Effects of TIPS on global end-diastolic volume and cardiac output and renal resistive index in ICU patients with advanced alcoholic cirrhosis

Andreas Umgelter,* Wolfgang Reindl,* Fabian Geisler,* Bernd Saugel,* Wolfgang Huber,* Hermann Berger,** Roland M Schmid*

* 2nd Medical Department, Klinikum rechts der Isar, Technical University of Munich, Germany
** Department of Interventional Radiology, Institute of Radiology, Klinikum rechts der Isar, Technical University of Munich, Germany

ABSTRACT

The transjugular porto-systemic stent-shunt (TIPS) reduces portal pressure in cirrhotic patients and is used as a nonsurgical treatment for refractory ascites, recurrent variceal hemorrhage or hepatorenal syndrome. There are concerns regarding a negative impact on cirrhotic cardiomyopathy and deterioration of hyperkinetic circulatory dysfunction. We analyzed a prospectively maintained database containing hemodynamic data on cirrhotic ICU patients. Hemodynamic monitoring was performed using transpulmonary thermodilution (PiCCO, Pulsion Medical Systems, Munich, Germany). Renal perfusion was assessed by Doppler ultrasound during studies of portal and TIPS perfusion before and after the procedure. Complete data sets of 8 patients (4 male, 4 female, age 60 years (52-67), Child-Pugh-Turcotte score 10 (8-12)) were available. After TIPS, there was a substantial increase of GEDVI (646 ml/m² (580-737) to 663 ml/m² (643-792); p=0.036) that was even more pronounced at 24 hours (716 ml/m² (663-821); P=0.012). CI increased from 3.3 L/min/m² (3.1-4.2) to 3.9 L/min/m² (3.6-5.3) (p=0.012) and 3.9 L/min/m² (3.7-5.2) (p=0.017), respectively. There was a significant decrease of renal RI from 0.810 (0.781-0.864) to 0.746 (0.710-0.798) (p=0.028) and a transient increase of fractional excretion of sodium. SVRI (1737 dyn·s/cm²/m² (1088 - 2115) vs. 1917 dyn·s/cm²/m² (1368-2177) was not significantly altered immediately after TIPS but decreased to 1495 dyn·s/cm²/m² (833-1765) at 24 hours (p=0.036)). There were no significant changes of mean arterial pressure (MAP). In conclusion, TIPS resulted in a pronounced increase of central blood volume. The observed hemodynamic effects are compatible with a preload driven increase of cardiac output and secondary decreases in SVRI and RI.


INTRODUCTION

The transjugular porto-systemic stent shunt (TIPS) is a non-surgical treatment for complications of portal hypertension. It has been established as a treatment for refractory variceal hemorrhage and refractory ascites. The most prominent side-effect is the development of hepatic encephalopathy that is responsive to treatment with osmotic laxatives in most of the cases.

As a consequence of portal hypertension, cirrhotic patients display specific circulatory disturbance consisting of splanchnic vasodilation, pooling of blood in the mesenteric system, decreased effective arterial blood volume and compensatory activation of endogenous vasopressor systems. Renal vasoconstriction results in retention of sodium and free water, formation of ascites, and, finally, functional renal failure termed hepatorenal syndrome.

A recent meta-analysis of data of individual patients treated with TIPS or paracentesis for refractory ascites suggested a survival benefit for the patients treated with TIPS. Stratification of patients according to severity of the underlying liver disease showed this survival benefit to be consisten-
tly present in all strata. As a means of reducing portal hypertension, TIPS has also been used successfully as a treatment for hepatorenal syndrome.3 There is some concern that TIPS could cause volume overload in patients possibly affected by cirrhotic cardiomyopathy.4 On the other hand, improving right-ventricular return could increase cardiac preload and thus ameliorate the effects of a reduced effective arterial blood volume. Thus, TIPS may be of particular interest in the hemodynamic management of cirrhotic intensive care patients.

