing TIPS and peritoneovenous shunt in the treatment of intractable ascites. Gastroenterology 1996; 110: A1368(Abstract).
43 Brensing KA, Textor J, Raab P, *et al.* Sustained improvement of Hepatorenal syndrome after TIPS-insertion in patients with terminal liver cirrhosis not eligible for transplantation. Gastroenterology 1996; 110: A1158(Abstract).
44 Alam I, Bass NM, La Berge J, Ring EJ, Somberg KA. Treatment of hepatorenal syndrome with the transjugular intrahepatic portosystemic shunt (TIPS). Gastroenterology 1995; 108: A1024(Abstract).
45 Ochs A, Rossle M, Haag K, *et al.* TIPS for hepatorenal syndrome. Hepatology 1994; 20: 114A(Abstract).
46 Lake JR, Ring EJ, La Berge JM, Gordon RL, Roberts JP, Ascher NL. Transjugular intrahepatic portocaval stent-shunts in patients with renal insufficiency. Transplant Proc 1993; 25: 1766–7.
47 Spahr L, Fenyves D, N'guyen VV, Roy L, Legault L, Dufresne MP, Pomier Layrargues G. Improvement of hepatorenal syndrome by transjugular intrahepatic portosystemic shunt. Am J Gastroenterol 1995; 90: 1169–71.
48 Sturgis TM. Hepatorenal syndrome: Resolution after transjugular intrahepatic portosystemic shunt. J Clin Gastroenterol 1995; 20: 241–3.
49 Halff G, Todo S, Tzakis AG, Gordon RD, Starzl TE. Liver transplantation for the Budd–Chiari syndrome. Ann Surg 1990; 211: 43–9.
50 Ochs A, Sellinger M, Haag K, *et al.* Transjugular intrahepatic portosystemic stent-shunt (TIPS) in the treatment of Budd–Chiari syndrome. J Hepatol 1993; 18: 217–25.
51 Blum U, Rossle M, Haag K, *et al.* Technical, haemodynamic and clinical results of treatment with transjugular intrahepatic portosystemic shunt. Radiology 1995; 197: 815–11.
52 Rogopoulos A, Gavelli A, Sakai H, McNamara M, Huguet C. Transjugular intrahepatic portosystemic shunt for Budd–Chiari syndrome after failure of surgical shunting. Arch Surg 1995; 130: 227–8.
53 Radosevich PM, Ring EJ, La Berge J, *et al.* Transjugular Intrahepatic Portosystemic Shunts in patients with portal vein occlusion. Radiology 1993; 186: 523–7.
54 Blum U, Haag K, Rossle M, *et al.* Noncavernomatous portal vein thrombosis in hepatic cirrhosis: Treatment with transjugular intrahepatic portosystemic shunt and local thrombolysis. Radiology 1995; 195: 153–7.
55 Jalan R, Redhead DN, Simpson KJ, Elton RA, Hayes PC. Transjugular intrahepatic portosystemic stent-shunt (TIPSS): longterm follow-up. Q J Med 1994; 87: 565–73.
56 Haskal ZJ, Zuckerman J. Resolution of hepatic hydrothorax after transjugular intrahepatic portosystemic shunt (TIPS) placement. Chest 1994; 106: 1293–5.
57 Strauss RM, Martin LG, Kaufman SL, Boyer TD. Transjugular intrahepatic portosystemic shunt for the management of symptomatic cirrhotic hydrothorax. Am J Gastroenterol 1994; 89: 1520–2.
58 Andrade RJ, Martin Palanca A, Fraile JM, *et al.* Transjugular intrahepatic portosystemic shunt for the management of hepatic hydrothorax in the absence of ascites. J Clin Gastroenterol 1996; 22: 305–7.
59 Alvarez OA, Lopera GA, Patel V, Encarnacion CE, Palmaz JC, Lee M. Improvement of thrombocytopenia due to hypersplenism after transjugular intrahepatic portosystemic shunt placement in cirrhotic patients. Am J Gastroenterol 1996; 91: 134–7.
60 Michielsen PP, Pelkmans PA, D'Archambeau OC, *et al.* Transjugular intrahepatic portosystemic shunt improves liver function in veno-occlusive disease (3). J Hepatol 1994; 21: 685–6.
61 Allgaier HP, Haag K, Ochs A, *et al.* Hepatopulmonary syndrome: Successful treatment by transjugular intrahepatic portosystemic stent-shunt (TIPS). J Hepatol 1995; 23: 102.
62 Menegaux F, Keeffe EB, Baker E, *et al.* Comparison of after transjugular intrahepatic portosystemic shunts on the outcome of liver transplantation. Arch Surg 1994; 129: 1018–24.
63 Aboulijoud MS, Levy MF, Rees CR, *et al.* A comparison of treatment with transjugular intrahepatic portosystemic shunt or distal splenorenal shunt in the management of variceal bleeding prior to liver transplantation. Transplantation 1995; 59: 226–9.
64 Lerut JP, Laterre PF, Goffette P, *et al.* Transjugular intrahepatic portosystemic shunt and liver transplantation.Transpl Inter 1996; 9: 370–5.
65 John TG, Jalan R, Stanley AJ, Redhead DN, Hayes PC, Sanfey HA, Garden OJ. Insertion as a prelude to orthotopic liver transplantation in patients with severe portal hypertension. Eur J Gastroenterol Hepatol 1996; 8: 1145–9.
66 Roessle M, Noeldge G, Haag K, *et al.* Transjugular intrahepatic portosystemic stent-shunt (TIPS): technical and early clinical complications. Hepatology 1992; 6: 246A(Abstract).
67 Cohen GS, Ball DS. Delayed wallstent migration after a transjugular intrahepatic portosystemic shunt procedure: relocation with a loop snare. J Vasc Intervent Radiol 1993; 4: 559–60.
68 Pattynama PMT, Van Hoek B, Kool LJS. Inadvertent arteriovenous stenting during transjugular intrahepatic portosystemic shunt procedure and the importance of hepatic artery perfusion. Cardiovasc Intervent Radiol 1995; 18: 186–8.
69 Finkielman JD, Gimenez M, Pietangelo C, Blanco MV. Endocarditis as a complication of a transjugular intrahepatic portosystemic stent-shunt. Clin Infect Dis 1996; 22: 385–6.
70 Jalan R, Elton RA, Redhead DN, Finlayson NDC, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy fol-

lowing the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol 1995; 23: 123–8.
71 Encarnacion CE, Palmaz JC, Rivera FJ, *et al.* Transjugular intrahepatic portosystemic shunt placement for variceal bleeding: predictors of mortality. J Vasc Intervent Radiol 1995; 6: 687–94.
72 Somberg KA, Hahn J, Bacchetti P, Docherty C, La Berge JM, Ring EJ. Predictors of survival after transjugular intrahepatic portosystemic shunts (TIPS). Gastroenterology 1995; 108: A1175(Abstract).
73 Haskal ZJ, Yin D. Computerized models for predicting patient survival after transjugular intrahepatic portosystemic shunts. Gastoenterology 1996; 110: A1205(Abstract).
74 Malinchoc M, Kamath PS, Peine CJ, Rank J, Gordon FD. A revised model for predicting survival in patients undergoing elective transjugular intrahepatic portosystemic shunts (TIPS). Gastroenterology 1996; 110: A1255(Abstract).
75 Hauenstein KH, Haag K, Ochs A, Langer M, Rossle M. The reducing stent: Treatment for transjugular intrahepatic portosystemic shunt-induced refractory hepatic encephalopathy and liver failure. Radiology 1995; 194: 175–9.
76 Haskal ZJ, Cope C, Soulen MC, Shlansky-Golberg RD, Baum RA, Redd DC. Intentional reversible thrombosis of transjugular intrahepatic portosystemic shunts. Radiology 1995; 195: 485–8.
77 Rose SE, Katz MD. Intentional occlusion of a transjugular intrahepatic portosystemic shunt. Cardiovasc Intervent Radiol 1995; 18: 109–11.
78 Riggio O, Merli M, Pedretti G, *et al.* Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Incidence and risk factors. Dig Dis Sci 1996; 41: 578–84.
79 Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP, III, Luketic VA, Cheatham AK. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: Results of a prospective controlled study. Hepatology 1994; 20: 46–55.
80 Somberg KA, Riegler JL, La Berge JM, *et al.* Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: incidence and risk factors. Am J Gastroenterol 1995; 90: 549–55.
81 Lind CD, Malisch TW, Chong WK, *et al.* Incidence of shunt occlusion or stenosis following transjugular intrahepatic portosystemic shunt placement. Gastroenterology 1994; 106: 1277–83.
82 La Berge JM, Ferrell LD, Ring EJ, Gordon RL. Histopathological study of stenotic and occluded transjugular intrahepatic portosystemic shunts. J Vasc Intervent Radiol 1993; 4: 779–86.
83 Haskal ZJ, Pentecost MJ, Soulen MC, Schlansky Goldberg RD, Baum RA, Cope C. Transjugular intrahepatic portosystemic shunt stenosis and revision: Early and midterm results. Am J Roenterol 1994; 163: 439–44.
84 Jalan R, Harrison DJ, Redhead DN, Hayes PC. Transjugular intrahepatic portosystemic stent-shunt (TIPSS) and the role of biliary venous fistulae. J Hepatol 1996; 24: 169–76.
85 Lawrence SR, Lezotte DC, Durham JD, Kumpe DA, Everson GT, Bilir BM. Course of thrombocytopenia of chronic liver disease after transjugular intrahepatic portosystemic shunts (TIPS): A retrospective analysis. Dig Dis Sci 1995; 40: 1575–80.
86 Foshager MC, Ferral H, Nazarian GK, Castaneda Zuniga WR, Letourneau JG. Duplex sonography after transjugular intrahepatic portosystemic shunts (TIPS): Normal hemodynamic findings and efficacy in predicting shunt patency and stenosis. Am J Roenterol 1995; 165: 1–7.
87 Chong WK, Malisch TA, Mazer MJ, Lind CD, Worrell JA, Richards WO. Transjugular intrahepatic portosystemic shunt: US assessment with maximal flow velocity. Radiology 1993; 189: 789–93.
88 Ferral H, Foshager MC, Bjarnson H, *et al.* Early sonographic evaluation of the transjugular intrahepatic portosystemic shunt (TIPS). Cardiovasc Intervent Radiol 1993; 16: 275–9.
89 Dodd GD, III, Zajko AB, Orons PD, Martin MS, Eichner LS, Santaguida LA. Detection of transjugular intrahepatic portosystemic shunt dysfunction: Value of duplex Doppler sonography. Am J Roenterol 1995; 164: 1119–24.
90 Hausegger KA, Sternthal HM, Klein GE, Karaic R, Stauber R, Zenker G. Transjugular intrahepatic portosystemic shunt: Angiographic follow-up and secondary intervention. Radiology 1994; 191: 177–81.
91 Ferguson J, Jalan R, Redhead DN, Hayes PC, Allan PL. The role of duplex and colour Doppler ultrasound in the follow-up evaluation of transjugular intrahepatic portosystemic stent-shunt. Brit J Radiol 1995; 68: 587–9.
92 Bartolone CJ, Owens C, Warner D, *et al.* Assessment of patency in transjugular intrahepatic portosystemic shunts (TIPS): a prospective double-blind study comparing ultrasound (US) assessment with direct portal venography. Gastroenterology 1996; 110: A1147(Abstract).
93 Eustace S, Buff B, Kruskal J, *et al.* Magnetic resonance angiography in transjugular intrahepatic portosystemic stenting: Comparison with contrast hepatic and portal venography. Eur J Radiol 1994; 19: 43–9.
94 Krause T, Siegerstetter V, Haag K, Hauenstein KH, Rossle M. Evaluation of thrombogenicity of metallic stents in patients with TIPS using technel abelled platelets. Eur J Nucl Med 1994; 21: 741A.
95 Sauer P, Theilmann L, Richter G, Roeren T, Stremmel W, Steihl A. Phenprocoumon for prevention of early shunt occlusion after transjugular intrahepatic portosystemic stent-shunt (TIPS): results of a randomized trial. Gastroenterology 1995; 108: A1164(Abstract).
96 Nishimine K, Saxon RR, Kichikawa K, *et al.* Improved transjugular intrahepatic portosystemic shunt patency with PTFE-covered stent grafts: Experimental results in swine. Radiology 1995; 196: 341–7.
97 Azoulay D, Castaing D, Dennison A, Martino W, Eyraud D, Bismuth H. Transjugular intrahepatic portosystemic shunt worsens the hyperdynamic circulatory state of the cirrhotic patient: Preliminary report of a prospective study. Hepatology 1994; 19: 129–32.
98 Colombato LA, Martinet JP, Dufresne MP, Lafortune M, Pomier G. Acute hemodynamic effect of TIPS in cirrhotic patients. Hepatology 1994; 19: 531A(Abstract).

99 Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Deviere J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: Effects on right ventricular function. Hepatology 1996; 23: 1003–11.
100 Sanyal AJ, Freedman AM, Purdum PP, Mitchell L, Shiffman ML, Luketic VA. The hematologic consequences of transjugular intrahepatic portosystemic shunts. Hepatology 1996; 23: 32–9.
101 Jalan R, Redhead DN, Allan PL, Hayes PC. Prospective evaluation of haematological alterations following the transjugular intrahepatic portosystemic shunt (TIPSS). Eur J Gastroenterol Hepatol 1996; 8: 381–5.
102 Conn HO. Hemolysis after transjugular intrahepatic portosystemic shunting: The naked stent syndrome. Hepatology 1996; 23: 177–81.
103 Alvarez OA, Lopera GA, Patel V, Enarnacion CE, Palmaz JC, Lee M. Improvement of thrombocytopenia due to hypersplenism after transjugular intrahepatic portosystemic shunt placement in cirrhotic patients. Am J Gastroenterol 1996; 91: 134–7.

Seminar

Portal hypertension and variceal haemorrhage

Adrian J Stanley, Peter C Hayes

Portal hypertension commonly complicates cirrhosis, and variceal haemorrhage is its worst and most life-threatening complication. The introduction of new pharmacological agents, endoscopic variceal band ligation, and transjugular intrahepatic portosystemic stent-shunt (TIPSS) has increased the therapeutic options available for this disorder. However, despite these advances, mortality remains high.

Pathophysiology of portal hypertension

Increased resistance to portal blood flow is the initiating factor in the development of portal hypertension. In western countries, the most common cause is cirrhosis, in which the main resistance to flow occurs in the hepatic sinusoids. Alternatively, resistance to flow in the portal or splenic veins leads to prehepatic portal hypertension and in the hepatic veins leads to posthepatic portal hypertension.

Collateral vessels open and partially decompress the portal system. Collateral vessels arise most commonly in the retroperitoneal area, but are most visible and troublesome when they occur at the gastro-oesophageal junction. Collateral vessels also arise at the perianal, periumbilical, splenorenal, ovarian, and choledochal regions; in the peritoneum; and at areas of surgical anastamoses or ileostomy or colostomy sites. However, despite formation of these collaterals, portal hypertension is maintained by increased splanchnic arterial flow, leading to increased portal blood flow (figure 1).

Stellate cells (analogous to tissue pericytes) are found in the perisinusoidal space. After liver injury, these cells are transformed into contractile myofibroblasts that are central to the start of fibrogenesis.[1] They also regulate sinusoidal resistance and flow in response to vasoactive substances, especially endothelin and nitric oxide.[2] Therefore, at least part of the resistance to portal venous flow is dynamic.

