Effect of transjugular intrahepatic portosystemic shunt on pulmonary gas exchange in patients with portal hypertension and hepatopulmonary syndrome

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Abstract

AIM: To assess the impact of transjugular intrahepatic portosystemic shunt (TIPS) on pulmonary gas exchange and to evaluate the use of TIPS for the treatment of hepatopulmonary syndrome (HPS).

METHODS: Seven patients, three of them with advanced HPS, in whom detailed pulmonary function tests were performed before and after TIPS placement at the University of Alabama Hospital and at the Hospital Clinic, Barcelona, were considered.

RESULTS: TIPS patency was confirmed by hemodynamic evaluation. No changes in arterial blood gases were observed in the overall subset of patients. Transient arterial oxygenation improvement was observed in only one HPS patient, early after TIPS, but this was not sustained 4 mo later.

CONCLUSION: TIPS neither improved nor worsened pulmonary gas exchange in patients with portal hypertension. This data does not support the use of TIPS as a specific treatment for HPS. However, it does reinforce the view that TIPS can be safely performed for the treatment of other complications of portal hypertension in patients with HPS.

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Key words: Portal hypertension; Transjugular intrahepatic portosystemic shunt; Pulmonary gas exchange; Hepatopulmonary syndrome

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INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) has been used increasingly in patients with cirrhosis complicated by bleeding varices and refractory ascites[1]. Recently, TIPS has also been proposed as a potential treatment for pulmonary vasodilatation associated with cirrhosis, the so-called hepatopulmonary syndrome (HPS)[2]. However, both hemodynamic and metabolic effects of TIPS have been widely studied, little data exists on the effects of TIPS on pulmonary gas exchange in patients with portal hypertension.

HPS occurs when intrapulmonary vasodilatation causes abnormal pulmonary gas exchange in the setting of liver disease[8]. The abnormalities in pulmonary gas exchange result from microvascular dilatation and involve varying degrees of ventilation-perfusion imbalance, oxygen diffusion limitation (diffusion-perfusion defect), and increased intrapulmonary shunting[9]. Although the natural history of HPS is poorly understood, pulmonary gas exchange abnormalities are generally progressive, even in the setting of clinically stable hepatic dysfunction[10]. Currently, liver transplantation is the only therapeutic approach that can resolve HPS. However, perioperative mortality remains high (16-38% within 1 year) and appears to be greatest in those with more advanced HPS[11,12].

HPS has been described most commonly in patients...
with cirrhosis of the liver, although it has also been reported in patients with severe acute hepatitis and in non-cirrhotic portal hypertension\textsuperscript{[13-15]}. These findings suggest that portal hypertension plays an important role in the development of intrapulmonary vasodilatation and in the occurrence of HPS. TIPS, by correcting portal hypertension\textsuperscript{[11]}, could improve HPS. Indeed, TIPS may be an attractive alternative therapeutic option in selected patients with advanced HPS who are not transplant candidates or in whom liver function is well preserved, particularly if HPS is of sufficient severity to increase transplant mortality or if the waiting time for transplantation is expected to be prolonged. However, the small number of case reports published to date have had variable clinical features and results, and the majority TIPS placement was performed for an acute indication other than HPS\textsuperscript{[2-7]}. Therefore, it is difficult to determine if TIPS specifically improves HPS. In addition, TIPS is known to further exacerbate the hyperdynamic circulation present in patients with cirrhosis and portal hypertension, a fact that might trigger or increase pulmonary vasodilatation and adversely affect pulmonary gas exchange\textsuperscript{[16-19]}.

Accordingly, in the present study, we aimed to assess the impact of TIPS on pulmonary gas exchange in patients with portal hypertension and to evaluate the use of TIPS for the treatment of HPS.

**MATERIALS AND METHODS**

Patients submitted to TIPS treatment at the University of Alabama Hospital and at the Hospital Clinic, Barcelona, were reviewed and the characteristics of patients in whom pulmonary function was evaluated was recorded in a period of less than 6 mo before TIPS placement and no more than 1 year after, were included. In three of these patients, TIPS was placed specifically for the treatment of HPS. The diagnosis of HPS was made on the basis of established criteria: the presence of an increase of alveolar-arterial oxygen difference (AaPO\textsubscript{2} >15 mmHg); with or without hypoxemia; and evidence of pulmonary vascular dilatation by means of contrast-enhanced echocardiography and/or nuclear isotope lung perfusion scanning, in the context of liver disease\textsuperscript{[20,21]}. The presence of mild intrinsic cardiopulmonary disease was not considered as an exclusion criterion for the diagnosis of HPS\textsuperscript{[22,23]}.