We conducted this retrospective analysis of a prospectively maintained database of hemodynamic, laboratory and Doppler ultrasound measurements in cirrhotic ICU-patients to evaluate systemic and renal hemodynamic short-term effects of TIPS insertion.

METHODS

A database containing hemodynamic data of all patients monitored invasively in our intensive care unit has been maintained ever since the introduction of transpulmonary thermodilution as standard monitoring in 2002. Thermodilution measurements are routinely performed three times daily for calibration of the system and, additionally, before and after procedures thought to affect preload or arterial compliance, such as plasma expansion, introduction of vasopressor treatment, paracentesis or TIPS. Since Doppler ultrasound became available in our ICU in 2005, patients receiving TIPS also received renal Doppler examinations with determination of renal resistive index before and after the procedure in combination with Doppler evaluation of portal flow and TIPS-patency.

According to our standard protocols, transpulmonary thermodilution was performed using a commercially available system, which works as described elsewhere.5 Briefly, the system requires the presence of a central venous line and an arterial line tipped with a thermistor. Cold saline is used as an indicator. It is injected into the central venous line, passing through the right cardiac atrium and ventricle, the pulmonary vasculature and the left atrium and ventricle before appearing and being detected at the thermistor-tipped arterial line. From the area under the indicator curve, the mean appearance time and the downslope-time of the indicator curve, among others, cardiac output and global end-diastolic volume can be derived. All measurements where done in triplicate in a supine position with the pressure transducer zeroed at the mid-axillary line. Cardiac power index (CPI) was calculated as mean arterial pressure (MAP) * cardiac index (CI) / 451, arterial compliance (comp(a)) as stroke volume / (RRsys – RRdia) and pulse pressure index (PPI) as (RRsys – RRdia)/RRsys.

Doppler ultrasound was used to determine renal resistive index of intercolumnar arteries. All measurements were done by the same investigator (AU) immediately before the corresponding hemodynamic measurements before TIPS placement and 30 to 60min after completion of the TIPS procedure. Doppler examinations were done in triplicate at the cranial, middle and caudate poles of the kidneys. Renal Doppler examinations where available for 6 of 8 patients.

The TIPS procedure was performed as described by Rössle, et al.6 with some modifications. As all patients had central venous lines in place, introducers were inserted by the use of Seldinger technique. A coaxial puncture technique was used to establish a transhepatic track from the right hepatic vein to a portal vein. Portal pressure and porto-atrial gradient were measured and the intraparenchymal tract was dilated. A self-expandable stent (Wallstent, Boston Scientific, Ratingen, Germany) was inserted and calibrated to 8-10mm with balloon-dilatation to achieve a gradient < 12mmHg or less than 50% of the initial gradient.

Corresponding laboratory and clinical data were extracted from our hospitals mainframe database system and the ICU charts.

Statistics

Data are presented as median (25th percentile – 75th percentile). We used the Wilcoxon test for comparisons of paired data. All comparisons were two-tailed and significance was assumed for p < 0.05. All calculations were done with SPSS 16 for Mac. (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Clinical results

From 2003 to 2008 TIPS was successfully performed in 10 ICU-patients. Of these, 8 patients had invasive hemodynamic monitoring before and after the procedure. Baseline and demographic data of these patients is presented in table 1. None of these patients had received vasoactive or cardiotropic drugs or diuretics during for at least 48 hours before TIPS-insertion. Three patients were listed for a liver transplant. One of them died from sepsis with a pulmonary focus while still in the ICU. Two patients received an orthotopic liver transplant 18 and 53
Table 1. Patients’ baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>M/F</th>
<th>Age (years)</th>
<th>Child-class B/C</th>
<th>Child: Pugh-Turcotte-score</th>
<th>MELD-score</th>
<th>Serum bilirubin (µmol/L)</th>
<th>Serum creatinine (µmol/L)</th>
<th>INR</th>
<th>Serum sodium (mmol/L)</th>
<th>Hemoglobin (g/DL)</th>
<th>Platelets (G/L)</th>
<th>Cause of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4/4</td>
<td>60 (52-67)</td>
<td>4/4</td>
<td>10 (8-12)</td>
<td>17 (14-24)</td>
<td>30 (16-68)</td>
<td>154 (106-203)</td>
<td>1.6</td>
<td>134 (131-139)</td>
<td>9.2 (7.7-10.7)</td>
<td>108 (89-123)</td>
<td>Acute renal failure 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute on chronic liver failure 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variceal hemorrhage 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcoholic liver disease 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Refractory ascites 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recidivating variceal hemorrhage 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal failure 2</td>
</tr>
</tbody>
</table>

MELD: model of end-stage liver disease. INR: international normalized ratio.