This resistance to portal flow is the "backward" component of portal hypertension. The "forward" component is the increased splanchnic inflow, secondary to peripheral vasodilatation. This low systemic vascular resistance and the associated raised cardiac output lead to the characteristic hyperdynamic circulation of cirrhosis. Studies have suggested that the main site of low systemic vascular resistance is the splanchnic circulation.[3]

Much work has gone into defining the part played by nitric oxide in the circulatory abnormalities of cirrhosis. Vasodilatation is proposed to result from increased concentrations of nitric oxide, secondary to raised concentrations of endotoxins and cytokines in cirrhosis, although evidence suggests that increases in both the constitutive and inducible isoforms of nitric-oxide synthase are involved. Yet this mechanism remains unproven and studies have reported variable circulatory effects after administration of nitric-oxide-synthetase inhibitors to patients with cirrhosis.[4]

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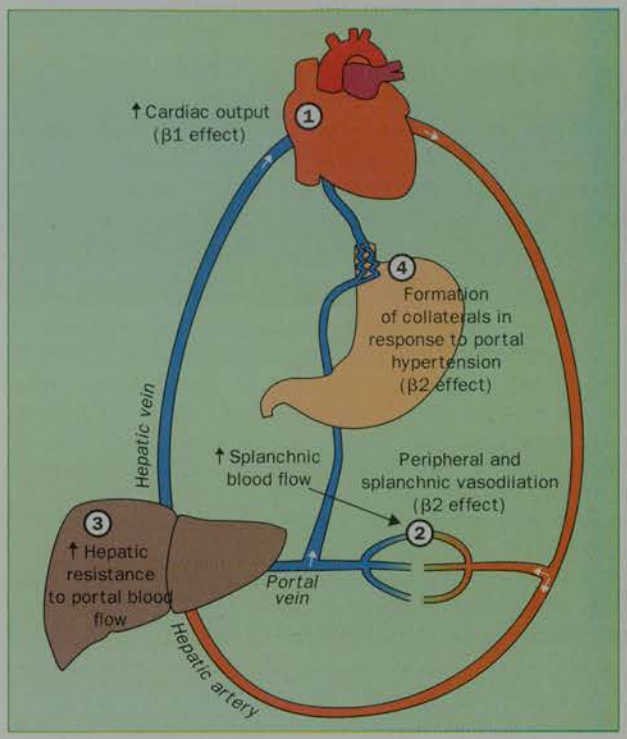

Figure 1: **Haemodynamic changes in portal hypertension and possible targets for therapeutic intervention**
1) reduction of cardiac output by β-1 blockade; 2) reduction of splanchnic blood flow by β-2 blockade or vasoconstrictors such as α-adrenergic agonists or vasopressin analogues; 3) reduction of intrahepatic resistance by vasodilators; 4) reduction of variceal or collateral flow by β-2 blockade, balloon tamponade, or endoscopic therapy.

The vasodilated circulation of cirrhosis is probably due to a disturbed balance between vasodilatory (eg, nitric oxide, glucagon, atrial natriuretic peptide, substance P, vasoactive intestinal peptide, bile acids) and vasoconstrictive substances (eg, endothelin, the renin-angiotensin-aldosterone and sympathetic nervous systems, antidiuretic hormone). The contributions of the parenchymal liver disease itself and the intrahepatic, portosystemic, and intrapulmonary shunts to alterations in this balance remain unclear.

Risk of bleeding

Portal pressure in individuals is dynamic, with circadian change. The highest pressures occur during the night, and increase postprandially and in response to coughing, sneezing, and exercise.[5] Such variations may combine with local factors in vessel walls to contribute to a pressure surge that can lead to a variceal bleed. However, the exact mechanisms that bring about variceal bleeding are unclear.

The risk of a variceal haemorrhage increases with the severity of liver disease, variceal size, and the presence of red markings on the varices.[6] Bleeding has been identified as unlikely with differences in pressure of less than 12 mm Hg between the portal vein and inferior vena cava.[7] The risk of bleeding is also low if a reduction in pressure of 20% or more is achieved.[8]

Acute variceal haemorrhage

About a third of patients with varices will bleed. Mortality from a first bleed is around 50% and most survivors will have a rebleed, with an associated inpatient mortality of 30%.[9] Most bleeding related to portal hypertension occurs from oesophageal varices, but bleeding can also arise from gastric or ectopic varices, or from portal hypertensive gastropathy or enteropathy. A suggested algorithm for the management of suspected variceal haemorrhage is shown in figure 2.

Initial resuscitation

Early and adequate initial resuscitation is vital. Endotracheal intubation with or without ventilation is commonly required to provide airway protection and avoid aspiration, especially in patients with a major bleed or substantial encephalopathy. Restoration of the circulating blood volume with colloid followed by crossmatched whole blood should be guided in most cases by regular monitoring of central venous pressure and urine volume.

Although prompt fluid replacement is essential to protect renal perfusion, overfilling may increase portal pressure, leading to variceal rebleeding. Right-atrial pressure should be kept between 0 and 5 mm Hg. Right-heart catheterisation is an option in patients with ascites or pre-existing cardiopulmonary disease, or haemodynamic instability. Coagulopathy in these patients should be treated with fresh-frozen plasma and platelet infusions, although evidence that this treatment is beneficial is scarce.

Although a 90% success in stopping variceal bleeding with balloon tamponade and endoscopic and pharmacological treatment has been reported, up to 70% of episodes of variceal haemorrhage stop spontaneously.[10]

Endoscopic management

Endoscopy allows accurate identification of the source of bleeding and direct therapeutic intervention. For many years, endoscopic sclerotherapy with sodium tetradecyl sulphate, polidocanol, or ethanolamine has been the therapy of choice to control bleeding from oesophageal varices and for their eradication. However, five randomised studies and a meta-analysis have shown that band ligation reduces complications, speed of variceal eradication, rebleeding rates, and bleeding-related mortality compared with sclerotherapy.[11] Band ligation did have complications related to the overtube, required for repeated banding, but the development of devices with multiple bands has removed the need for the overtube.

Therefore, band ligation should now be the endoscopic treatment of choice for oesophageal varices. However, with active bleeding, injection sclerotherapy may achieve initial haemostasis more easily before band ligation at subsequent endoscopies is undertaken.[12]

Pharmacological management

Although drugs have been used in the management of variceal bleeding for nearly half a century, new interest has arisen after reports and meta-analyses that show similar efficacy to sclerotherapy with somatostatin or its synthetic analogue octreotide acetate in the control of acute variceal haemorrhage.[13] One report showed a reduction in early rebleeding among patients treated with band ligation plus a 5-day infusion of octreotide acetate compared with banding alone.[14] The dose and the length of therapy vary widely in studies and further trials are required to identify the optimum treatment regimen.

Terlipressin, a synthetic analogue of vasopressin with a longer biological half-life, allows bolus administration every

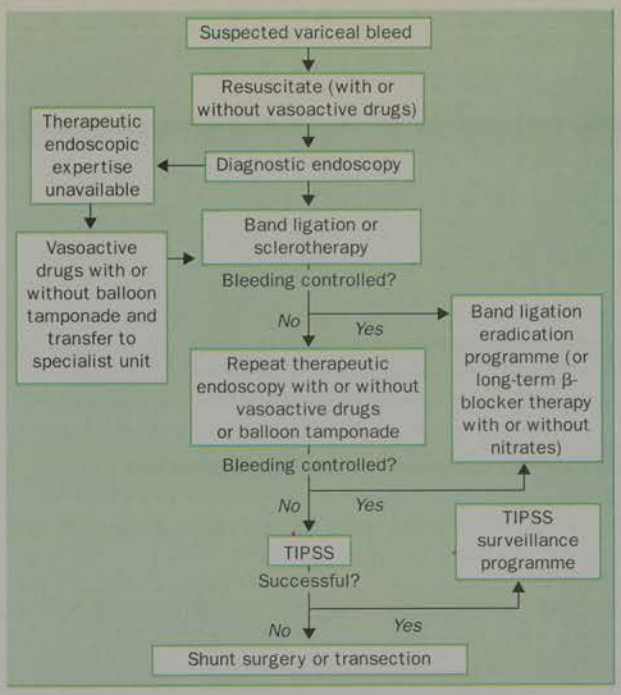

Figure 2: **Suggested algorithm for management of variceal haemorrhage**
Vasoactive drugs: octreotide or somatostatin, or terlipressin.

4 h. It has fewer systemic side-effects than vasopressin, but concomitant administration of nitrates to reduce ischaemic side-effects is still recommended. Terlipressin is as effective as somatostatin, octreotide acetate, or balloon tamponade in controlling variceal haemorrhage and is the only drug shown to lower mortality from variceal bleeding.[15] Benefits are seen with early therapy, with improved bleeding control and survival in cirrhotic patients with gastrointestinal bleeding given terlipressin and nitroglycerine as emergency treatment in the home before transfer to hospital.[16]

Although pharmacological agents are useful alternatives when early endoscopy is unavailable, any beneficial effects are temporary. Therefore, endoscopy should be arranged as soon as possible to confirm the source of bleeding and for endoscopic therapy if required. When substantial bleeding obscures the view of the endoscopist, administration of octreotide, somatostatin, or terlipressin with nitrates may help to achieve haemostasis before repeat endoscopy.

Balloon tamponade

Balloon tamponade with a Minnesota or Sengstaken-Blackmore tube can be lifesaving in the presence of substantial bleeding when carried out by experienced staff. However, placement by inexperienced staff is associated with a death rate of 6–20%, due largely to oesophageal perforation and pulmonary aspiration.

The tube should be passed orally, well into the stomach before inflation of the gastric balloon with about 300 mL air. Firm traction maintains the position of the gastric balloon under tension at the oesophagogastric junction. The oesophageal balloon is only inflated if bleeding continues and should be deflated for 30 min every 4–6 h and not used for more than 12 h. After this time, the risk of complications from the gastric balloon also increases. Because 50% of patients will rebleed when the tube is deflated, immediate definitive endoscopic therapy must be undertaken.[17]

Study	Number of patients receiving TIPSS/sclerotherapy	Follow-up (months)	Rebleeding (%)		Encephalopathy (%)		Survival (%)	
			TIPSS	Endoscopy	TIPSS	Endoscopy	TIPSS	Endoscopy
Cabarera et al	31/32	15	23	52‡	33	13‡	80	84
Sanyal et al	41/39	33	22	21	29	13‡	71	82‡
Cello et al	24/25	19	12	48‡	58	44	79	84 (30 day)
Rossle et al*	61/65	14	15	41‡	36	18‡	90	89 (1 year)
Sauer et al*	42/41	18	9	44 (1 year)‡	29	10‡	77	85 (1 year)
G d'ElAH*	32/33	12	41	61	..	..	50	48
Sauer et al†	17/17	7	18	54 (1 year)‡	25	12	89	91 (1 year)
Jolan et al†	31/27	16	10	50§	22	8	81	89 (30 day)
Riggio et al	38/43	19	21	51 (1 year)‡	50	16‖	83	85 (1 year)
Garcia-Villarreal et al	18/19	15	11	47‖	26	22	94	56‖

*Used concomitant propanolol in sclerotherapy group. †Used band ligation as endoscopic therapy. ‡p<0·05. §p<0·001. ‖p<0·01.

Summary of trials comparing TIPSS with endoscopic therapy for prevention of variceal bleeding

TIPSS

TIPSS is a new radiological intervention that creates a portosystemic tract through the liver parenchyma, through which an 8–12 mm expandable metal stent is inserted. In the 8 years since its introduction into clinical practice, TIPSS has become the treatment of choice as rescue therapy for the 10–20% of patients with variceal haemorrhage unresponsive to endoscopic management. Failure of emergency endoscopic therapy has been defined as further variceal bleeding after two endoscopic treatments during a single hospital admission for an acute bleeding episode.[18] Treatment with balloon tamponade should be followed by TIPSS or, less commonly, surgery in this situation.

Although few trials have been done, TIPSS is easier to carry out than surgical shunt procedures or oesophageal transection, has lower associated morbidity and mortality, and does not compromise subsequent liver transplantation. A study suggested benefits from small-diameter H-graft portacaval shunts compared with TIPSS for refractory variceal bleeding,[19] but TIPSS can be used for patients who are too ill for major surgery.

The main limitations of TIPSS are the development of encephalopathy in about 20% of patients and progressive development of shunt insufficiency.[20] Encephalopathy is generally easy to manage with lactulose and protein restriction, although some patients require a reduction in the size of the shunt. Shunt insufficiency is more difficult to manage and requires regular, long-term Doppler and portographic surveillance and treatment.

Surgery

TIPSS has in many cases replaced surgery for variceal haemorrhage unresponsive to endoscopic treatment. However, technical failure occurs in 5–10% of cases. In these patients, the options are shunt surgery or oesophageal transection with or without devascularisation, but the mortality rate is high, particularly among patients with decompensated liver disease.

Gastric or ectopic varices and portal hypertensive gastropathy

Gastric varices are the source of bleeding in 10–36% of patients with variceal haemorrhage. Higher rates are reported for patients with "sinistral" or left-sided portal hypertension due to portal-vein or splenic-vein thrombosis. Unless the gastric varices are located in a hiatus hernia or on the proximal lesser curve in continuation with oesophageal varices, endoscopic bleeding control is generally unhelpful. For this reason, and because of the difficulty in obtaining adequate endoscopic vision, early TIPSS or shunt surgery have been advocated for gastric variceal bleeding.

The management of gastric variceal haemorrhage with endoscopic injection of thrombin or tissue adhesives needs further study.[21] Ideally, randomised trials should compare endoscopic methods, TIPSS, and surgery. In the meantime, control of any active bleeding with pharmacological agents or endoscopy, if possible, seems valid before proceeding to TIPSS. For similar reasons, the 3% of patients who have troublesome bleeding from ectopic varices are probably best managed by TIPSS.

Bleeding from portal hypertensive gastropathy or enteropathy accounts for 5–8% of bleeding episodes in cirrhosis. Although major bleeding from these sources is uncommon, when it occurs, its diffuse nature precludes the use of endoscopic therapy and the treatment options are pharmacological therapy, TIPSS, or surgery, dependent on the severity of bleeding, the degree of liver impairment, and likely compliance with drug therapy.

Prevention of rebleeding

After an initial variceal bleed, most patients will rebleed, commonly within the first few weeks. To reduce this risk, further treatment, such as endoscopic variceal eradication, pharmacological therapy, or portosystemic shunt creation, is necessary.

Endoscopy

After a variceal haemorrhage, most units enrol patients into an endoscopic sclerotherapy or band ligation programme to eradicate the varices. A meta-analysis of eight trials comparing sclerotherapy with non-active treatment in the prevention of variceal rebleeding showed reductions in rebleeding and mortality in the sclerotherapy group.[13] However, band ligation has advantages over sclerotherapy,[11] and banding should now be the endoscopic treatment of choice for variceal eradication. Generally, band ligation is done every 1–2 weeks until varices are eradicated. Thereafter, periodic endoscopic surveillance is necessary. Unsuccessful long-term endoscopic management has been defined as either recurrent bleeding, despite adequate endoscopic therapy, or oesophageal varices that are difficult to eradicate by endoscopy. For these cases, TIPSS or selective shunt surgery should be undertaken.

Pharmacological agents

The most widely used drugs to prevent rebleeding are β-blockers. The most commonly investigated β-blocker is propranolol, although some studies have assessed nadolol, which can be given once daily and, unlike propranolol, is not metabolised by the liver. 13 randomised trials and three meta-analyses have confirmed the efficacy of β-blockers and have suggested an improvement in survival compared with placebo. Overall, β-blockers seem to lower the risk of rebleeding by about 40% and mortality by 20%.[22,23]

Ideally, reduction in portal pressure in response to drug therapy should be haemodynamically assessed by hepatic venous catheterisation, with measurement of the hepatic venous-pressure gradient. Such assessment is especially important in patients with alcoholic cirrhosis in whom a spontaneous fall of more than 20% is possible with abstinence. Although a reduction of 25% in the resting pulse rate is commonly used to guide the dosage of β-blockers, the splanchnic haemodynamic effects of β-blockers are unpredictable and correlate poorly with systemic effects.

Most studies have shown that β-blockers and sclerotherapy have similar efficacy in the prevention of variceal rebleeding, although complications are more frequent and severe with sclerotherapy. There is no clear evidence of a benefit from combined β-blocker therapy and sclerotherapy compared with either treatment alone.

The addition of nitrates (generally isosorbide-5-mononitrate) to β-blockers improves the portal hypotensive response. Reduced rebleeding has been reported with this drug combination compared with endosopic sclerotherapy.[24]

Studies are needed to compare pharmacological therapy with band ligation for the prevention of rebleeding, since this is now the endoscopic treatment of choice and is widely used by hepatologists.

TIPSS

Although TIPSS is an accepted treatment for recurrent variceal haemorrhage unresponsive to endoscopic therapy, current debate centres on whether or not TIPSS should be placed after an initial variceal haemorrhage to prevent rebleeding. Ten randomised studies have been published (including six in abstract form) comparing TIPSS with endoscopic treatment, with or without β-blockers, to prevent variceal rebleeding (table). Generally, the studies show reduced rebleeding in the TIPSS group, but higher rates of encephalopathy and no difference in survival. Data on cost and quality of life are awaited before advice can be given about the optimum treatment for this patient population.

Surgery

Early randomised trials comparing portacaval shunt surgery with non-specific treatment in the prevention of variceal rebleeding reported reductions in rates of bleeding but increased rates of encephalopathy in surgical groups. The use of more selective distal-splenorenal or small portacaval H-shunts seems to lower the incidence of encephalopathy. A meta-analysis of trials comparing shunt surgery with sclerotherapy to prevent variceal rebleeding found reduced bleeding rates but higher encephalopathy rates in the surgical group.[13] No difference in mortality was detected.