Before TIPS placement, all patients underwent measurements of forced spirometry, plethysmography, and single-breath carbon monoxide diffusing capacity (DL\textsubscript{CO}) after correcting appropriately for hemoglobin concentration. Arterial blood gases were collected while breathing room air in the upright position. The AaPO\textsubscript{2} was calculated according to the alveolar gas standard equation using 0.8 as the standard respiratory exchange ratio. Arterial blood gases were repeated after a 20-min period of 100% oxygen breathing in the upright position in patients with HPS.

The TIPS procedure was similar in both institutions and has been previously described\textsuperscript{[11]}. After TIPS, patients underwent close follow-up with US-Doppler and hemodynamic evaluation of TIPS patency. Clinical and biochemical evolution, pulmonary gas exchange analysis, and systemic and pulmonary hemodynamics after TIPS placement were recorded for at least 1 mo following TIPS.

**RESULTS**

Pulmonary gas exchange was assessed before and after TIPS placement in seven patients. Three patients had HPS and the specific indication for TIPS in each of these patients was treatment of HPS. The remaining four patients had no HPS, but one of them had mild hypoxemia due to a moderate obstructive ventilatory pattern, and the indication for TIPS in these patients was variceal bleeding in three and refractory ascites in one. Demographic and clinical data are summarized in Table 1. TIPS substantially reduced the portal pressure gradient (PPG) (from 15±2 to 5±2 mmHg). In each case, the PPG immediately after TIPS was below 12 mmHg. In addition, during follow-up, TIPS patency, defined as a PPG <12 mmHg, was confirmed by hemodynamic evaluation. The clinical course of pulmonary function in patients without HPS was stable during all the study period. Pulmonary function tests and gas exchange data before and at least 3 mo after TIPS placement in patients with normal gas exchange prior to placement are shown in Table 2. As shown, TIPS neither influenced arterial blood gases nor pulmonary function tests in these patients.

Individual data of patients with HPS are shown in Table 3. All patients had advanced HPS as evidenced by PaO\textsubscript{2}<60 mmHg with low PaCO\textsubscript{2} values; only Patient #2 responded favorably to 100% oxygen administration. Patients #1 and #2 had a mild restrictive ventilatory pattern possibly related to a coexistent diffuse interstitial

![Table 1 Demographic and clinical characteristics (mean±SD, n)](image-url)}
lung disease (Patient #1) and unilateral pleural fibrosis (Patient #2), respectively. Pulmonary angiography excluded the presence of arterio-venous communications. Ventilation-perfusion (V/A/Q) studies in these two patients, using the multiple inert gas elimination technique \(^{[23]}\), was consistent with HPS, showing increased intrapulmonary shunt (43% and 11% of cardiac output) with a mild to moderate degree of V/A/Q mismatch, characterized by areas with low V/A/Q units (6.4% and 0.1% of cardiac output). All three patients exhibited a very severely reduced diffusing capacity (<25% predicted). Transient improvement in arterial oxygenation was observed in only one patient early after TIPS placement (Patient #1) but this was not maintained 4 mo later despite TIPS patency. In the other two patients, no improvement in gas exchange was observed early after TIPS and progressive deterioration in arterial oxygen saturation was evident at 4 mo in Patient #2 and at 4 wk in Patient #3 after TIPS. Patient #1 was excluded for liver transplantation because of the potential coexistence of diffuse interstitial pulmonary disease and severe hypoxemia with a poor response to 100% oxygen breathing. He died of progressive deterioration of pulmonary, hepatic, and renal function. Patient #2 was transplanted, 8 mo after TIPS placement. At the time of liver transplantation, he had persistent severe oxygenation abnormalities. Ten months after orthotopic liver transplant (OLT), pulmonary gas exchange was markedly improved with normal arterial oxygenation and contrast-enhanced echocardiography confirmed resolution of intrapulmonary vasodilatation. Patient #3 was excluded for liver transplantation due to severe hypoxemia. Subsequently, she developed progressive hypoxemia 4 wk after TIPS and died of multisystem organ failure one week later.

**DISCUSSION**

Portal hypertension is characteristically associated with a hyperkinetic circulation reflected by an increased cardiac output and splanchnic and peripheral vasodilatation \(^{[23]}\). A number of mechanisms contribute to these hemodynamic changes including increased bioavailability of vasodilators, such as nitric oxide \(^{[23]}\). HPS is most commonly observed in the setting of portal hypertension and likely appears to result from a disequilibrium between vasodilator and vasoconstrictor factors in the pulmonary microcirculation. Increased production of nitric oxide has also been proposed as one major determinant of pulmonary vascular dilatation in human HPS \(^{[23]}\). However, whether the same mechanisms that drive the splanchnic and peripheral vasodilatation are operative in the pulmonary microvasculature in HPS is still unknown.