Table 2. Hemodynamic effects of TIPS insertion.

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
<th>Before TIPS</th>
<th>After TIPS</th>
<th>p</th>
<th>24 hours</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (BPM)</td>
<td>86 (67-92)</td>
<td>98 (71-103)</td>
<td>0.025</td>
<td>90 (79-100)</td>
<td>0.017</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>90 (76-95)</td>
<td>94 (80-102)</td>
<td>0.183</td>
<td>85 (60-96)</td>
<td>0.310</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.3 (3.1-4.2)</td>
<td>3.9 (3.6-5.3)</td>
<td>0.012</td>
<td>3.9 (3.7-5.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>SVRI (dyn*s/cm²/m²)</td>
<td>1917 (1368-2177)</td>
<td>1737 (1088-2115)</td>
<td>0.484</td>
<td>1495 (833-1765)</td>
<td>0.036</td>
</tr>
<tr>
<td>GEDVI (mL/m²)</td>
<td>646 (580-737)</td>
<td>663 (643-792)</td>
<td>0.036</td>
<td>716 (663-821)</td>
<td>0.012</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>44.1 (35.0-57.4)</td>
<td>45.4 (37.0-69.9)</td>
<td>0.123</td>
<td>47.8 (40.1-57.3)</td>
<td>0.028</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>9 (4-13)</td>
<td>12 (6-13)</td>
<td>0.397</td>
<td>13 (9-18)</td>
<td>0.106</td>
</tr>
<tr>
<td>ELWI (mL/kg)</td>
<td>8 (6-10)</td>
<td>8 (6-10)</td>
<td>0.916</td>
<td>9 (6-13)</td>
<td>0.551</td>
</tr>
<tr>
<td>CPI (W/m²)</td>
<td>0.68 (0.62-0.79)</td>
<td>0.86 (0.75-0.97)</td>
<td>0.012</td>
<td>0.80 (0.69-0.85)</td>
<td>0.093</td>
</tr>
<tr>
<td>comp(a) (mL/mmHg)</td>
<td>1.05 (0.84-1.48)</td>
<td>1.09 (0.90-1.66)</td>
<td>0.123</td>
<td>1.25 (1.07-1.62)</td>
<td>0.012</td>
</tr>
<tr>
<td>PPI</td>
<td>0.55 (0.47-0.66)</td>
<td>0.54 (0.52-0.59)</td>
<td>0.674</td>
<td>0.55 (0.41-0.58)</td>
<td>0.123</td>
</tr>
<tr>
<td>RI</td>
<td>0.810 (0.781-0.864)</td>
<td>0.746 (0.710-0.798)</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI corr</td>
<td>0.810 (0.786-0.837)</td>
<td>0.766 (0.739-0.794)</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


days after TIPS placement, respectively. One of them died from recurrent hepatocellular carcinoma one year later, the other is alive and well 18 months after transplantation. Another patient is still alive 4 years after TIPS insertion, but now suffers from refractory ascites despite a persistently functional TIPS. Two more patients are alive 10 and 12 months after TIPS insertion. Two more patients died 60 and 108 days after TIPS.

Laboratory parameters

24 hours after TIPS, serum bilirubin increased significantly from 30 (16-68) µmol/L to 35 (20-78) µmol/L. There were no significant changes in INR or serum creatinine. Fractional excretion of sodium significantly rose from 0.11% (0.06-0.24) to 0.20% (0.12-0.61) 6 hours after TIPS but returned to values not significantly different from baseline at 24 hours.