Orthotopic liver transplantation

Liver transplantation is the definitive treatment for deteriorating liver disease. Any patient with advanced cirrhosis and a variceal haemorrhage should be considered for transplantation. Unlike most surgical shunts, TIPSS does not seem to compromise subsequent transplant surgery and has been successfully used as a bridging therapy in patients with variceal bleeding.[25]

Primary prophylaxis of variceal haemorrhage

Because of the availability of proven primary prophylactic therapies, all patients with cirrhosis should have a screening endoscopy to confirm the presence of varices. If no varices are found, surveillance endoscopy should be done every 1–2 years, dependent on the severity of liver disease. If varices are present and thought to have a high risk of bleeding, the patient should be offered primary prophylactic therapy. Treatment should probably be limited to patients with such varices, because many studies have excluded patients with varices with low bleeding risk. If varices at low risk of bleeding are found, surveillance endoscopies should be more frequent to assess any changes.

Pharmacological agents

Nine controlled studies and three meta-analyses have confirmed the efficacy of β-blockers compared with placebo in the prevention of a first variceal haemorrhage. The risk of bleeding is reduced by about 45% with β-blocker therapy and in most studies there is a trend towards improved survival. Benefits seem to have been consistently found for patients with moderate or large oesophageal varices from all forms of liver disease. Side-effects of β-blockers are reported in about 15% of patients, requiring withdrawal of therapy in less than half of these cases.[26]

Nitrates may be as effective as β-blockers in the primary prophylaxis of variceal bleeding and offer an alternative to patients who are intolerant of β-blockers.[27] A reduced incidence of first variceal haemorrhage among patients given combined nitrates and β-blockers has been reported, compared with those given β-blockers alone.[28] No effect on survival was seen. This drug combination may, therefore, be the optimum therapy in the primary prophylaxis of variceal bleeding, but confirmatory studies are awaited.

Various other drugs have been shown to reduce portal pressure in haemodynamic studies, including diuretics, α-adrenoreceptor antagonists, endothelin antagonists, and vasodilating β-blockers. However, clinical studies of these drugs for primary prophylaxis of variceal bleeding are limited.

Endoscopy

19 trials have compared sclerotherapy with non-active treatment in the primary prophylaxis of variceal bleeding. Although meta-analysis shows reduced bleeding risk and improved survival, there is substantial heterogeneity between the trials and a higher mortality in the sclerotherapy group in the largest study.[29] In addition, complications of sclerotherapy seem to outweigh the benefits, especially among patients with smaller varices at low risk of bleeding.

Two studies have compared sclerotherapy with propranolol to prevent first variceal haemorrhage. One study showed a lower rate of bleeding in the propranolol group but no difference was found in the other study. Propranolol is also superior to combined propranolol and sclerotherapy in this situation.[30]

Trials are needed to compare band ligation with drug therapy for the primary prophylaxis of variceal haemorrhage. However, at present, patients with known high-risk varices should receive non-selective β-blockers (or nitrates if β-blockers are contraindicated or not tolerated) as primary prophylaxis against bleeding.

References

1 Friedman SL. Seminars in medicine of the Beth Israel Hospital, Boston: the cellular basis of hepatic fibrosis—mechanisms and treatment strategies. *N Engl J Med* 1993; **328:** 1828–35.

2 Rockey D. The cellular pathogenesis of portal hypertension: stellate cell contractility, endothelin, and nitric oxide. *Hepatology* 1997; **25:** 2–5.

3 Maroto A, Gines P, Arroyo V, et al. Brachial and femoral artery flow in cirrhosis: relationship to kidney dysfunction. *Hepatology* 1993; **17:** 788–93.

4 Whittle, BJR, Moncada S. Nitric oxide: the elusive mediator of the hyperdynamic circulation of cirrhosis. *Hepatology* 1992; **16:** 1089–92.

5 Garcia-Pagan JC, Feu F, Castells A, et al. Exercise, circadian variations of portal pressure and variceal hemorrhage in patients with cirrhosis. *Gastroenterology* 1996; **111:** 1300–06.

6 North Italian Endoscopic Club (NIEC) for the study and treatment of esophageal varices. Prediction of the first variceal haemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N Engl J Med* 1988; **319:** 983–89.

7 Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985; **5:** 419–24.

8 Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995; **346:** 1056–59.

9 Christensen R, Gaverholdt I, Schlicting P, et al. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisolone. *Gastroenterology* 1981; **81:** 944–52.

10 Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; **80:** 800–09.

11 Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. *Ann Intern Med* 1995; **123:** 180–87.

12 Williams SGJ, Westaby D. Recent advances in the endoscopic management of variceal bleeding. *Gut* 1995; **36:** 647–48.

13 D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995; **22:** 332–54.

14 Sung JJY, Chung SCS, Yung MY, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995; **346:** 1666–69.

15 Soderlund C, Magnusson I, Torngren S, Lundell L. Terlipressin (triglycyl-lysine vasopressin) controls acute bleeding oesophageal varices: a double-blind, randomized, placebo-conrolled trial. *Scand J Gastroenterol* 1990; **25:** 622–30.

16 Levacher S, Letoumelin P, Pateron D, Blaise M, Lapondry C, Pourriat J-L. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; **346:** 865–68.

17 Vlavianos P, Gimson AES, Westaby D, Williams R. Balloon tamponade in variceal bleeding: use and misuse. *BMJ* 1989; **298:** 1158.

18 Terblanche J, Burroughs AK, Hobbs KEF. Controversies in the management of bleeding esophageal varices. *N Engl J Med* 1989; **320:** 1393–98.

19 Rosemurgy AS, Goode SE, Zwiebel BR, Black TJ, Brady PG. A prospective trial of transjugular intrahepatic portosystemic stent shunts versus small diameter prostheteic H-graft portocaval shunts in the treatment of bleeding varices. *Ann Surg* 1996; **224:** 378–84.

20 Stanley AJ, Jalan R, Forrest EH, Redhead DN, Hayes PC. Longterm follow up of transjugular intrahepatic portosystemic stent shunt (TIPSS) for the treatment of portal hypertension: results in 130 patients. *Gut* 1996; **39:** 479–85.

21 Binmoeller KF, Soehendra N. "Superglue": the answer to variceal bleeding and fundal varices? *Endoscopy* 1995; **27:** 392–96.

22 Hayes PC, Davis JM, Lewis JA, Bouchier IAD. Meta-analysis of value of propranolol in prevention of variceal haemorrhage. *Lancet* 1990; **336:** 153–56.

23 Lebrec D. Pharmacotherapeutic agents in the treatment of portal hypertension. *J Gastroenterol Hepatol* 1997; **12:** 159–66.

24 Villanueva C, Balanzo J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; **334:** 1642–49.

25 Ring EJ, Lake JR, Roberts JP, et al. Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. *Ann Intern Med* 1992; **116:** 304–09.

26 Poynard T, Cales P, Pasta L, et al. Beta-adrenergic antagonists in the prevention of first gastrointestinal bleeding in patients with cirrhosis and oesophageal varices: an analysis of data and prognostic factors in 589 patients from four randomized clinical trials. *N Engl J Med* 1991; **324:** 1532–38.

27 Angelico M, Carli L, Piat C, et al. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; **104:** 1460–65.

28 Merkel C, Marin R, Enzo E, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; **348:** 1677–81.

29 The Veterans Affairs Cooperative Variceal Sclerotherapy Group. Prophylactic sclerotherapy for esophageal varices in alcoholic liver disease: a randomized, single blind, multicenter clinical trial. *N Engl J Med* 1991; **324:** 1779–84.

30 The PROVA Study Group. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: a randomized multicenter trial. *Hepatology* 1991; **14:** 1016–24.

Further reading

Pathophysiology

Abelman WH. Hyperdynamic circulation in cirrhosis: a historical perspective. *Hepatology* 1994; **20:** 1356–58.

Benoit JN, Granger DN. Slanchnic hemodynamics in chronic portal hypertension. *Semin Liver Dis* 1986; **6:** 287–98.

Bomzon A, Blendis L. The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. *Hepatology* 1994; **20:** 1343–50.

Genecin P, Groszmann RJ. Portal hypertension. In: Sciff E, Shiff L, eds. Diseases of the liver, 7th edn, vol 2. Philadelphia: Lippincott, 1993: 935–73.

Groszmann RJ. Hyperdynamic circulation of liver disease 40 years later: pathophysiology and clinical consequences. *Hepatology* 1994; **20:** 1359–63.

Mehta R, Gottstein J, Zeller PW, Lichtenberg R, Blei AT. Endotoxin and the hyperdynamic circulation of portal vein ligated rats. *Hepatology* 1990; **12:** 1152–56.

Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; **337:** 776–78.

Acute management

Bonman PC, Krige JEJ, Terblanche J. Management of oesophageal varices. *Lancet* 1994; **343:** 1079–84.

DeFranchis R: Developing consensus in portal hypertension. *J Hepatol* 1996; **25:** 390–94.

Goustout CJ, Viggiano TR, Balm RK. Acute gastrointestinal bleeding from portal hypertensive gastropathy: prevalence and clinical features. *Am J Gastroenterol* 1993; **88:** 2030–33.

Hayes PC. The coming of age of band ligation. *BMJ* 1996; **312:** 1111–12.

Heaton ND, Howard ER. Complications and limitations of injection sclerotherapy in portal hypertension. *Gut* 1993; **34:** 7–10.

Millikan WJ, Henderson JM, Galloway JR, Dodson TF, Shires GT, Stewart M. Surgical rescue for failures of cirrhotic sclerotherapy. *Am J Surg* 1990; **160:** 117–21.

Pagliaro L, D'Amico G, Luca A, et al. Portal hypertension: diagnosis and treatment. *J Hepatol* 1995; **23** (suppl 1): 36–44.

Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalance, classification and natural history of gastric varices: a long-term follow-up in 568 portal hypertension patients. *Hepatology* 1992; **16:** 1343–49.

Imperiale TF, Teran JC, McCullough AJ. A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. *Gastroenterology* 1995; **109:** 1289–94.

Prevention of recurrent bleeding and primary prophylactic therapy

Burroughs AK, Mezzanotte G, Phillips A, et al. Cirrhotics with variceal haemorrhage: the importance of the time interval between admission and the start of analysis for survival and rebleeding rates. *Hepatology* 1989; **9:** 801–07.

Burroughs AK. The natural history of varices. *J Hepatol* 1993; **17:** S10–13.

Feu F, García Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995; **346:** 1056–59.

Pagliaro L, D'Amico G, Pasta L, et al. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ, eds. Portal hypertension, pathophysiology and treatment. Oxford: Blackwell Scientific, 1994; **5:** 72–92.

Pagliaro L, D'Amico G, Sorensen TIA, et al. Prevention of first bleeding in cirrhosis: a meta-analysis of randomised clinical trials of non-surgical treatment. *Ann Intern Med* 1997; **17:** 59–90.

Stanley AJ, Redhead DN, Hayes PC. Update on the role of transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of complications of portal hypertension. *Aliment Pharmacol Ther* 1997; **11:** 261–72.

Teran JC, Imperiale TF, Mullen KD, Tavill AS, McCullough AJ. Primary prophylaxis of variceal bleeding in cirrhosis: a cost effectiveness analysis. *Gastroenterology* 1997; **112:** 473–82.

Vorbioff J, Groszmann RJ, Picabea E, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10 year prospective study. *Gastroenterology* 1996; **111:** 701–09.

Vaccine series

Applications of molecular microbiology to vaccinology

E Richard Moxon

Genetics, cell biology, and whole-genome sequencing of pathogens have changed dramatically the opportunities to investigate the epidemiology, pathogenesis, diagnosis, and control of microbial diseases. For example, recombinant DNA and PCR are powerful tools used to isolate genes whose role in pathogenicity can be investigated in biologically relevant virulence assays. Vaccines that target one or more of these genes can then be developed. Complete genome sequences of microbes provide an inventory of the genes encoding every virulence factor and potential immunogen. Candidate vaccines can be selected and developed using various approaches, including the recent innovation of immunisation with nucleic acids. Although many successful vaccines have been and will continue to be developed through empirical approaches, molecular microbiology provides a rational basis for discovery, development, and implementation of safer, more effective and, potentially cheaper vaccines.

In the Golden Age of microbiology (the latter part of the 19th and early part of the 20th Century), it was discovered that particular microbes were responsible for specific diseases. Allied with the concept of host immunity, this eventually led to the development of vaccines which have controlled several major microbial diseases (yellow fever, diphtheria, tetanus, pertussis, poliomyelitis, measles, mumps, and rubella) and eradicated small pox.

Starting with sulphonamides and penicillin, the decades of 1930, 1940, 1950, and 1960 witnessed the discovery of most of the important classes of antimicrobial drugs. By the middle of the 1990s, improved socioeconomic circumstances, immunisation, and antibiotics had transformed our capacity to treat, control, and even prevent the ravages of many of the most common and serious microbial diseases, at least in relatively affluent societies. In retrospect, this seems to have caused an inappropriate complacency concerning the impact of infections. Towards the end of this century, there has been appropriate recognition of the continuing public-health challenges posed by microbes, including the emergence of new pathogens, or old foes with novel attributes, antibiotic resistance, and of the vast unmet challenges of many infections for which vaccines are not available.

Over the past three decades, the Golden Age of molecular biology, genetics, and cell biology have been used to dissect the details of host microbial interactions. This has brought about a revolution which has transformed our knowledge of epidemiology, pathogenesis, diagnosis, and prevention of microbial diseases. This article attempts to place in perspective some of the opportunities and the challenges, especially those emanating from the impact of molecular microbiology, in the field of vaccinology.

From birth until death, man is besieged by a myriad of viruses, bacteria, fungi, and parasites competing to stay alive and to perpetuate their genes. Starting at birth, a variety of microbes establish themselves on the skin, mucous membranes, or gastrointestinal tract in the process of colonisation. In most instances, microbes and man coexist in a mutually benign or even beneficial partnership since these commensal microflora stimulate host immunity to protect against other invading organisms and may contribute micronutrients or growth factors. Rarely, colonisation by these living invasive organisms results in infectious disease and the impairment of health. This potential to injure or kill hosts (pathogenicity) is a general characteristic of all microbes and, directly or indirectly, is a constant challenge to human health. Pathogenicity is dependent on both the state of the host and a variety of microbial factors, and this mutuality and the implicit co-evolutionary implications are key concepts.

Molecular approaches to vaccinology

The application of molecular biology to the identification of virulence genes has opened the door to understanding the fundamental basis of the pathogenic personality of virulent microbes. Starting from the classical version of Koch's postulates, the new genetics has given us the molecular tools to help our understanding of virulence, as follows:[1] identify a gene, or group of genes, responsible for virulence; isolate the gene through recombinant DNA technology (cloning) or PCR; make many copies of these genes in vitro; and show the essential role of this gene in pathogenicity by showing that a mutation of a specific gene results in attenuation of virulence in an appropriate model or that a monoclonal antibody specific to this gene product can protect against disease.

The major functions of virulence genes include: tropism for the host species, or even for specific cells of individual hosts; mechanisms for the microbe to survive host clearance and multiply in the host; and the capacity to cause tissue damage or cytoxicity. For each of these, there are examples of vaccines which are effective because they target one or more of the virulence molecules responsible for these virulence functions (table).

The molecular genetic definition of virulence has enormous implications for vaccinology. Although the concept of inducing immunity to essential virulence determinants is not new, the use of molecular techniques has helped in the discovery of many more ways of

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Q J Med 1998; **91**:19–25

Haemodynamic parameters predicting variceal haemorrhage and survival in alcoholic cirrhosis

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Summary

The relationship between the various haemodynamic abnormalities observed in cirrhosis and their prognostic value remains unclear. We report haemodynamic measurements on 96 patients with alcoholic cirrhosis (mean Childs-Pugh Score, CPS, 9.0 ± 0.2, mean age 55.6 ± 1.0 years) and assess their value in predicting variceal bleeding and death during a mean follow-up of 19.3 ± 1.5 months. Baseline CPS correlated with hepatic venous pressure gradient (HVPG) ($p = 0.001$), azygos blood flow ($p < 0.05$), cardiac index ($p < 0.05$), and inversely with mean arterial pressure ($p < 0.01$) and systemic vascular resistance index ($p < 0.05$). Renal blood flow was not related to any haemodynamic parameter or CPS. Thirty-eight patients died during follow-up, and 16 had a variceal bleed. Death ($p = 0.001$) and variceal bleeding ($p < 0.05$) were more likely in patients with HVPG > 16 mmHg than in those with HVPG < 16 mmHg, and variceal bleeding was more likely in patients with HVPG > 12 mmHg (vs. HVPG < 12 mmHg, $p < 0.05$). HVPG also predicted death and variceal haemorrhage on univariate and multivariate analyses. No other haemodynamic parameter predicted death or bleeding. In alcoholic cirrhosis, severity of liver disease is related to HVPG, collateral blood flow and degree of systemic circulatory abnormalities. HVPG is a useful predictor of survival and variceal bleeding in these patients.