Since HPS is associated with the presence of portal hypertension, portal pressure reduction through TIPS placement may be a useful therapeutic alternative. Till date, six case reports have evaluated the effects of TIPS on gas exchange in HPS \(^{[2–7]}\). Surprisingly, five demonstrated some

### Table 2 Pulmonary gas exchange before and after TIPS placement in patients without HPS (mean±SD)

| Patients | Pre-TIPS | Post-TIPS |
|----------|----------|-----------|
| PaO\(_2\) (mmHg) | 95±16 | 95±27 |
| PaCo\(_2\) (mmHg) | 29±16 | 31±17 |
| AaPO\(_2\) (mmHg) | 18±12 | 18±20 |
| FEV\(_1\) (% pred) | 72±9 | 74±15 |
| FVC (% pred) | 76±6 | 80±12 |
| FEVI/FVC | 75±10 | 76±18 |
| DLCO (mL/(min×mmHg)) | 22±4 | 20±5 |
| DLCO (% pred) | 67±13 | 63±19 |

Pa\(_2\): partial pressure of arterial oxygen; PaCo\(_2\): partial pressure of arterial carbon dioxide; AaPO\(_2\): alveolar to arterial oxygen partial pressure gradient; FEV\(_1\): forced expiratory volume at 1 s; FVC: forced vital capacity; FEVI/FVC: ratio of forced expiratory volume at 1 s to forced vital capacity; DL\(_{50}\)C: single-breath carbon monoxide diffusing capacity.

### Table 3 Pulmonary gas exchange and hemodynamics before and after TIPS placement in patients with HPS

| Patients | Pre-TIPS | Post-TIPS <1 mo | Post-TIPS >4 mo |
|----------|----------|----------------|----------------|
| FEV\(_1\) (% pred) | #1 | #2 | #3 | #1 | #2 | #3 | #1 | #2 | #3 |
| 69 | 77 | 100 | 58 | 61 | 31 | 33 | 34 |
| 66 | 77 | 113 | 31 | 27 | 38 | 26 | 34 |
| 77 | 80 | 82 | 53 | 69 | 71 | 87 | 73 |
| 68 | 70 | 83 | 32 | 59 | 28 | 28 | 35 |
| 27 | 28 | 35 | 88 | 86 | 78 |
| 88 | 64 | 606 | 63 | 64 | 15.9 | 18 | 1.5 | 18 |
| 49 | 41 | 11 | 32 | 40 | 22 | 3 | 3 | 3 |
| 773 | 415 | 11 | 21 | 22 | 8 | 38 | 18 |
| 8.3 | 10.4 | 6.47 | - | 11 | 7.8 | 105 | 11.3 |
| 14 | 11 | 19 | 11 | 11 | 22 | 18.5 | 11 |
| 5 | 4 | 3 | 7 | 2.5 | 19 | 8.5 | 2.5 |
| 17 | 12 | 16 | 7 | 8.5 | 3 | 10.5 | 8.5 |

FEV\(_1\): forced expiratory volume at 1 s; FVC: forced vital capacity; TLC: total lung capacity; DL\(_{50}\)C: single-breath carbon monoxide diffusing capacity; PaO\(_2\): partial pressure of arterial oxygen; PaCo\(_2\): partial pressure of arterial carbon dioxide; AaPO\(_2\): alveolar to arterial oxygen partial pressure gradient; PP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; Q\(_{T}\): cardiac output; PP: portal pressure; IVCP: inferior vena cava pressure; PPG: portocaval pressure gradient.
degree of improvement in oxygenation. However, short-term (<1 mo) duration of follow-up in two patients\(^\text{[2,3]}\) and the presence of coexistent hepatic hydrothorax in the third one\(^\text{[4]}\) limit the evaluation of the utility of TIPS for hypoxemia in these cases. In two other reports\(^\text{[5,4]}\), with a longer follow-up (>7 mo), arterial desaturation improved after TIPS and in one of these, a 11-year-old female with biliary atresia, gas exchange improvement was associated with a remarkable reduction in intrapulmonary shunt\(^\text{[4]}\). In the sixth report\(^{[7]}\), TIPS failed to improve arterial hypoxemia in one patient. Altogether these reports suggest that portal pressure reduction per se does not consistently improve pulmonary gas exchange in HPS.