Hemodynamic and Doppler parameters

TIPS placement resulted in a significant reduction of portal pressure from 28 mmHg (27-32) to 22 mmHg (20-25) (p = 0.011) and of porto-caval pressure gradient from 19 mmHg (15-25) to 10 mmHg (6-12) (p=0.012). Hemodynamic parameters before
and after TIPS insertion are reported in table 2 and presented in figure 1. Immediately after TIPS insertion, global end-diastolic volume index (GEDVI), heart rate (HR), cardiac index (CI) and cardiac power index increased significantly and remained elevated at 24 hours, compared to baseline. In addition, at 24 hours, there was a reduction in systemic vascular resistance index (SVRI) and an increase in stroke volume index (SVI). There were no changes in MAP, central venous pressure (CVP), PPI or extravascular lung water index (ELWI). Renal resistance index (RI) decreased significantly. As there was a concomitant increase in HR, possibly affecting RI, a correction for heart rate was performed according to Mostbeck. The values obtained (RI corr) still showed a significant decrease after TIPS.

**DISCUSSION**

The main findings of this study are an immediate increase of global end-diastolic volume after TIPS, associated with increased stroke volume index, cardiac output and cardiac power index, and a decrease in renal resistance index not explained by changes in heart rate or pulse pressure index.

Acute increases of cardiac output, and pulmonary arterial occlusion pressure and decreases in SVRI after TIPS have been previously described. These changes have been interpreted as evidence for a deterioration of the hyperdynamic circulatory derangement found in advanced cirrhosis. According to the hypothesis of arterial vasodilation in portal hypertension, vasodilation in cirrhotic circulatory disturbance occurs primarily in the splanchnic system, whereas vasoconstriction is prominent in other, namely the renal, vascular beds. Deterioration of cirrhotic circulatory disturbance would therefore imply an increase in splanchnic vasodilation with more volume retention in the abdomen and a further reduction in effective arterial blood volume. Portal hypertension as the initiating event of splanchnic vasodilation, however, is reduced after TIPS insertion. Therefore, deterioration of vasodilation ought to be due to additional factors, for example increased shunting of vasodilators such as nitric oxide from the splanchnic system to the systemic circulation. In contrast, reduction of portal pressure could diminish production of vasodilators and, as a consequence, would reduce compensatory activation of vasoconstrictor systems and, therefore, vasoconstriction in other vascular beds, e.g. the renal vasculature. This hypothesis is supported by the finding of reduced plasma-levels of vasoconstrictors after TIPS. Stable over-all peripheral vascular resistance could be a result of opposed changes of similar magnitude in different vascular beds.

In cirrhotic circulatory dysfunction, in addition to arterial vasodilation and splanchnic vasopressor hyporesponsiveness, there is also effective hypovolemia with a reduction of intrathoracic blood volume. It has been asserted that this relative hypovolemia is not amenable to plasma expansion. Our previous findings indicate that central blood volume in patients with advanced cirrhosis can be increased by plasma expansion resulting in increases in cardiac output, SVI and a reduction in compensatory peripheral vasoconstriction. This would suggest a preload-responsive state of cardiac output in cirrhotic patients. An important issue, however, is the hemodynamic relevance of cirrhotic cardiomyopathy. Myocardial function and morphology in cirrhotic patients are clearly altered. Apart from electrophysiological changes, echocardiographic parameters of diastolic dysfunction have been described and case reports have borne out concerns about cardiac volume overload after TIPS. In our patients we did not observe a case of clinically ob-
vious pulmonary edema and extravascular lung water remained unaltered. The small size of our 
sample means that we cannot exclude such effects to 
 occur in a fraction of patients after TIPS.