Introduction

Cirrhotic patients exhibit a hyperdynamic circulation with raised cardiac output and low systemic vascular resistance, but paradoxical renal vasoconstriction.[1] The exact relationship of these circulatory abnormalities to each other and to the degree of portal hypertension and severity of liver disease remains unclear.

The majority of patients with cirrhosis develop oesophageal varices secondary to the development of portal hypertension, and approximately one third will eventually bleed from these varices with an associated mortality of up to 50%.[2] It is therefore important to identify patients at high risk of variceal haemorrhage, to target treatment strategies.

The prognosis of cirrhotic patients depends largely on the severity of the liver disease. However, it has been suggested that haemodynamic assessment of the systemic, cardiopulmonary, and particularly the portal circulation, may offer additional indicators of prognosis.[3]

The aim of this study was to clarify the relationships between systemic, cardiopulmonary and portal haemodynamic parameters in patients with alcohol-related cirrhosis, and assess their prognostic value with regard to variceal bleeding and survival.

Methods

Patients

From November 1992 to September 1996, 96 patients with alcohol-related cirrhosis underwent haemodynamic assessment either as baseline measurements prior to acute pharmacological intervention trials, or as part of a detailed assessment of their

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Table 1 Patient characteristics at time of haemodynamic study ($n=96$)

Characteristic	Value
Sex (M/F)	63/33
Age (years)	
Mean ± SEM	55.6 ± 1.0
Range	35–80
Childs-Pugh score	
Mean ± SEM	9.0 ± 0.2
Childs grade	
A	15 (15.6%)
B	36 (37.5%)
C	45 (46.9%)

liver disease. Cirrhosis was diagnosed by liver biopsy or by clinical assessment (varices or ascites in the absence of other causes and in the presence of chronic biochemical derangement of liver function tests). Full patient characteristics are shown in Table 1.

Twenty-four patients had suffered a previous variceal bleed and were on long-term variceal obliteration programmes with band ligation. Three patients were in a similar programme as part of a study assessing band ligation in the primary prophylaxis of variceal haemorrhage. No patient was encephalopathic, and none had suffered a variceal bleed in the 10 days prior to haemodynamic assessment. All patients were haemodynamically stable at the time of study, and none were taking haemodynamic altering medications except for diuretic therapy ($n=51$).

Haemodynamic measurements

On the day of study, a full clinical examination was undertaken and blood taken for measurement of serum bilirubin and albumin, and prothrombin time. Ethical approval was given by Lothian Ethics Committee, and all patients gave witnessed, informed written consent.

Mean arterial pressure (MAP) was recorded and a right femoral venous introducer sheath inserted after infiltration of local anaesthetic (2% lignocaine). All catheters were placed under fluoroscopic guidance, and due to the complexities of multiple catheter placement, not all measurements were undertaken at each study. Through the introducer, a Sidewinder II torque balloon catheter (Cordis) was positioned in the right hepatic vein, and free and wedged hepatic venous pressures (FHVP and WHVP) were measured in 82 patients. The hepatic venous pressure gradient (HVPG) was calculated as WHVP minus FHVP.

Azygos blood flow (AzBF) ($n=62$) and left renal vein flow (RBF) ($n=42$) were recorded using a double-thermister reverse-thermodilution catheter (Webster Laboratories) via the introducer sheath as previously reported.[4,5] In 28 patients, a Swan-Ganz catheter (Baxter Healthcare) was inserted through the introducer into the right pulmonary artery after measurement of the right atrial pressure (RAP). Cardiac output (CO) was then measured by the thermodilution technique and systemic vascular resistance (SVR) was calculated as:

$$SVR = 79.96(MAP\text{-}RAP)/CO$$

Cardiac index and systemic vascular resistance index were calculated, respectively, as:

$$CO/m^2 \text{ and } SVR/m^2$$

Patients were followed up at 3-monthly intervals or earlier if complications arose. Mean ± SEM follow-up to most recent clinical review, death or liver transplantation ($n=2$) was 19.3 ± 1.5, months and episodes of endoscopically-proven variceal haemorrhage during follow-up were recorded.

Data analysis

Results are expressed as means ± SEM. Relationship between variables was assessed using Spearman's correlation, and comparisons between groups were analysed by the unpaired Students t-test and Mann-U-Whitney test, for parametric and non-parametric data, respectively.

Patients were grouped into Childs Class A/B and Childs Class C for survival analysis, into HVPG <12 mmHg and >12 mmHg for bleeding analysis, and into HVPG <16 mmHg or >16 mmHg for both bleeding and survival analysis. These groups were chosen because it has been suggested that variceal bleeding does not occur at HVPG <12 mmHg,[6] and that HVPG of 16 mmHg may be a threshold value above which bleeding and death is more likely.[7] Survival and bleeding were compared between groups using the Kaplan-Meier method with log rank test.

Cox's regression was used to test the univariate and multivariate significance of the haemodynamic parameters described above, in addition to serum albumin, bilirubin, prothrombin time, the presence of ascites, the CPS, diuretic therapy and the occurrence of a previous variceal bleed in predicting variceal bleeding and death.

Results

The baseline values of the haemodynamic measurements are shown in Table 2. Both the HVPG and AzBF correlated with CPS ($r=0.38$, $p=0.001$ and $r=0.29$, $p<0.05$ respectively; Figures 1 and 2) but not with other haemodynamic parameters. CPS was

Table 2
Baseline haemodynamic measurements

Measurement	Mean ± SEM
MAP (mmHg)	90.51 ± 1.38
CI (l/min/m^2)	3.94 ± 0.20
SVRI (dynes.s/cm^5/m^2)	1858.43 ± 124.97
HVPG (mmHg)	16.69 ± 0.59
AzBF (ml/min)	474.68 ± 43.07
RBF (ml/min)	398.98 ± 38.83

also related to HR, MAP, CI and SVRI ($r=0.38$, $p<0.001$; $r=-0.28$, $p<0.01$; $r=0.40$, $p<0.05$; $r=-0.44$, $p<0.05$ respectively, Figure 3). CI and SVRI also both correlated with HR ($r=0.55$, $p<0.005$ and $r=-0.62$, $p<0.005$ respectively) but not with other haemodynamic measurements. There was no relationship between RBF and any other haemodynamic parameter or CPS.

During follow-up, 16 patients suffered a variceal haemorrhage (only one of whom had a baseline HVPG of <12 mmHg). Variceal bleeding occurred in seven (29.2%) patients who had previously bled and nine (12.5%) who had not ($p=$NS). Baseline HVPG was higher in those patients who subsequently bled compared with those who did not (18.7 ± 1.2 vs. 16.3 ± 0.7 mmHg; $p<0.02$) and bleeding was more likely to occur in those with a baseline HVPG >12 mmHg compared with those with HVPG <12 mmHg ($p<0.05$; Figure 4), and also in those with HVPG >16 mmHg vs. those with HVPG <16 mmHg ($p<0.05$). Variceal bleeding was only predicted in the univariate or multivariate analysis by HVPG ($p<0.01$).

Baseline CI was higher in those patients who bled during follow-up compared with those who did not (6.1 ± 0.5 vs. 3.8 ± 0.2 l/min/m^2; $p<0.01$), but AzBF, RBF, SVRI, HR, MAP and CPS were no different between those who subsequently bled and those who did not.

During follow-up, 38 patients died. Survival was significantly greater in patients with Childs grade A or B compared with grade C disease ($p<0.0001$) (Figure 5), and in those with baseline HVPG <16 mmHg compared with HVPG >16 mmHg ($p=0.001$) (Figure 6). Baseline CPS and HVPG were

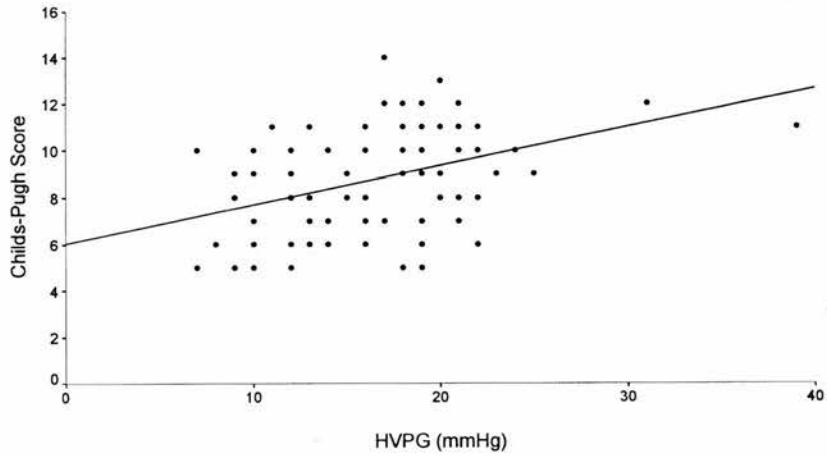

Figure 1. Correlation between Childs-Pugh Score and hepatic venous pressure gradient (HVPG) ($r=0.38$, $p=0.001$).

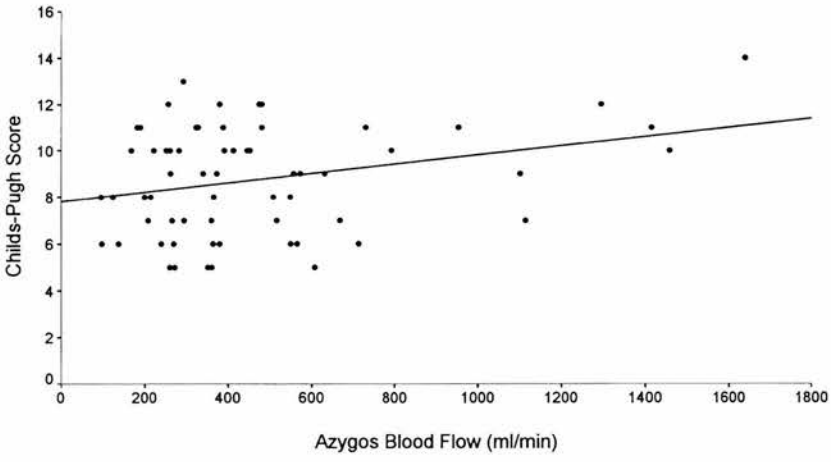

Figure 2. Correlation between Childs-Pugh Score and Azygos blood flow ($r=0.29$, $p<0.05$).

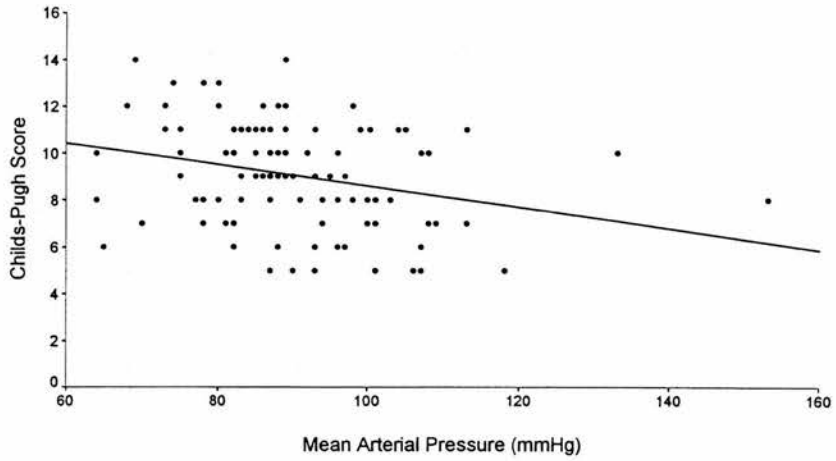

Figure 3. Correlation between Childs-Pugh Score and mean arterial pressure ($r=-0.28$, $p<0.01$).

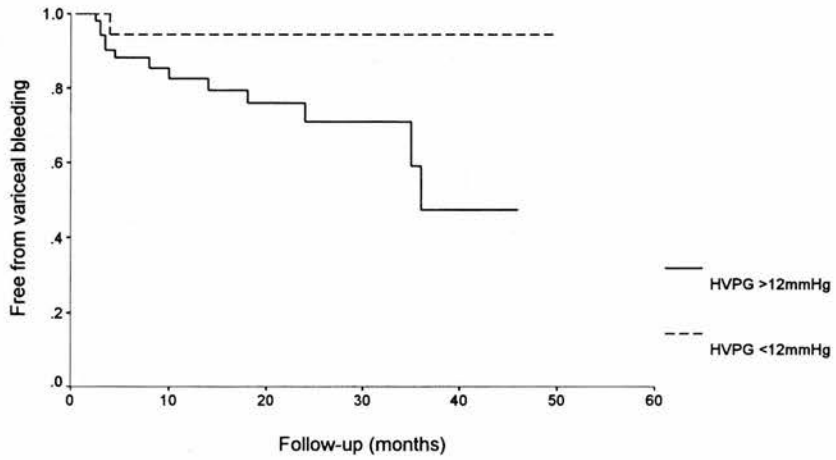

Figure 4. Kaplan-Meier analysis comparing variceal bleeding during follow-up between patients with HVPG <12 mmHg and those with HVPG >12 mmHg ($p<0.05$).

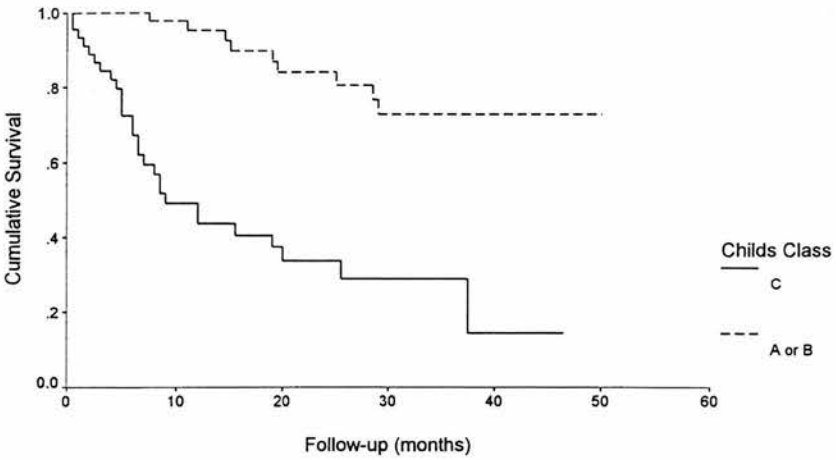

Figure 5. Kaplan-Meier analysis comparing cumulative survival between patients with Childs grade A or B liver disease with those with grade C disease ($p<0.0001$).

higher in patients who died during follow-up then in those who survived (10.3 ± 0.3 vs. 8.2 ± 0.3 ($p<0.001$); and 19.2 ± 1.0 vs. 15.1 ± 0.7 mmHg ($p=0.001$), respectively). Baseline AzBF, RBF, CI, SVRI or MAP was not different between those who died and survived on follow-up.

Variables predicting death in the univariate analysis were CPS ($p<0.0001$), prothrombin time

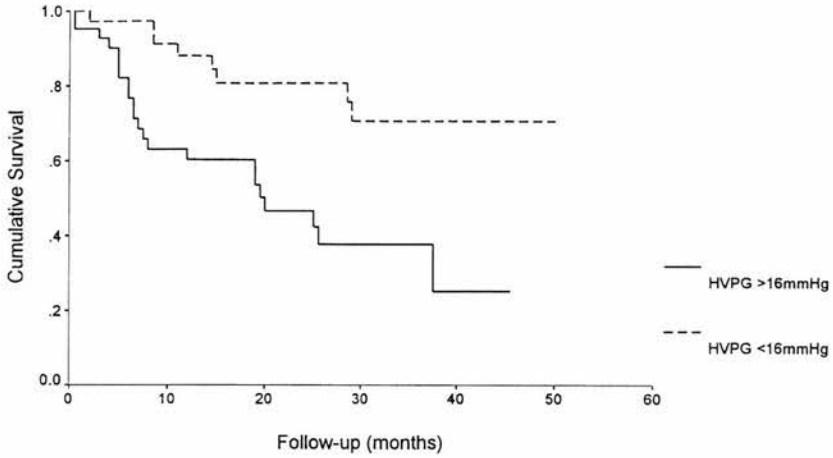

Figure 6. Kaplan-Meier analysis comparing cumulative survival between patients with HVPG <16 mmHg and those with HVPG >16 mmHg ($p=0.001$).

($p<0.0001$), HVPG ($p=0.0001$), presence of ascites ($p<0.001$), serum albumin ($p<0.001$), serum bilirubin ($p<0.05$), and diuretic therapy ($p<0.05$). No other haemodynamic parameter predicted death. On multivariate analysis, only the CPS and HVPG retained independent predictive significance ($p<0.0001$ and $p<0.05$, respectively).

Discussion

This large study indicates a strong relationship between severity of liver disease and the associated haemodynamic changes, including a fall in MAP and SVRI, and a rise in HVPG, CI and AzBF. We also confirm the prognostic value of HVPG measurement in patients with alcoholic cirrhosis.