Portal pressure reduction after TIPS is also associated with an exacerbation of the hyperdynamic circulatory state, an effect that persists for at least 3 mo following TIPS placement\(^{[6-9]}\). During this time, pulmonary vascular resistance may also decline\(^{[17,18,23]}\). The mechanisms by which TIPS accentuate the hyperdynamic circulation are not well understood but may involve porto-systemic shunting of vasoactive substances through the TIPS which alter NO production\(^{[17,26-28]}\). The net result could enhance pulmonary vasodilation, thereby resulting in the development and/or worsening of HPS. In two of our patients with HPS who underwent TIPS, we confirmed obviously decreased systemic and pulmonary vascular resistance early after placement. Despite these hemodynamic changes, arterial oxygenation did not significantly deteriorate. In addition, in our four other patients without HPS who underwent successful TIPS, no changes in gas exchange were shown following TIPS placement. These findings complement and extend the findings of prior reports and support that the exacerbation of the hyperdynamic state following TIPS placement is not associated with arterial oxygenation worsening.

The portal pressure gradient (PPG) was reduced below 10 mmHg in each of our patients who underwent TIPS for HPS. Despite this, none of them had a sustained improvement in arterial blood gases. One patient did have a transient improvement in arterial oxygenation early after TIPS placement. Conceivably, one explanation for this improvement could be improved ventilation-perfusion matching induced by a rise in cardiac output resulting in increased blood flow, selective redistribution to the upper lobes of the lung, where vasodilation is typically less severe in HPS. A similar mechanism may have been operative in the study by Selim et al\(^{[6]}\) where oxygenation improved after TIPS in association with a rise in cardiac output despite significant persistent intrapulmonary shunting. Alternatively, the increased cardiac output may improve \(\text{PaO}_2\) through increased mixed venous \(\text{PO}_2\) other things being equal. Our study and patients were different from prior case reports in that our group represented patients who specifically underwent TIPS for HPS. In four of the six prior reports, another acute indication for TIPS was present, including variceal bleeding and hepatic hydrothorax. The presence and resolution of other major complications of portal hypertension could have influenced favorably arterial blood gases in these cases.

In addition, our patients had more severe gas exchange abnormalities than those in prior studies and it is unknown whether or not the severity of pulmonary vasodilation may modulate the response to TIPS. Finally, our findings are clearly different from the report by Paramesh et al\(^{[7]}\), where TIPS placement resulted in a sustained and dramatic improvement in both pulmonary vasodilatation and arterial oxygenation. However, this case involved a child with biliary atresia and whether pathophysiologic mechanisms and responses to portal decompression in this setting are applicable to adults with other causes of liver disease is unknown\(^{[3]}\).

In summary, our findings suggest that treatment with TIPS in patients with portal hypertension has no deleterious effects on pulmonary gas exchange, despite coexisting exacerbation of the hyperdynamic circulatory state. However, portal decompression with TIPS as a specific therapy for HPS is ineffective. This data supports the use of TIPS in patients with HPS for the treatment of other accepted indications for TIPS, but not as a specific therapy to improve arterial oxygenation defects in HPS.

**REFERENCES**

1. Casado M, Bosch J, García-Pagán JC, Bru C, Bañeres R, Bandi JC, Escorsell A, Rodríguez-Láz JM, Gilabert R, Feu F, Schorlemmer C, Echenagusia A, Rodés J. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. *Gastroenterology* 1998; 114: 1296-1303
2. Riegler JL, Lang KA, Johnson SP, Westerman JH. Transjugular intrahepatic portosystemic shunt improves oxygenation in hepatopulmonary syndrome. *Gastroenterology* 1995; 109: 978-983
3. Lasch HM, Fried MW, Zacks SL, Odell P, Johnson MW, Gerber DA, Sandhu FS, Fair JH, Shrestha R. Use of transjugular intrahepatic portosystemic shunt as a bridge to liver transplantation in a patient with severe hepatopulmonary syndrome. *Liver Transpl* 2001; 7: 147-149
4. Selim KM, Akriviadis EA, Zuckerman E, Chen D, Reynolds TB. Transjugular intrahepatic portosystemic shunt: a successful treatment for hepatopulmonary syndrome. *Am J Gastroenterol* 1998; 93: 455-458
5. Allgaier HP, Haag K, Ochs A, Hausentein KH, Jeserich M, Krause T, Heilmann C, Gerok W, Rossle M. Hepatopulmonary syndrome: successful treatment by transjugular intrahepatic portosystemic shunt (TIPS) (letter). *J Hepatol* 1995; 23: 102-105
6. Corley DA, Scharschmidt B, Bass N, Somberg K, Gold W. Lack of efficacy of TIPS for hepatopulmonary syndrome. *Gastroenterology* 1997; 113: 728-730
7. Paramesh AS, Husain SZ, Schneider B, Guller J, Tokat I, Gondolesi GE, Moyer S, Emre S. Improvement of hepatopulmonary syndrome after transjugular portosystemic shunting: case report and review of literature. *Pediatric Transplant* 2003; 7: 157-162
8. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J* 2004; 24: 861-880
9. Fallon MB, Abrams GA. Pulmonary dysfunction in chronic liver disease. *Hepatology* 2000; 32: 859-865
10. Martínez-Pallí G, Barberà JA, Visa J, Rimola A, Paré JC, Roca J, Navasa M, Rodés J, Rodriguez-Roisin R. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol* 2001; 34: 651-657
11. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality
in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* 2003; 37: 192-197