The increase in cardiac power index upon increa-
sing preload after TIPS observed in our cohort sug-
gests that myocardial function was not deteriorating 
in these patients. The acute elevation of GEDVI seen 
in our patients rather indicates an increase of pre-
load after TIPS observed in our cohort sug-

Baseline renal RI in our patients was in the expec-
ted range for patients with advanced cirrhosis.21 Re-
duced CI in the face of deteriorating arterial 
vaso-dilation is a risk factor for the development of 
heporenal failure due to increasing renal vasocon-
striction.22 The reduction of RI with no change in 
MAP or PPI and despite an increasing arterial com-
pliance in our patients suggests improving renal per-
fusion. An increase of fractional excretion of sodium 
also pointed to an improved renal circulation.

Apart from the small sample size, this study has 
several limits. It represents a retrospective analysis, 
which may, in principle, affect reproducibility of data. 
Because the source database was prospectively main-
tained with defined time-points of measurements, we 
believe there is a low likelihood of bias. Doppler exa-
minations were only available for the last six pa-
tients due to the later introduction of routine 
Doppler examinations in our intensive care unit. In 
addition, only patients with alcoholic cirrhosis, who 
represent the vast majority of our patients, are pre-
sent in this study. Alcohol disease may affect cardiac 
function and it has been argued that alcoholic cardio-
myopathy may additionally impair cardiac function 
in patients with alcoholic cirrhosis. In contrast, we 
did not find evidence of impaired cardiac function, as 
ELWI remained stable upon increased preload. The 
results, however, may not be generalized to patients 
with other causes of cirrhosis.

Despite these obvious limits, we believe that the 
observed changes argue against the notion that 
TIPS aggravates the hyperkinetic circulatory distur-
bance of cirrhotic patients. Also, we found no 
evidence for cirrhotic cardiomyopathy being a limit 
to compensatory augmentation of CI in the face of 
deteriorating vasodilation. Instead, the observed in-
crease in CI may be interpreted as a result of impro-
ved cardiac filling with secondary relaxation of 
vasoconstriction in the renal vasculature.

In conclusion, our observations of hemodynamic 
changes after TIPS in patients with advanced cirr-

ABBREVIATIONS

- **CI.** Cardiac index.
- **comp(a).** Arterial compliance.
- **CPI.** Cardiac power index.
- **CVP.** Central venous pressure.
- **ELWI.** Extra-vascular lung water index.
- **GEDVI.** Global end-diastolic volume index.
- **HR.** Heart rate.
- **INR.** International normalized ratio.
- **MAP.** Mean arterial pressure.
- **MELD.** Model of end-stage liver disease.
- **PPI.** Pulse pressure index.
- **RI.** Renal resistance index.
- **RI (corr).** Renal resistance index, corrected for HR.
- **RR(sys).** Systolic blood pressure.
- **RR (dia).** Diastolic blood pressure.
- **SVI.** Stroke volume index.
- **SVRI.** Systemic vascular resistance index.
- **TIPS.** Transjugular porto-systemic stent-shunt.

REFERENCES

JHJR. Peripheral arterial vasodilation hypothesis: a propos-

2. Salerno F, Cammà C, Enea M, Rössle M, Wong F. Transjugu-
lar intrahepatic portosystemic shunt for refractory ascites: 
a meta-analysis of individual patient data. Gastroenterology 2007; 133(3): 825-34.

W, et al. Transjugular intrahepatic portosystemic shunt in 
hepatorenal syndrome: effects on renal function and vas-

4. Braverman AC, Steiner MA, Picos D, White H. High-output 
congestive heart failure following transjugular intrahe-

5. Sakka SG, Ruhl CC, Pfeiffer UJ, Beale R, McLuckie A, Rein-
hart K, et al. Assessment of cardiac preload and extravas-
cular lung water by single transpulmonary thermodilution.

JM, et al. The Transjugular Intrahepatic Portosystemic 
Stent-Shunt Procedure for Variceal Bleeding. NEJM 1994; 

7. Mostbeck GH, Gössinger HD, Mallek R, Siostronzeck P, Schnei-
der B, Tscholakoff D. Effect of heart rate in doppler 
measurements of resistive index in renal arteries. Radiolo-
gy 1990; 175(2): 511-3.