The haemodynamic changes in cirrhosis have long been recognized, but the relationship between the systemic, renal and portal circulations in these patients remains unclear. These alterations in systemic haemodynamics are thought to arise secondary to vasodilators of splanchnic origin gaining access to the systemic vasculature via collateral vessels and reduced hepatic clearance.[8] It has also been suggested that the splanchnic circulation is the main site of reduced vascular resistance in cirrhosis.[9] This leads to activation of neurohumoral systems, causing sodium and water retention and renal vasoconstriction, which in turn can lead to ascites formation and functional renal abnormalities.[8,10]

We have shown that the severity of the hyperdynamic circulatory disturbances observed in cirrhosis is related to the degree of hepatic impairment as assessed by the CPS. The relationship between systemic hypotension and disease severity has previously been noted, and Llach and colleagues reported that MAP independently predicts survival on multivariate analysis in cirrhotic patients with ascites.[11]

The HVPG is an indirect measurement of portal pressure which accurately reflects the pressure gradient between the portal and hepatic veins in patients with sinusoidal portal hypertension such as alcoholic cirrhosis, but not in those with pre- or post-sinusoidal portal hypertension.[12] Consistent with earlier studies, we have found that HVPG correlates with CPS.[13]

Recently, a number of studies have assessed the prognostic usefulness of HVPG measurement in cirrhosis, with some authors suggesting it should be used much more frequently in such patients.[14] In addition, early reports of a 'bleeding threshold' of an HVPG of 12 mmHg, below which variceal bleeding did not occur,[6] have subsequently been confirmed.[15,16] In our study, only one patient with an HVPG <12 mmHg went on to have a variceal bleed. However, this patient was studied when abstinent from alcohol, then subsequently returned to drinking prior to the variceal haemorrhage. Active drinking has been shown to increase the HVPG and therefore the risk of variceal bleeding.[17] Obviously other patients in our study may have returned to or continued drinking during follow-up, but we did not analyse this factor with regard to its effect on patient outcome, as it is difficult to be entirely sure of abstinence in this patient group.

Although a number of patients were on a band ligation surveillance programme and others were on diuretic therapy at the time of study, endoscopic treatment of varices does not appear to affect HVPG[18] and it remains unclear whether diuretics have an effect.[19,20] There was no difference in the HVPG between patients who were on diuretic therapy and those not on diuretics in our study.

Using Cox's regression, we found that HVPG was the only haemodynamic, laboratory or clinical parameter to predict bleeding on multivariate analysis, and in particular, had better predictive value than

CPS. It is interesting that one measurement of HVPG appears to predict variceal haemorrhage over the next 2 years, despite the fact that a number of patients subsequently had pharmacological intervention as attempted prophylaxis for variceal bleeding. This study was designed to assess the prognostic value of a 'snap-shot' haemodynamic assessment, and we did not evaluate the individual benefit of any subsequently administered drugs.

Endoscopic signs such as variceal size and the presence of red spots on the varices have also been shown to predict variceal bleeding.[21] However, few of our patients underwent endoscopy around the time of the haemodynamic study, therefore we were unable to include endoscopic signs in the analysis.

We found no relationship between AzBF, which is a marker of collateral flow, and the risk of bleeding. This finding has been previously reported by Cales *et al.*,[22] and is probably explained by the fact that the azygos vein also drains mediastinal channels in addition to the oesophageal submucosa. Presumably for similar reasons, AzBF was not related to survival. However, consistent with Braillon and colleagues, we did find that AzBF correlated with CPS.[13]

A number of studies have suggested that the measurement of HVPG may predict survival in cirrhosis above and beyond the information given by the CPS.[7,23,24] We have confirmed Merkel and colleagues earlier report of a lower survival in patients with HVPG >16 mmHg.[7] HVPG has also previously been shown to be an independent predictor of survival on multiple regression analysis.[7,24,25]

We found that only HVPG and the CPS predicted survival on multivariate analysis. HVPG retained independent significant predictive value for survival even when patients with a previous history of variceal bleeding, or those with death due to bleeding were omitted from analysis. The CPS is of course a composite score of five clinical and laboratory parameters. When HVPG was compared with these individual parameters on multivariate analysis with the exclusion of the CPS, only the prothrombin time and the presence of ascites were superior to HVPG in predicting death. Therefore, incorporation of HVPG into a scoring system including some or all of the current CPS parameters is likely to lead to an improved prognostic score.

Implications for management

Measurement of HVPG is a relatively simple and safe procedure that takes less than 20 min to perform. In our patients, five had self-limiting bruising over the femoral venous site, but no other complications were encountered. Apart from its possible prognostic value for survival, HVPG measurement can help target therapy for patients at high risk of bleeding. We believe measurement of HVPG should become part of the routine assessment of patients with cirrhosis and certainly those with varices.

Patients with an HVPG >12 mmHg who have not previously bled should receive primary prophylaxis with beta-blockers with or without nitrates, as these have been shown to reduce the risk of variceal bleeding.[26] Although sclerotherapy is not recommended as a primary prophylactic therapy for variceal haemorrhage, due to its complication rate,[27] band ligation has been shown to be at least as effective as sclerotherapy but with fewer complications.[28] A recent report has suggested a role for band ligation in the primary prophylaxis of variceal bleeding,[29] although randomized trials comparing this with drug therapy are required.

Although band ligation is now considered the gold standard for the endoscopic eradication of varices in patients who have suffered a variceal bleed,[30] studies are currently underway to compare pharmacological agents and transjugular intrahepatic portosystemic stent-shunts (TIPSS) with band ligation in this situation.[31] Ideally, any patient undergoing pharmacological therapy as primary or secondary prophylaxis for variceal haemorrhage should undergo serial measurements of HVPG, which can act as a 'splanchnic sphygmomanometer'.[14] This will identify patients not responding to treatment, who can then be offered alternative therapeutic strategies.[15,16]

In conclusion, we have shown a relationship between the severity of liver disease and HVPG, AzBF and the systemic haemodynamic abnormalities observed in alcohol-related cirrhosis. In addition, HVPG measurement predicts variceal bleeding and survival in this patient group, and merits more widespread use.

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References

1. Groszmann RJ. Hyperdynamic circulation of liver disease 40years later: Pathophysiology and clinical consequences. *Hepatology* 1994; **20**:1359–63.
2. Christensen F, Fauerholdt I, Schlicting P, *et al.* Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effects of prednisolone. *Gastroenterology* 1981; **81**: 844–52.
3. Gluud C, Henriksen JH, Nielsen G, and the Copenhagen

Study Group For Liver Disease. Prognostic indicators in alcoholic cirrhotic men. *Hepatology* 1988; **8**:222–7.

4. Hayes PC, Terrace D, Peaston I, Bouchier IAD, Redhead DN, Brash HM. Computerised system for the continuous measurement of azygos venous blood flow. *Gut* 1992; **33**:372–4.
5. Forrest EH, Bouchier IAD, Hayes PC. Acute effect of low dose theophylline on the circulatory disturbances of cirrhosis. *Gut* 1997; **40**:139–44.
6. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M: Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985; **5**:419–24.
7. Merkel C, Bolognesi M, Bellon S, *et al.* Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. *Gastroenterology* 1992; **102**:973–9.
8. Schrier RW, Arroyo V, Bernardi M *et al.* Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**:1151–7.
9. Marato A, Gines P, Arroyo V, *et al.* Brachial and femoral artery flow in cirrhosis: relationship to kidney dysfunction. *Hepatology* 1993; **17**:788–93.
10. Bosch J, Arroyo V, Betriu A, *et al.* Hepatic hemodynamics and the renin-angiotensin-aldosterone system in cirrhosis. *Gastroenterology* 1980; **78**:92–9.
11. Llach J, Gines P, Arroyo V, *et al.* Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology* 1988; **94**:482–7.
12. Boyer TD, Triger DR, Horisawa M, Redeker AG, Reynolds TB. Direct transhepatic measurement of portal vein pressure using a thin needle. Comparison with wedge hepatic vein pressure. *Gastroenterology* 1977; **72**:584–9.
13. Braillon A, Cales P, Valla D, *et al.* Influence of the degree of liver failure on systemic and splanchnic haemodynamics and on response to propranolol in patients with cirrhosis. *Gut* 1986; **27**:1204–9.
14. Armonis A, Patch D, Burroughs AK. Hepatic venous pressure measurement: An old test as a new prognostic marker in cirrhosis? *Hepatology* 1996; **25**: 245–8.
15. Groszmann RJ, Bosch J, Grace ND, *et al.* Hemodynamic events in a prospective trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990; **99**:1401–7.
16. Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, Rodes J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995; **346**:1056–9.
17. Vorbioff J, Groszmann RJ, Picabea E, *et al.* Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: A 10-year prospective study. *Gastroenterology* 1996; **111**:701–9.
18. Lo GH, Liang HL, Lai KH, *et al.* The impact of endoscopic variceal ligation on the pressure of the portal venous system. *J Hepatol* 1996; **24**:74–80.
19. Nevens F, Lijnen P, VanBilloen H, Fevery J. The effect of long-term treatment with spironolactone on variceal pressure in patients with portal hypertension without ascites. *Hepatology* 1996; **23**:1047–52.
20. Sogni P, Soupison T, Moreau R, LeMoine O, Bacq Y, Hadengue A, Lebrec D. Hemodynamic effects of acute administration of furosemide in patients with cirrhosis receiving B-adrenergic antagonists. *J Hepatol* 1994; **20**:548–52.
21. North Italian Endoscopic Club (NIEC) for the study and treatment of esophageal varices. Prediction of the first variceal haemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med* 1988; **319**:983–9.
22. Cales P, Braillon A, Jiron MI, Lebrec D. Superior portosystemic collateral circulation estimated by azygos blood flow in patients with cirrhosis. Lack of correlation with oesophageal varices and gastrointestinal bleeding. Effect of propranolol. *J Hepatol* 1984; **1**:34–46.
23. Vinel JP, Cassigneul J, Levade M, Voigt JJ, Pascal JP. Assessment of short term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of portohepatic gradient. *Hepatology* 1986; **6**:116–17.
24. Gluud C, Henriksen JH, Nielsen G and the Copenhagen Study Group for Liver Disease. Prognostic indicators in alcoholic cirrhotic men. *Hepatology* 1988; **8**:222–7.
25. Armonis A, Patch D, McCormick PA, *et al.* Prognostic significance of hepatic venous pressure measurements in cirrhosis. J Hepatol1997(Suppl 1); **26**:76.
26. D'Amico G, Pagliaro L, Bosch J. The Treatment of Portal Hypertension: A Meta-Analytic Review. *Hepatology* 1995; **22**:332–54.
27. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. Prophylactic sclerotherapy for esophageal varices in alcoholic liver disease: a randomized, single blind, multicenter clinical trial. *N Engl J Med* 1991; **324**:1779–84.
28. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Int Med* 1995; **123**:280–7.
29. Lay CS, Tsai YT, Teg CY, Shyu WS, Guo WS, Wu KL, Lo KJ. Endosopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. *Hepatology* 1997; **25**:1346–50.
30. Hayes PC. The coming of age of band ligation. *BMJ* 1996; **312**:1111–12.
31. Stanley AJ, Redhead DN, Hayes PC. Update on the role of transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of complications of portal hypertension. *Aliment Pharmacol Ther* 1997; **11**:261–72.

Acute effect of propranolol and isosorbide-5-mononitrate administration on renal blood flow in cirrhotic patients

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Abstract

***Background*—Propranolol and isosorbide-5-mononitrate (ISMN) are increasingly used in the prophylaxis of variceal haemorrhage in cirrhosis. However, recent studies have suggested that these drugs may compromise renal function, possibly by reducing renal blood flow.**

***Aims*—To assess the acute effects of propranolol and ISMN on renal blood flow and other haemodynamic parameters in cirrhosis.**

***Patients and methods*—Twenty six cirrhotic patients were given either 80 mg propranolol, 20 mg ISMN, or a combination of the two drugs. Unilateral renal blood flow (RBF), azygos blood flow (AZBF), hepatic venous pressure gradient (HVPG), mean arterial pressure (MAP), and heart rate (HR) were recorded prior to and one hour after drug administration.**

***Results*—Propranolol caused a reduction in HR ($p<0.005$), AZBF ($p<0.01$), and HVPG ($p=0.05$), but no change in MAP or RBF (454.1 (77.3) versus 413.9 (60.3) ml/min). ISMN reduced MAP ($p<0.005$) and HVPG ($p<0.01$), but had no effect on HR, AZBF, or RBF (302.5 (49.4) versus 301.7 (58.8) ml/min). Combined treatment reduced MAP ($p<0.005$), AZBF ($p<0.05$), and HVPG ($p=0.002$), but HR and RBF (419.2 (62.6) versus 415.1 (61.1) ml/min) remained unchanged.**

***Conclusions*—Despite the anticipated changes in other haemodynamic parameters, acute propranolol and/or ISMN administration did not reduce RBF. These drugs do not seem to compromise RBF in cirrhosis.**

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Keywords: cirrhosis; portal hypertension; renal blood flow; propranolol; nitrates

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Propranolol is widely used in the primary and secondary prophylaxis of variceal haemorrhage in cirrhotic patients. It reduces portal pressure and collateral blood flow in cirrhosis and numerous studies have confirmed its efficacy as prophylaxis against portal hypertensive related gastrointestinal bleeding.[1–5] Isosorbide-5-mononitrate (ISMN) is a long acting venodilator that reduces portal pressure and hepatic vascular resistance.[6–8] It has been shown to reduce the risk of variceal bleeding,[9 10] and can be used as an alternative treatment for patients with portal hypertension who are intolerant to β blockade. More recently, reports have suggested that the combination of propranolol and ISMN may be the optimum treatment to reduce portal pressure and overcome the problem of non-response to propranolol.[11 12]

Several recent studies have suggested that β blockers and particularly nitrates may compromise renal function in cirrhosis, possibly due to a reduction in renal perfusion secondary to the associated reduced systemic blood pressure.[12–17] The aim of our study was to investigate the effect of propranolol, ISMN, and the combination of both drugs on renal blood flow and systemic and splanchnic haemodynamics in cirrhotic patients.

Patients and methods

Twenty six patients (12 female, mean age 51.1 years (range 33–70), mean Child-Pugh score (CPS) 9.2 (0.6)) with cirrhosis were studied. Eighteen patients had ascites at the time of study which was clinically graded as mild, moderate, or severe. Diagnosis of cirrhosis was based on liver biopsy (20 patients) or the presence of chronic liver biochemical abnormalities and endoscopically proven varices (six patients). Cirrhosis was alcohol related in 21 patients, and secondary to primary biliary cirrhosis in two, primary sclerosing cholangitis in one, sarcoid in one, and α_1 antitrypsin deficiency in one. No patient had biochemical evidence of renal dysfunction prior to study (serum urea greater than 6.6 mmol/l or serum creatinine greater than 150 μmol/l) and none was receiving vasoactive medication at the time of study. In addition, no patient had suffered a gastrointestinal haemorrhage within the previous four months. All patients gave informed consent and the study was approved by the Lothian Ethics Committee.

Studies were undertaken in the Department of Medicine catheter laboratory, on fasted patients in the supine position. Vascular catheters were positioned under fluoroscopic guidance via an 8.5 FG right femoral venous introducer (Baxter Healthcare Corporation, USA), inserted after local infiltration with 2% lignocaine. A balloon catheter (Sidewinder II, Cordis Corporation, USA) was inserted through the introducer to record both the free (FHVP) and wedged (WHVP) hepatic venous pressure. Hepatic venous pressure gradient (HVPG) was calculated as WHVP minus FHVP.

A double thermister, reverse thermodilution catheter (Webster Laboratories, California, USA) was then inserted through the introducer

Table 1 Patient characteristics

	Propanolol (n=9)	*ISMN (n=8)*	*Combined treatment (n=9)*
Age (y)	52.7 (2.3)	50.5 (2.8)	51.1 (1.9)
Child-Pugh score	9.2 (1.0)	9.4 (1.5)	9.1 (1.1)
No with ascites (mild or moderate/severe)	5/0	4/1	7/1
Serum creatinine (μmol/l), mean (range)	83.1 (63–136)	92.1 (65–142)	88.8 (66–126)
Aetiology (ALD/other)	8/1	6/2	7/2

ALD, alcoholic liver disease.

and positioned in the left renal vein. The proximal thermister was confirmed to be within the lumen of the renal vein by injection of 5 ml dilute contrast media (Conray 280, May & Baker Ltd, Dagenham, UK). Recordings of unilateral renal blood flow (RBF) were made using a custom built interface (B55724 type CF) and an IBM microcomputer processor (PS2–286) as previously reported.[18] Mean blood flows were recorded over a 30 second period with the patient breathing normally at rest.