12 **Krowka MJ**, Porayko MK, Plevak DJ, Pappas SC, Steers JL, Krom RA, Wiesner RH. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc* 1997; 72: 44-53

13 **Babbs C**, Warne TW, Haboubi NY. Non cirrhotic portal hypertension with hypoxaemia. *Gut* 1988; 29: 129-131

14 **De BK**, Sen S, Biswas PK, Mandal SK, Das D, Das U, Guru S, Bandyopadhyay K. Occurrence of hepatopulmonary syndrome in Budd-Chiari syndrome and the role of venous decompression. *Gastroenterology* 2002; 122: 897-903

15 **Abrams GA**, Fallon MB. The hepatopulmonary syndrome. *Clin Liver Dis* 1997; 1: 185-200, xiii

16 **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: 129-132

17 **Rodriguez-Laiz JM**, Banares R, Echenagusia A, Casado M, Camunez F, Perez-Roldan F, de Diego A, Cos E, Clemente G. Effects of transjugular intrahepatic portosystemic shunt (TIPS) on splanchnic and systemic hemodynamics, and hepatic function in patients with portal hypertension. Preliminary results. *Dig Dis Sci* 1995; 40: 2121-2127

18 **Van der Linden P**, Le Moine O, Ghysels M, Ortiz H, Devière J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. *Hepatology* 1996; 23: 982-987

19 **Francois E**, Garcia-Pagan JC, Bru C, Feu F, Gilsalbert R, Escorsell A, Bosch J, Rodes J. Effects of percutaneous infrahepatic portosystemic shunt on splanchic and systemic hemodynamics in patients with portal hypertension. *Gastroenterol Hepatol* 1997; 20: 11-14

20 **Martinez G**, Barberá JA, Navasa M, Roca J, Visa J, Rodriguez-Roisin R. Hepatopulmonary syndrome associated with cardiorespiratory disease. *J Hepatol* 1999; 30: 882-889

21 **Krowka MJ**. Caveats concerning hepatopulmonary syndrome. *J Hepatol* 2001; 34: 756-758

22 **Roca J**, Wagner PD. Contribution of multiple inert gas elimination technique to pulmonary medicine. I. Principles and information content of the multiple inert gas elimination technique. *Thorax* 1994; 49: 815-824

23 **Bosch J**, Garcia-Pagán JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol* 2000; 32: 141-156

24 **Cremona G**, Higenbottam TW, Mayoral V, Alexander G, Demonchaux E, Boirland C, Roe P, Jones GJ. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J* 1995; 8: 1883-1885

25 **Lotterer E**, Wegert A, Fleig WE. Transjugular intrahepatic portosystemic shunt: short term and long-term effects on hepatic and systemic hemodynamics in patients with cirrhosis. *Hepatology* 1999; 29: 632-639

26 **Bernadich C**, Bandi JC, Melin P, Bosch J. Effects of F-180, a new selective vasoconstrictor peptide, compared with terlipressin and vasopressin on systemic and splanchnic hemodynamics in a rat model of portal hypertension. *Hepatology* 1997; 26: 262-267

27 **Jalan R**, Damink SO, Deutz N, Redhead D, Lee A. Increased cerebral and peripheral vasodilation, and whole body nitric oxide (NO) production after insertion of a transjugular intrahepatic portosystemic stent-shunt (TIPS) in patient with cirrhosis. *J Hepatol* 2002; 36: A178:55

28 **Colombatto 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

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