Finally, the reverse thermodilution catheter was positioned in the azygos vein and azygos blood flow (AZBF) recorded in a similar manner to RBF. The catheter was then left in position for the duration of the study.

When recruited for the study, patients were matched for age and CPS for each therapeutic regimen (table 1). Nine patients were then given 80 mg oral propranolol, eight patients 20 mg oral ISMN, and nine patients both treatments. One hour later AZBF was again recorded, then the reverse thermodilution catheter was manouevred back into the initial position in the left renal vein and repeat RBF measurement made as described above. Finally, repeat measurements of the WHVP and FHVP were recorded using the balloon catheter. The sheath was then removed and firm pressure applied until haemostasis was obtained. Heart rate (HR) and mean arterial pressure (MAP) were also recorded for the duration of the study and for four hours thereafter. In all patients, the duration of the study was less than 3.5 hours.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM) or range where indicated. For parametric data, the paired Student's *t* test and Pearson's correlation were used. The Wilcoxon signed ranked test and Kendall correlation were used for non-parametric variables. A p value of less than 0.05 was taken to be significant.

Results

All patients completed the study without difficulty and no side effects were observed or reported. There was no statistical difference between the three therapeutic groups with regard to baseline RBF or other haemodynamic parameters. Baseline RBF did not correlate with CPS, HVPG, or ascites severity. Table 2 shows changes in HR and MAP for each treatment group at one hour following medication.

Following administration of propranolol, there was a fall in HVPG from 16.3 (2.2) to 12.9 (1.9) mm Hg (p=0.05) and in AZBF from 471.5 (85.8) to 293.4 (42.6) ml/min (p<0.01) (fig 1). There was no effect on RBF (454.1 (77.3) versus 413.9 (60.3) ml/min) (fig 2).

ISMN treatment led to a fall in HVPG from 14.9 (1.9) to 11.0 (1.3) mm Hg (p<0.01), but had no effect on either AZBF (573.4 (183.1) versus 576.0 (145.1) ml/min) (fig 1) or RBF (302.5 (49.4) versus 301.7 (58.8) ml/min) (fig 2).

Following administration of the combination of propranolol and ISMN, HVPG fell from 15.1 (1.8) to 8.9 (1.1) mm Hg (p=0.002) and AZBF fell from 612.5 (187.6) to 358.2 (57.0)

Table 2 Systemic haemodynamic effects

	Propanolol		*ISMN*		*Combined treatment*	
	Before	*After*	*Before*	*After*	*Before*	*After*
HR (bpm)	81.6 (3.9)	71.7 (4.2)*	86.8 (3.5)	91.0 (3.3)	79.9 (4.8)	71.4 (4.4)
MAP (mm Hg)	82.6 (3.4)	78.2 (3.3)	84.5 (3.3)	76.9 (3.6)*	78.1 (4.6)	68.7 (3.4)*

*p < 0.005.

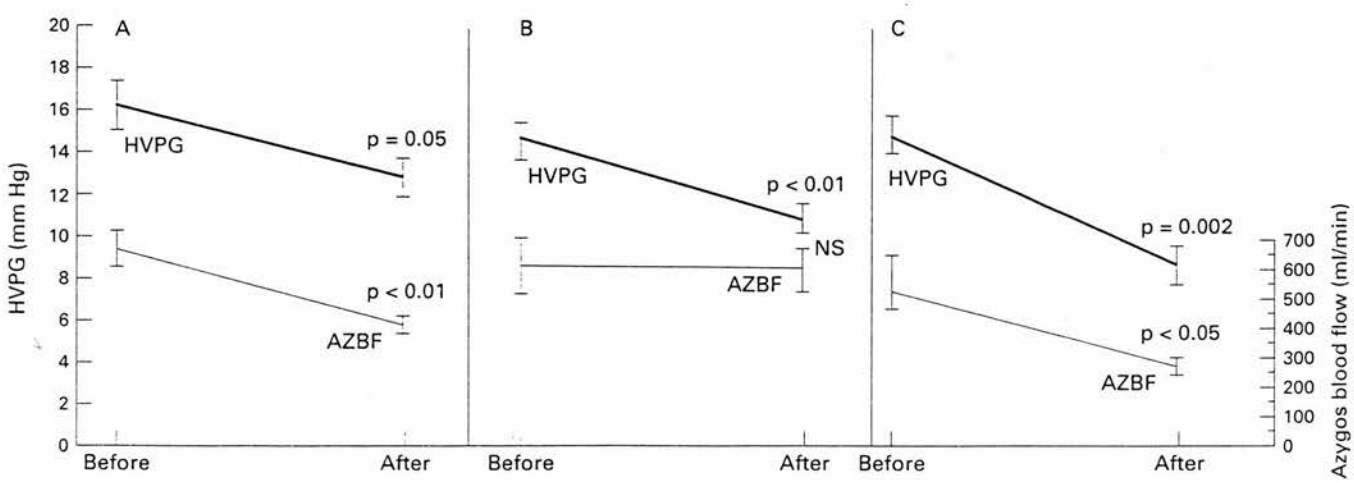

Figure 1 Changes in HVPG and AZBF one hour after a single dose of (A) propranolol, (B) ISMN, or (C) combined treatment.

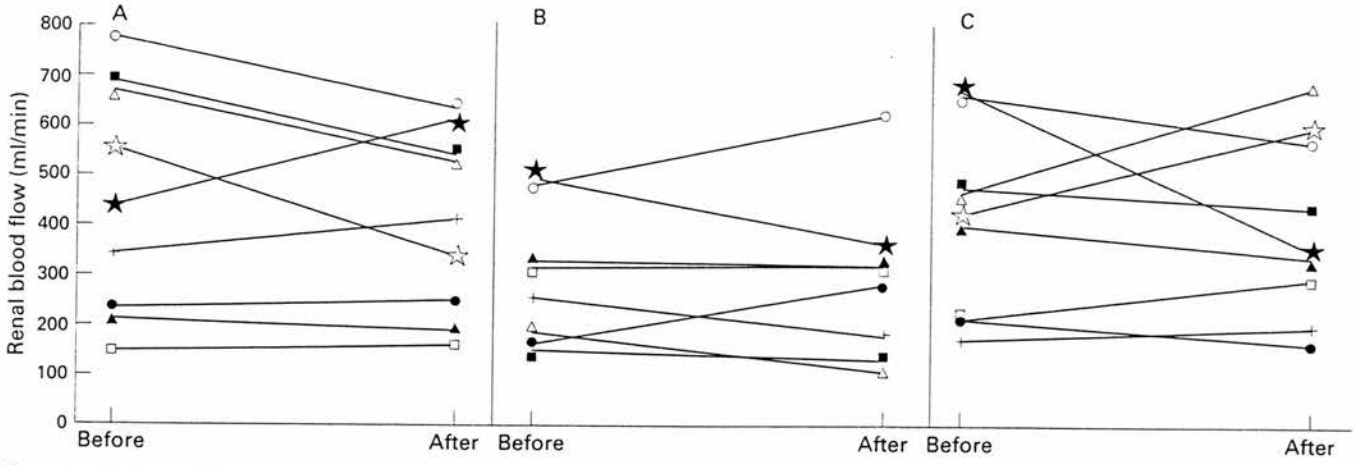

Figure 2 Unilateral RBF one hour after a single dose of (A) propranolol, (B) ISMN, or (C) combined treatment.

ml/min ($p<0.05$) (fig 1). Again, there was no effect on RBF (419.2 (62.6) versus 415.1 (61.1) ml/min) (fig 2).

When the 18 patients with ascites were considered alone, there remained no effect on RBF of any treatment when these patients were grouped together, or when analysed in treatment subgroups.

Discussion

We undertook this study to assess the acute effect of propranolol, ISMN, and the combination of both drugs on RBF in cirrhotic patients. Despite the anticipated changes in other haemodynamic parameters, no change in RBF was detected.

Any reduction in renal function is critical in cirrhotic patients, because they are already at risk of renal impairment due to reduced RBF, glomerular filtration rate (GFR), and sodium and water excretion.[19] Recent suggestions that β blockers and nitrates may have deleterious renal effects in cirrhosis include reports of reduced renal sodium excretion[12 13 16] and reduced renal perfusion[14–17] following administration of these drugs. This is important in view of their increasing use as prophylaxis against variceal haemorrhage.[1–5 9 10]

Generally, autoregulation in the kidney maintains a constant RBF over a wide range of arterial blood pressures.[20] Henriksen and Ring-Larsen suggest that in cirrhosis, a pharmacologically induced fall in MAP may compromise renal perfusion and GFR, leading to a subsequent reduction in sodium and water excretion, partly due to a shift in this autoregulation.[17]

β Blockers are the most widely used drugs in the prophylaxis of variceal haemorrhage. Most investigators have studied propranolol in this role, although nadolol has been used by some researchers. In addition to their portal hypotensive action, these drugs reduce cardiac output and increase systemic vascular resistance but have less effect on MAP.[21]

The renal effects of β blockers are complex due to their haemodynamic and neurohumoral actions. Propranolol treatment leads to increased circulating concentrations of noradrenaline which can cause sodium and water retention[22]; however, reduced levels of renin, angiotensin, and aldosterone (β_1 blockade) are also observed which increase salt and water excretion.[23] In addition, renal vasoconstriction due to β_2 blockade has been suggested as a mechanism by which β blockers may impair RBF and GFR.[20] However, the clinical significance of these changes remains unclear and data on cirrhotic patients are limited.

β Blockers have been shown to reduce the frusemide stimulated increase in renal interlobular arterial flow,[14] and reduce estimated RBF in cirrhosis as assessed by Doppler ultrasonography.[15] However, Bataille *et al* found no effect on RBF of acute propranolol treatment when given to cirrhotic patients,[24] and no difference in creatinine clearance was detected between cirrhotic patients given diuretics alone and those given propranolol and diuretics.[13] In addition, propranolol has been reported as having no effect on GFR in cirrhosis despite suppressing renin secretion,[25] and Bernardi *et al* found that propranolol actually increased GFR and natriuresis in ascitic cirrhotics with high sympathetic tone.[23] Other studies have reported both decreased[13] and increased[26] natriuresis in cirrhotic patients in response to propranolol.

Up to 40% of cirrhotic patients do not have a reduction in portal pressure in response to propranolol despite a fall in AZBF and are termed "non-responders". In addition, approximately 15% of patients are intolerant of the drug.[27 28] Therefore, nitrates are commonly used as an alternative treatment, or in combination with propranolol.

Nitrates are venodilators that reduce cardiac output and MAP in cirrhosis.[7 16 29] They are effective in reducing portal pressure and can convert propranolol non-responders into responders. This is consistent with our findings of only a mild reduction in HVPG following propranolol, but a significant reduction following ISMN and particularly the combination treatment. Recent studies have suggested that the combination of ISMN and β blockers may be the optimum treatment in portal hypertension.[11 12]

There has been concern that nitrates may compromise renal function in patients with advanced liver disease, due to the associated fall in blood pressure and activation of the

sympathetic and renin-angiotensin-aldosterone systems. Vorobioff *et al* found that 57% of cirrhotic patients with ascites or a history of ascites developed worsening of ascites when given propranolol and nitrates, compared with no worsening of ascites in any patient given propranolol alone.[12] ISMN has also been shown to reduce renal plasma flow, GFR, and sodium and water excretion and increase renin and aldosterone values in cirrhosis.[16] The fall in GFR and free water clearance was greater in those patients who had ascites.

However, Morrillos *et al* found no effect on inulin clearance, free water clearance, plasma renin activity, aldosterone concentration, or ascites outcome in cirrhotic patients given long term propranolol and ISMN, despite a reduction in blood pressure.[30] In addition, Merkel *et al* found no deterioration in renal function in cirrhotic patients given six months of ISMN and nadolol compared with patients given nadolol alone.[31] Although there was a correlation between the fall in blood pressure and the rise in serum creatinine in the group as a whole, it was only the patients given combination treatment who had a reduction in their ascites.

More recently, Salerno *et al* reported that acute ISMN treatment in cirrhosis reduced diuresis and natriuresis, and reduced GFR in patients with ascites.[32] However, the same study also showed that chronic administration of ISMN did not affect renal function if patients did not have ascites, but reduced diuresis and natriuresis in ascitic patients. No effect on GFR or renal plasma flow was detected.

It is clear that there are conflicting data in the literature on this subject which may be due to differences in the study populations or in the duration of treatment. Although we did not assess sodium and water excretion or GFR in this study, we found no change in RBF despite the expected changes in MAP, HVPG, and AZBF following administration of propranolol and/or ISMN. Despite the fact that all patients in our study had normal serum creatinine concentrations, it is possible that some may have had a degree of renal impairment not evident from their serum creatinine. However, when ascitic patients alone were assessed, there was still no effect on RBF. We assessed only the acute effect of these drugs on RBF, therefore we cannot draw conclusions regarding prolonged treatment. It is possible that administration of these drugs to cirrhotic patients may compromise renal function by mechanisms other than a reduction in RBF, such as neurohumoral or tubular effects. However, the main concern of many of the above studies was a possible reduction in renal perfusion consequent on the systemic haemodynamic changes induced by these drugs.

In view of our desire to assess both AZBF and RBF in this study, we had to move the thermodilution catheter out of the renal vein between the two recordings of RBF. The initial position of the catheter in the left renal vein was recorded fluoroscopically and the catheter repositioned to the exact same position for the one hour recording of RBF using fluoroscopic guidance. To ensure validity of these measurements, three other cirrhotic patients had multiple RBF recordings made over one hour, with the catheter moved in and out of the left renal vein under similar conditions. The coefficient of variation in RBF recordings was less than 10%.

Most studies assessing renal plasma flow and GFR rely on clearance of *p*-aminohippuric acid and inulin respectively, but such methods rely on high renal extraction of these substances. In the presence of sepsis or other pathological conditions leading to tissue hypoxia, microvasular abnormalities, and shunting of blood such as in cirrhosis, these methods are largely invalid.[33] Although thermodilution measurement of RBF has been shown to correlate well with half the renal blood flow as calculated from *p*-aminohippuric acid infusion,[34] thermodilution methods may be more accurate than clearance techniques in pathological states.

Using the thermodilution technique, we found no acute effect on RBF in patients given propranolol and/or ISMN. The possibility of a type II error exists, but the numbers studied produced significant results with regard to the other haemodynamic parameters, and particularly in the propranolol group, the patients with the lower initial RBF (whose renal function would be of most concern) actually had a rise in RBF following treatment. Although the patients given ISMN had slightly lower baseline RBF compared with those given propranolol or combination treatment, this difference was not significant, and as in the other therapeutic groups, these patients had no change in RBF after treatment.

In conclusion, we have detected no effect on RBF following acute administration of propranolol, ISMN, or a combination of the two drugs to cirrhotic patients, despite the anticipated changes in MAP, HVPG, and AZBF. Therefore any effect of these drugs on renal function in cirrhosis does not seem to be due to an acute reduction in RBF.

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1 Pascal JP, Cales P, Multicenter Study Group. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987;**317**:856–61.
2 Hayes PC, Davis JM, Lewis JA Bouchier IAD. Meta-analysis of the value of propranolol in prevention of variceal haemorrhage. *Lancet* 1990;**1**:153–6.
3 Conn HO, Grace N, Bosch J, *et al* and members of the Boston-New Haven-Barcelona portal hypertension study group. Propranolol in the prevention of the first variceal hemorrhage from oesophageal varices: results of a randomized double-blind cooperative clinical trial. *Hepatology* 1991;**13**:902–12.
4 Poynard T, Cales P, Pasta L, *et al* and the Franco-Italian Multicenter study group. β-adrenergic-antagonists in the prevention of first gastrointestinal bleeding in patients with cirrhosis and oesophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. *N Engl J Med* 1991;**324**:1532–8.
5 Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *J Hepatol* 1997;**26**:312–24.

6 Hayes PC, Westaby D, Williams R. Effects and mechanisms of action of isosorbide-5-mononitrate. *Gut* 1988;**29**: 757–65.
7 Navasa M, Chesta J, Bosch J, Rodes J. Reduction of portal pressure by isosorbide-5-mononitrate in patients with cirrhosis: effects on splanchnic and systemic hemodynamics and liver function. *Gastroenterology* 1989;**96**:1110–8.
8 Garcia-Pagan JC, Feu F, Navasa M, *et al.* Long-term hemodynamic effects of isosorbide-5-mononitrate in patients with cirrhosis and portal hypertension. *J Hepatol* 1990;**11**: 189–95.
9 Angelico M, Carli L, Piat C, Gentile S, Rinaldi V, Bologna E, Capocaccia L. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993;**104**:1460–5.
10 Bertoni G, Sassatelli R, Fornaciari G, *et al.* Oral isosorbide-5-mononitrate reduces the rebleeding rate during the course of injection sclerotherapy for esophageal varices. *Scand J Gastroenterol* 1994;**29**:363–70.
11 Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared to propranolol plus isosorbide-5-mononitrate for portal hypertension: a randomised controlled study. *Ann Intern Med* 1991;**114**:869–73.
12 Vorobioff J, Picabea E, Gamen M, *et al.* Propranolol compared with propranolol plus isosorbide dinitrate in portal-hypertensive patients: long-term hemodynamic and renal effects. *Hepatology* 1993;**18**:477–84.
13 Rector WG Jr, Reynolds TB. Propranolol in the treatment on cirrhotic ascites. *Arch Intern Med* 1984;**144**:1761–3.
14 Ljubicic N, Bilic A, Plavsic V. Effect of propranolol on urinary prostaglandin E2 excretion and renal interlobar arterial blood flow after furosemide administration in patients with hepatic cirrhosis. *Eur J Clin Pharmacol* 1992;**43**: 555–8.
15 Bolognesi M, Sacerdoti D, Merkel C, Gatta A. Duplex Doppler sonographic evaluation of splanchnic and renal effects of single agent and combined therapy with nadolol and isosorbide-5-mononitrate in cirrhotic patients. *J Ultrasound Med* 1994;**13**:945–52.
16 Salmeron JM, Ruiz del Arbol L, Gines A, *et al.* Renal effects of acute isosorbide-5-mononitrate administration in cirrhosis. *Hepatology* 1993;**17**:800–6.
17 Henriksen JH, Ring-Larsen H. Renal effects of drugs used in the treatment of portal hypertension. *Hepatology* 1993;**18**:688–95.
18 Hayes PC, Terrace D, Peaston I, Bouchier IAD, Redhead DN, Brash HM. Computerised system for the continuous measurement of azygos venous blood flow. *Gut* 1992;**33**: 372–4.
19 Epstein M, ed. *The kidney in liver disease.* Baltimore: Williams & Wilkins, 1988:1–656.
20 Wilkinson R. β-Blockers and renal function. *Drugs* 1982;**23**; 195–206.
21 Henriksen JH, Bendtsen F, Gerbes AL, Christensen NJ, Ring-Larsen H, Sorensen TIA. Estimated central blood volume in cirrhosis: relationship to sympathetic nervous activity, beta-adrenergic blockade and atrial natriuretic factor. *Hepatology* 1992;**16**:1163–70.
22 Best JH, Halter JB. Blood pressure and norepinephrine spillover during propranolol infusions in humans. *Am J Physiol* 1985;**248**:R400–6.
23 Bernardi M, De Palma R, Trevisani F, *et al.* Renal function and effective β-blockade in cirrhosis with ascites. *J Hepatol* 1989;**8**:279–86.
24 Bataille C, Bercoff E, Pariente EA, Valla D, Lebrec D. Effects of propranolol on renal blood flow and renal function in patients with cirrhosis. *Gastroenterology* 1984;**86**: 129–33.
25 Wilkinson SR, Bernardi M, Smith IK, Jowet TP, Slater JDH, Williams R. Effect of β-adrenergic blockade on the renin-angiotensin system, sodium excretion, and renal hemodynamics in cirrhosis with ascites. *Gastroenterology* 1977;**73**:659–63.
26 Hayes PC, Stewart WW, Bouchier IAD. Influence of propranolol on weight and salt and water homeostasis in chronic liver disease. *Lancet* 1984;ii:1064–8.
27 Garcia-Tsao G, Grace ND, Groszman RJ, *et al.* Short-term effects of propranolol on portal pressure. *Hepatology* 1986; **6**:101–6.
28 D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;**22**: 332–51.
29 Merkel C, Finucci G, Zuin R. Effects of isosorbide dinitrate on portal hypertension in alcoholic cirrhosis. *J Hepatol* 1987;**4**:174–80.
30 Morrillos RM, Planas R, Cabre E, *et al.* Propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: long-term hemodynamic and renal effects. *Hepatology* 1994;**20**:1502–8.
31 Merkel C, Gatta A, Donada C, *et al* and the GTIP. Long-term effect of nadolol or nadolol plus isosorbide-5-mononitrate on renal function and ascites formation in patients with cirrhosis. *Hepatology* 1995;**22**:808–13.
32 Salerno F, Borroni G, Lorenzano E, *et al.* Long-term administration of isosorbide-5-mononitrate does not impair renal function in cirrhotic patients. *Hepatology* 1996;**23**:1135–40.
33 Brenner M, Schaer GL, Mallory DL, Suffredinin AF, Parrillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. *Chest* 1990;**98**: 170–9.
34 Hornych A, Brod J, Slechta V. The measurement of renal venous outflow in man by the local thermodilution method. *Nephron* 1971;**8**:17–32.

Natriuretic Effect of an Adenosine-1 Receptor Antagonist in Cirrhotic Patients With Ascites

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Background & Aims: The sodium and water retention and renal vasoconstriction exhibited by patients with cirrhotic ascites are similar to the changes observed by stimulation of renal adenosine 1 receptors. The aim of this study was to investigate the effects of FK352 (an adenosine 1 antagonist) on renal and systemic hemodynamics and renal function in cirrhotic patients with ascites. **Methods:** *p*-Aminohippuric acid and inulin clearance, urine flow rate, sodium and potassium excretion, and free water clearance were measured for 2 hours before and after FK352 administration. Cardiac output, systemic vascular resistance, plasma angiotensin II level, plasma renin activity, and noradrenaline, adrenaline, and adenosine 3′,5′-cyclic monophosphate (cAMP) levels were also measured before and after FK352. **Results:** Urine sodium excretion and urine flow rate increased after FK352 by a mean of 199.9% ± 43.0% ($P < 0.001$) and 51.2% ± 17.5% ($P < 0.02$), respectively. Plasma cAMP and angiotensin II levels and plasma renin activity also increased by 10.8% ± 3.2% ($P < 0.01$), 36.9% ± 11.3% ($P < 0.01$), and 247.9% ± 82.6% ($P < 0.02$), respectively. No change was detected in any other parameter. **Conclusions:** The isokaliuretic improvement in natriuresis and diuresis suggests a role for adenosine 1 antagonism in the treatment of the renal abnormalities found in advanced cirrhosis.

Patients with advanced cirrhosis have a hyperdynamic circulation with increased cardiac output and low systemic vascular resistance.[1] However, they also have evidence of renal vasoconstriction and tubular transport abnormalities that can lead to a spectrum of renal effects ranging from sodium and water retention to the development of the hepatorenal syndrome.[2]

Adenosine is an endogenous nucleoside produced locally by the intracellular degradation of adenosine triphosphate in response to hypoxia. It has potent vasoactive properties with renal hemodynamic and tubular effects.[3,4] Adenosine 1 receptors are present on the afferent renal artery and proximal renal tubule, and stimulation of these inhibit adenyl cyclase, resulting in renal vasoconstriction and sodium and water retention.[5,6] Adenosine 2 receptors are found in the vasculature of the systemic circulation, and stimulation leads to vasodilatation via activation of adenyl cyclase.[7] These effects are similar to the abnormalities found in cirrhotic patients, and it has been suggested that adenosine has a role in the hemodynamic and renal changes of cirrhosis.[8,9]

Methylxanthines are nonspecific adenosine antagonists, and studies have shown that they improve renal blood flow, glomerular filtration rate (GFR), urine volume, and sodium and water excretion in cirrhosis, with variable effects on systemic hemodynamics.[8,10,11] However, these drugs are far from ideal for use in cirrhosis because of side effects including tachycardia, gastrointestinal disturbances, arrhythmias, and convulsions. Cirrhotic patients also clear xanthines poorly, and the drugs act via phosphodiesterase inhibition at high plasma levels giving variable effects.[12] However, specific adenosine 1 blockade may be beneficial in cirrhotic patients with impaired sodium and water excretion or functional renal impairment.

FK352 is a novel pyrazolopyridine derivative that has been characterized in vitro as a highly selective adenosine-1 receptor antagonist. In animal studies, it has been shown to increase renal blood flow, diuresis, and natriuresis. We investigated its effect on renal and systemic hemodynamics and renal function in cirrhotic patients with ascites.

Patients and Methods

Patients

Twelve patients (8 men) with alcohol-induced cirrhosis and ascites were studied. The mean age was 51.3 ± 2.4 years, and the mean Child–Pugh score was 8.2 ± 0.5 (8 Child's class B, 4 Child's class C). Cirrhosis was confirmed by biopsy in 9 patients and by the combination of esophageal varices and

Abbreviations used in this paper: AUC, area under the curve; ERPF, estimated renal plasma flow; GFR, glomerular filtration rate; MAP, mean arterial pressure; PAH, *p*-aminohippuric acid; PRA, plasma renin activity; V, urine flow rate; UNa, urine sodium concentration; UnaV, sodium excretion rate.

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chronic derangement in biochemical liver function test results in the absence of portal vein thrombosis in 3 patients. All patients had earlier confirmation of ascites by ultrasonography, and at the time of study ascites was clinically graded as moderate in 7 patients and mild in 5. No patient was taking vasoactive medications, and all were on dietary salt restriction.

Ten patients were undergoing diuretic therapy before the study. Eight patients were taking spironolactone at a mean dose of 119 mg/day (1 of whom was also taking 40 mg frusemide daily) and 2 amiloride at a mean dose of 6.7 mg/day (1 of whom was also taking 40 mg frusemide daily). Spironolactone administration was stopped 1 week before and amiloride and frusemide 3 days before the study. No patient had biochemical evidence of renal impairment (defined as serum urea of >6.6 mmol/L or serum creatinine of >120 μmol/L). Patients abstained from alcohol, cigarettes, and caffeine-containing substances for 24 hours before the study.

Study Protocol

This was a phase II open-labeled pilot study, designed primarily to assess the efficacy and safety of FK352. A dose escalation was built into the study to identify any dose response. The study was approved by the Lothian Ethics Committee, and all patients gave informed written consent.

On the morning of the study, patients received a light breakfast (two slices of toast and half a pint of milk). At 8 AM, they drank 1 L of water and were then transferred to the hemodynamic suite where they remained supine until completion of the study. A urinary catheter was inserted, and a loading dose of *p*-aminohippuric acid (PAH) (450 mg) and inulin (3.5 g) was administered via a peripheral vein. This was followed at 9 AM by a constant infusion of PAH (16 mg/min) and inulin (20 mg/min). After local infiltration with 2% lignocaine, an 8.5F gauge right femoral venous introducer sheath (Baxter Healthcare Corp., Irvine, CA) was inserted, through which the renal venous and pulmonary artery catheters were positioned (see below).

A single bolus injection of FK352 (10 mg for the first 4 patients, 25 mg the next 4 patients, and 50 mg the final 4 patients) was administered over a 2-minute period through a separate peripheral vein at noon. PAH and inulin infusions were continued for 120 minutes after drug administration.

Clinical Tests

Plasma and urine analyses. Sixty minutes after commencement of the PAH and inulin infusions, 30-minute urine collections were obtained for the 2 hours before and the 2 hours after administration of FK352. Patients were required to drink 100 mL of water during each of these 30-minute periods. The urine collections were used to measure flow rate (V) and concentrations of PAH and inulin. Peripheral blood was sampled at the midpoint of these 30-minute urine collections to measure PAH and inulin concentrations and therefore calculate inulin clearance (estimated GFR) and PAH clearance (estimated renal plasma flow [ERPF]) for each 30-minute period as follows: {Clearance = (Urine Concentration) × V/(Plasma Concentration)}.

Four patients also had renal venous PAH concentrations measured before and after FK352 administration via a catheter (Webster Laboratories, Baldwin Park, CA) positioned through the femoral introducer sheath into the left renal vein under fluoroscopic guidance. The catheter was confirmed to be within the lumen of the renal vein by injection of 5 mL of dilute contrast media (Conray 280, May & Baker Ltd., Dagenham, England). The renal venous PAH levels were used to calculate the PAH extraction coefficient as follows: {= (Peripheral PAH Concentration − Renal Vein PAH Concentration)/(Peripheral PAH Concentration)}. In these 4 patients, this was used to give the corrected ERPF {= ERPF/PAH Extraction Coefficient}.

Plasma and urine osmolality and sodium and potassium concentration were measured to calculate the sodium excretion rate (UNaV, where *UNa* is the urine concentration of sodium), potassium excretion rate, and free water clearance {= V − (Urine Osmolality) × V/(Plasma Osmolality)} for each 30-minute period.

Plasma and urine was also collected at 15 minutes before and 15, 45, and 105 minutes after administration of FK352 to measure plasma angiotensin II level, plasma renin activity (PRA), and adrenaline, noradrenaline, and plasma and urine adenosine 3′,5′-cyclic monophosphate (cAMP) levels.

At the end of the study, the PAH and inulin infusions were discontinued and the urinary catheter was removed.

Hemodynamic measurements. Under fluoroscopic guidance, pulmonary artery catheterization (Swan–Ganz catheter; Baxter Healthcare Corp.) was performed via the femoral introducer sheath 30 minutes before administration of FK352, to measure cardiac output and systemic vascular resistance. These measurements were repeated 120 minutes after drug administration. During the study, continuous electrocardiograph monitoring was used and heart rate and mean arterial blood pressure (MAP) were recorded at 15-minute intervals.

After completion of the study (<6 hours in all cases), the femoral sheath was removed and pressure applied until hemostasis was obtained. The patient was then transferred to the ward, and monitoring of heart rate and MAP was undertaken for a further 4 hours. The patients were observed overnight and reviewed at 1 week for clinical and biochemical assessment.

Laboratory Analysis

Blood samples for PRA, angiotensin II, adrenaline, noradrenaline, and cAMP determinations were collected on ice. The supernatant serum from all blood samples and the urine samples for cAMP measurement were stored at −70°C until analysis. PRA was measured by I^{125}-radioimmunoassay of angiotensin I generation (Biodata Diagnostics, Rome, Italy), and angiotensin II by radioisotope assay with solid-phase separation step (Nichols Institute Ltd., Newport, Wales). Catecholamines were measured by high-performance liquid chromatography and cAMP by radioimmunoassay (Incstar Ltd., Wokingham, England). PAH and inulin were measured using high-performance liquid chromatography with fluoromet-

ric detection and spectrophotometric technique, respectively, as described previously.[13]

Data Analysis

Data are expressed as mean values ± SEM. In view of the repeated measurements on each patient, the drug effect was analyzed by area under the curve (AUC) based on percentage change from the mean baseline value. If the AUC was significant ($P < 0.05$), Student's t test was used to compare the mean predrug level with the value at each postdose time point using the Bonferroni correction. Therefore, the parameters with four postdose time points (V, UNaV, potassium excretion rate, and free water clearance) had a significance level of $0.05/4 = 0.0125$, and those with three postdose time points (PAH and inulin clearance and hormone parameters) had a significance level of $0.05/3 = 0.0167$.

Results

All patients tolerated the drug well and completed the study without difficulty. No clinical or biochemical abnormalities were detected at 24 hours or at the 1-week review. No dose response was detected; therefore, all results were analyzed for the 12 patients together.

Changes in Renal Function

After FK352 administration, UNaV increased by a mean of 199.9% ± 43.0% ($P < 0.001$) from a baseline mean of 185.9 ± 31.0 μmol/min, remaining elevated for at least 2 hours (Figure 1). Urine flow rate increased by 51.2% ± 17.5% ($P < 0.02$) from a mean of 6.49 ± 0.80 mL/min with a maximal increase immediately after drug administration (Figure 1). There was an increase in free water clearance by 92.7% ± 53.8% from a mean of 3.56 ± 0.56 mL/min before FK352, but this did not reach statistical significance ($P = 0.11$).

There was no change in potassium excretion rate after FK352 with an increase of 10.0% ± 6.8% from a baseline of 60.84 ± 9.88 μmol/min. Similarly, no change was observed in PAH or inulin clearance over the study period, with a change of 3.8% ± 10.6% and −3.8% ± 3.8% from baseline values of 592.2 ± 60.8 mL/min and 113.8 ± 12.8 mL/min, respectively. In the 4 patients in whom it was measured, the PAH extraction coefficent ranged from 0.21 to 0.81, with a mean change in corrected ERPF after FK352 of −1.3% ± 12.6% from a baseline value of 454.8 ± 150.3 mL/min.

Changes in Hemodynamics

There was no change in heart rate or MAP during the study. Similarly, cardiac output (before FK352, 6.42 ± 0.45 L/min; after FK352, 6.38 ± 0.47 L/min) and systemic vascular resistance (before FK352, 1025.3 ± 92.7 dyne · s^{-1} · cm^{-5}; after FK352, 1020.2 ± 102.0 dyne · s^{-1} · cm^{-5}) remained unchanged.

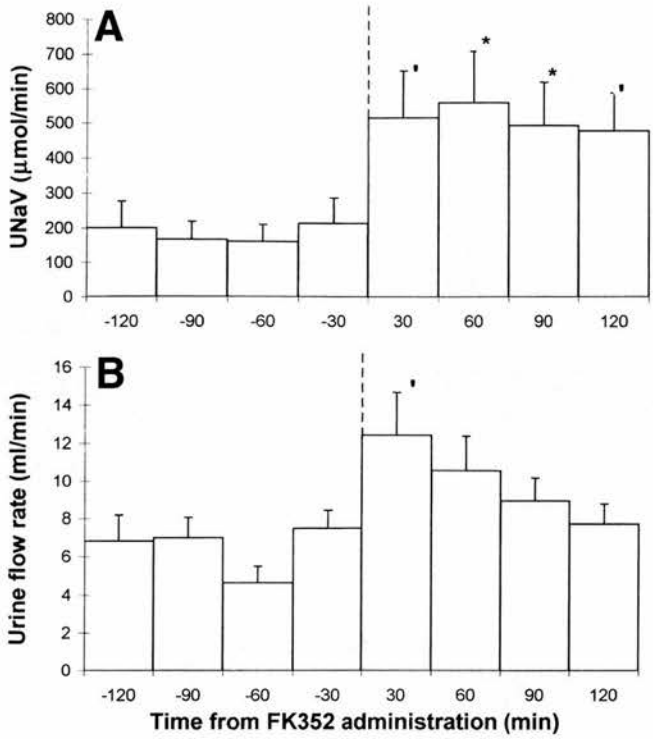

Figure 1. Graph showing changes in (*A*) UNaV (AUC, $P < 0.001$) and (*B*) urine flow rate (AUC, $P < 0.02$) after administration of FK352. Application of the Bonferroni correction for multiple comparisons at individual postdose time points gives a significance level of $P = 0.0125$. Therefore, the only individual significant values are $*P < 0.001$ and $'P < 0.005$ vs. mean pre-FK352 value.

Measurements of Angiotensin II, PRA, Catecholamines, and cAMP

Plasma cAMP and angiotensin II levels and PRA increased after FK352 by a mean of 10.8% ± 3.2% ($P < 0.01$), 36.9% ± 11.3% ($P < 0.01$), and 247.9% ± 82.6% ($P < 0.02$), respectively, but no change was observed in plasma adrenaline or noradrenaline or urine cAMP levels (Table 1).

Discussion

We have shown an improvement in urine flow and natriuresis after administration of an adenosine 1–specific antagonist (FK352) to cirrhotic patients with ascites. This is the first use of this drug in cirrhotic patients.

The renal abnormalities associated with cirrhosis are characterized by renal vasoconstriction and an impaired ability to excrete sodium and water,[2,14] but the exact mechanisms by which such "functional" renal abnormalities arise remain unclear. Increased oxygen demand and tissue hypoxia are found in cirrhosis,[15,16] which lead to release of vasodilating substances including adeno-

Table 1. Percentage Change From Baseline for Angiotensin II, PRA, Catecholamines, and cAMP After FK352 Administration

		Time after FK352 administration (*min*)			
	Baseline value	15	45	105	*P* value (AUC)
PRA	4.14 ± 1.75 ng · mL^{-1} · h^{-1}	202.7 ± 63.7[c]	243.7 ± 87.0	349.9 ± 117.7[d]	<0.02
Angiotensin II	30.80 ± 7.67 pg/mL	35.8 ± 10.2[a]	41.1 ± 17.8	40.7 ± 9.7[b]	<0.01
Adrenaline	0.18 ± 0.04 nmol/L	−2.2 ± 12.8	30.3 ± 27.5	30.4 ± 26.0	NS
Noradrenaline	2.76 ± 0.41 nmol/L	0.2 ± 6.3	2.5 ± 5.6	−1.9 ± 9.1	NS
Plasma cAMP	7.53 ± 0.46 nmol/L	8.9 ± 5.3	13.2 ± 3.2[b]	11.2 ± 4.1	<0.01
Urine cAMP	1072.00 ± 468.37 nmol/L	−14.4 ± 9.3	−15.5 ± 11.3	14.6 ± 27.2	NS

NOTE. Application of Bonferroni correction for multiple comparisons at individual postdose time points gives a significance level of $P = 0.0167$. Therefore, the only individual significant values are [a]$P < 0.005$, [b]$P < 0.002$, [c]$P < 0.01$, and [d]$P = 0.013$.

sine.[17,18] However, in the kidney, adenosine acts as a vasoconstrictor, reducing renal perfusion, GFR, and sodium excretion.[4–6,19] Cirrhotic patients seem to have an increased number of adenosine receptors and increased sensitivity to adenosine.[20–22]

Balakrishnan et al.[4] reported a decline in urine flow, natriuresis, free water clearance, and GFR after administration of adenosine to healthy subjects.[4] Llach et al.[9] showed that increasing extracellular adenosine levels by administration of dipyridamole to cirrhotic patients reduced sodium and free water excretion. In their study, ERPF and GFR were also reduced in patients with ascites and high basal renin levels. Animal studies have shown that stimulation of adenosine 1 receptors leads to renal hemodynamic and tubular effects similar to those found in cirrhosis.[5,6,23] These findings suggest that adenosine 1–specific antagonism may be beneficial in the treatment of the renal abnormalities of cirrhosis.

Previous use of adenosine 1 antagonists in animal studies has led to increased diuresis and natriuresis with minimal systemic effects[24] and amelioration of the acute renal failure induced by glycerol, endotoxin, and cisplatin.[25–27] Adenosine 1 antagonism has also been shown to attenuate the oliguria, hypofiltration, and electrolyte disturbance induced by adenosine in an animal model, suggesting that adenosine 1 antagonists may protect the kidney from the undesirable hemodynamic and tubular effects of adenosine.[28]

After administration of the adenosine 1 antagonist FK352, we observed an immediate isokaliuretic improvement in urine flow rate, an increase in natriuresis, and a tendency for free water clearance to increase. These effects are of obvious benefit to cirrhotic patients with ascites in whom sodium and water excretion is impaired and diuretic therapy often leads to potassium imbalance.[29] Little effect on systemic hemodynamics was observed, possibly reflecting the renal specificity of adenosine 1 receptors, although right heart catheterization was repeated 120 minutes after drug administration, which may have missed an earlier effect.

A potential holdover from spironolactone, water loading, and commencement of the supine position may have led to the relatively high baseline natriuresis and urine volumes. However, spironolactone was stopped in all patients 1 week before the study, and urine flow rate, natriuresis, and free water clearance remained stable for the 2 hours before FK352 administration. This was followed by an immediate increase in urine flow and natriuresis. Any relation of this effect to the fluid load and posture change 4 hours earlier is improbable and inconsistent with previous reports.[30,31]

Although the patients in our study all had clinical evidence of ascites, none had biochemical renal impairment or true refractory ascites as defined by Arroyo et al.[32]; we therefore cannot extend our findings to these patient groups. However, there was a consistent increase in urine flow rate and natriuresis when only patients with Child's grade C disease were considered. Therapeutic options for patients with refractory ascites or hepatorenal syndrome are limited, and any possible therapy requires evaluation.

The standard method for measuring renal blood flow is PAH clearance, but in the presence of hypoxia and shunting of blood (such as occurs in sepsis or cirrhosis), this method may be invalid because of low renal PAH extraction.[33] In normal subjects, PAH extraction should be >0.9, but in the 4 patients in whom we measured this, the PAH extraction ranged from 0.21 to 0.81. Allowing for this reduced extraction, the corrected ERPF was lower than the ERPF measured by the standard method, but there remained no obvious effect of FK352 administration. Inulin clearance remains the gold standard for GFR measurement, and no increase in GFR was detected despite the increased diuresis and natriuresis. It is possible that FK352 leads to tubular transport changes via antagonism of adenosine 1 receptors on the tubule cells, with little effect on renal plasma flow or GFR, which may be under greater influence from other humeral control mechanisms.

We observed an increase in plasma angiotensin II and

cAMP levels and in PRA but no change in plasma catecholamines or urinary cAMP after FK352 administration. Stimulation of adenosine 1 receptors inhibits renin release,[34,35] and suppression of this inhibition by theophylline or an adenosine-1 receptor antagonist has been reported to increase PRA.[36,37] It has been suggested that the activity of the renin-angiotensin-aldosterone system is closely related to impaired natriuresis in cirrhosis.[38] However, after administration of FK352 to cirrhotic patients, we observed an improvement in natriuresis and urine flow rate despite an increase in PRA and angiotensin II level. This suggests that adenosine 1 antagonism is unique in being able to counter the detrimental effects on the kidney of overactivity of the renin-angiotensin-aldosterone system without a deleterious effect on the peripheral vasculature.

Stimulation of adenosine 1 receptors leads to a decrease in cAMP via adenyl cyclase inhibition,[39] and antagonism of these receptors has been shown to inhibit this decrease in human glomeruli.[40] Therefore, adenosine 1 antagonism by FK352 may explain the observed increase in plasma cAMP levels. No effect of FK352 on peripheral catecholamine levels was observed, which may reflect a limited effect on systemic hemodynamics.

In conclusion, we have demonstrated efficacy and safety of a novel adenosine 1–specific antagonist in cirrhotic patients with ascites. Adenosine 1 antagonism offers a novel approach to the management of cirrhotic ascites and the spectrum of renal abnormalities found in cirrhosis. Further studies are required to assess its potential role in this condition.

References

1. Groszmann RJ. Hyperdynamic circulation in cirrhosis: a historical perspective. Hepatology 1994;20:1356–1358.
2. Henriksen JH. Cirrhosis: ascites and hepatorenal syndrome. Recent advances in pathogenesis. J Hepatol 1995;23(suppl 1):25–30.
3. Spielman WS, Thompson CI. A proposed role for adenosine in the regulation of renal hemodynamics and renin release. Am J Physiol 1982;242:F423–F425.
4. Balakrishnan VS, Coles GA, Williams JD. Effects of intravenous adenosine on renal function in healthy human subjects. Am J Physiol 1996;271:F374–F381.
5. Agmon Y, Dinour D, Brezis M. Disparate effects of adenosine A1 and A2 receptor agonists on intrarenal blood flow. Am J Physiol 1993;265:F802–F806.
6. Takeda M, Yoshitomi K, Imai M. Regulation of sodium bicarbonate cotransport in rabbit proximal convoluted tubule via adenosine A 1 receptor. Am J Physiol 1993;265:F511–F519.
7. Stiles GL, Adenosine receptors. J Biol Chem 1992;267:6451–6454.
8. Milani L, Merkel C, Gatta A. Renal effect of aminophylline in hepatic cirrhosis. Eur J Clin Pharmacol 1983;24:757–760.
9. Llach J, Gines P, Arroyo V, Salmeron JM, Gines A, Jimenez W, Gaya J, Rivera F, Rodes J. Effect of dipyridamole on kidney function in cirrhosis. Hepatology 1993;17:59–64.
10. Moreau R, Champigneulle B, Gaudin C, Poo JL, Kleber G, Bacq Y, Lebrec D. Effects of theophylline on hemodynamics and tissue oxygenation in patients with cirrhosis. J Hepatol 1992;15:323–329.
11. Forrest EH, Bouchier IAD, Hayes PC. Acute effect of low dose theophylline on the circulatory disturbances of cirrhosis. Gut 1997;40:139–144.
12. Fredholm BB. Are methylxanthine effects due to antagonism of endogenous adenosine? Trends Pharmacol Sci 1980;129–132.
13. Li Kam Wa TC, Freestone S, Samson RR, Jonhston NR, Lee MR. A comparison of the renal and neuroendocrine effects of two 5-hydroxytryptamine renal prodrugs in normal man. Clin Sci 1993;85:607–614.
14. Epstein M, ed. The kidney in liver disease. Baltimore, MD: Williams & Wilkins, 1988:3–72.
15. Martini GA, Baltzer G, Arndt H. Some aspects of circulatory disturbances in cirrhosis of the liver. Prog Liver Dis 1972;4:231–250.
16. Moreau R, Lee SS. Soupison T, Roche-Sicot J, Sicot C. Abnormal tissue oxygenation in patients with cirrhosis and liver failure. J Hepatol 1988;7:98–105.
17. Ohisalo JJ. Regulatory functions of adenosine. Med Biol 1987;65: 181–191.
18. Olsson RA, Pearson JD. Cardiovascular purinoceptors. Physiol Rev 1990;70:761–845.
19. Edlund A, Ohlsen H, Sollevi A. Renal effects of local infusion of adenosine in man. Clin Sci 1994;87:143–149.
20. Hall JE, Granger JP. Adenosine alters glomerular filtration control by angiotensin II. Am J Physiol 1986;250:F917–F923.
21. Paul S, Kurunwana B, Biaggioni I. Caffeine withdrawal: apparent heterologous sensitization to adenosine and prostacyclin actions in human platelets. J Pharmacol Exp Ther 1993;267:838–843.
22. Hasegawa M, Yamada S, Hirayama C. Fasting plasma caffeine level in cirrhotic patients: relationship to plasma levels of catecholamines and renin activity. Hepatology 1989;10:973–977.
23. Holz FG, Steinhausen M. Renovascular effects of adenosine receptor agonists. Renal Physiol 1987;10:272–282.
24. Kuan CJ, Herzer WA, Jackson EK. Cardiovascular and renal effects of blocking A1 adenosine receptors. J Cardiovasc Pharmacol 1993;21:822–828.
25. Kellet R, Bowmer CJ, Collis MG, Yates MS. Amelioration of glycerol-induced acute renal failure in the rat with 8-cyclopentyl-1,3-dipropylxanthine. Br J Pharmacol 1989;98:1066–1074.
26. Knight RJ, Bowmer CJ, Yates MS. The effects of 8-cyclopentyl-1,3-dipropylxanthine on E coli endotoxin–induced renal dysfunction (abstr). Br J Pharmacol 1992;106:18P.
27. Knight RJ, Collis MG, Yates MS, Bowmer CJ. Amelioration of cisplatin-induced acute renal failure with 8-cyclopentyl-1,3-dipropylxanthine. Br J Pharmacol 1991;104:1062–1068.
28. Barrett RJ, Wright KF. A selective adenosine A1 receptor antagonist attenuates renal dysfunction during controlled hypotension with adenosine in rats. Anesth Analg 1994;79:460–465.
29. Naranjo CA, Pontigo E, Valdenegro C, Gonzalez G, Ruiz I, Busto U. Furosemide-induced adverse reactions in cirrhosis of the liver. Clin Pharmacol Ther 1979;25:154–160.
30. Bernardi M, Treviasini F, Fornale L, Di Marco C, Gasbarrini A, Baraldini M, Ligabue A, Gasbarrini G. Renal sodium handling in cirrhosis with ascites: mechanisms of impaired naturetic response to reclining. J Hepatol 1994;21:1116–1122.
31. Madsen M, Pedersen EB, Danielsen H, Jensen LS, Sorensen SS. Impaired renal water excretion in early hepatic cirrhosis. Lack of relationship between renal water excretion and plasma levels of arginine vasopressin, angiotensin II and aldosterone after water loading. Scand J Gastroenterol 1986;21:749–755.
32. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Scholmerich J. Definition and diagnos-

tic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–176.
33. Brenner M, Schaer GL, Mallory DL, Suffredinin AF, Parillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. Chest 1990;98:170–179.
34. Deray G, Branch RA, Herzer WA, Ohnishi A, Jackson EK. Adenosine inhibits beta-adrenoceptor but not DBcAMP-induced renin release. Am J Physiol 1987;252:F46–F52.
35. Arend LJ, Thompson CI, Brandt MA, Spielman WS. Elevation of intrarenal adenosine by maleic acid decreases GFR and renin release. Kidney Int 1986;30:656–661.
36. Van Buren M, Bijlisma JA, Boer P, Van Rijn HJM, Koomans HA. Naturetic and hypotensive effect of adenosine-1 blockade in essential hypertension. Hypertension 1993;22:728–734.
37. Erley CM, Duda SH, Schlepckow S, Koehler J, Huppert PE, Strohmaier WL, Bohle A, Risler T, Osswald H. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int 1994;45:1425–1431.
38. Wong F, Sniderman K, Liu P, Blendis L. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. Gastroenterology 1997;112:899–907.
39. Burnatowska MA, Spielman WS. Effects of adenosine on cAMP production and cytosolic Ca^{2+} in cultured rabbit medullary thick limb cells. Am J Physiol 1991;260:C143–C150.
40. Toya Y, Umemura S, Iwamoto T, Hirawa N, Kihara M, Takagi N, Ishii M. Identification and characterization of adenosine A1 receptor cAMP system in human glomeruli. Kidney Int 1993;43:928–932.

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