

# Diagnosis of Portopulmonary Hypertension in Candidates for Liver Transplantation: A Prospective Study

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Portopulmonary hypertension represents a major risk factor for transplantation; therefore, preoperative detection is crucial. The aims of this study were to determine (1) whether Doppler echocardiography performed at evaluation is a reliable tool for detecting portopulmonary hypertension and (2) the incidence of acquired portopulmonary hypertension profile after evaluation. One hundred sixty-five patients had Doppler echocardiography and right heart catheterization at evaluation over a 9-year period. All patients had a prospective follow-up, and the results of catheterization at evaluation were compared with those obtained at the time of transplantation. Seventeen of 165 patients met the criteria for portopulmonary hypertension on Doppler echocardiography. Portopulmonary hypertension was confirmed by catheterization in 10 patients and ruled out in 7. There were no false negatives for echocardiography. Mean pulmonary artery pressure was significantly higher during the initial phase of transplantation than at evaluation ( $17.8 \pm 4.3$  vs.  $20.3 \pm 5.5$  mm Hg, respectively,  $P < .0001$ ), and there was no significant correlation between values obtained at these 2 time points. Three patients showed to have acquired portopulmonary hypertension profile while waiting for a graft within time intervals ranging from 2.5 to 5 months. In conclusion, Doppler echocardiography is a highly sensitive tool for detecting portopulmonary hypertension. However, because this technique has a poor positive predictive value, right heart catheterization is recommended for confirming portopulmonary hypertension. In addition, the absence of portopulmonary hypertension at evaluation does not exclude the occasional occurrence of acquired portopulmonary hypertension profile after listing. (HEPATOLOGY 2003;37:401-409.)

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**P**ulmonary hypertension associated with portal hypertension, the so-called *portopulmonary hypertension*, is a rare complication of cirrhosis. When severe, this condition is a major risk factor for transplantation because, in most cases, patients are at best partially

Abbreviations: MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

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responsive to medical therapies.<sup>1</sup> If it is impossible to lower mean pulmonary artery pressure below 40 to 50 mm Hg during transplantation procedure, any significant hemodynamic changes, such as those observed at the time of caval clamping and reperfusion of the graft, may result in irreversible cardiac arrest, especially if right ventricular function is impaired.<sup>2</sup> As a consequence, many authors consider that severe portopulmonary hypertension (*i.e.*, mean pulmonary artery pressure [MPAP] above 40 mm Hg) represents a contraindication for liver transplantation because it would carry an unacceptable mortality rate.<sup>3</sup>

Because portopulmonary hypertension is frequently asymptomatic until mean pulmonary pressure exceeds 40 mm Hg, most authors recommend systematic screening at evaluation. Several studies have suggested that Doppler echocardiography, when performed during pretransplantation evaluation, is a useful noninvasive tool to document or exclude portopulmonary hypertension,<sup>4-6</sup> even though this technique carries a significant proportion of

false positives.<sup>5,6</sup> However, in these studies, the results of Doppler echocardiography at the time of pretransplantation evaluation have been compared with those of catheterization at the time of surgery. It is likely that comparing different techniques used at different time points, either with or without general anesthesia, generates significant bias. In addition, because of prolonged time intervals between listing and transplantation (several months in most cases), it can be anticipated that some patients may develop portopulmonary hypertension while awaiting a donor, a risk that has not been assessed in previous studies.

This prospective study was designed to perform Doppler echocardiography and right heart catheterization under the same conditions at the time of pretransplantation evaluation and to compare these results with those of catheterization during surgery in a consecutive series of cirrhotic patients. In this study, we used a cut-off value of 30 mm Hg for systolic pulmonary artery pressure on Doppler echocardiography for detecting pulmonary hypertension at an early stage.

## Patients and Methods

From April 1993 to August 2001, 165 consecutive patients who were evaluated for liver transplantation and for whom transvenous liver biopsy was needed were prospectively included in this study. In this population, cirrhosis had been suspected on a set of clinical manifestations and chemical abnormalities and/or demonstrated by previous histologic examination. Indications for transvenous liver biopsy were either the absence of previous histologic demonstration of cirrhosis or the assessment of ongoing alcoholic liver injury. These 165 patients were part of the 416 patients with chronic liver disease (39%) who have been evaluated at our center during the study period.

These patients were 116 males and 49 females. Mean age was  $48 \pm 8$  years (range 20 to 63 years). Indications for liver transplantation were alcoholic cirrhosis in 58, hepatitis B virus-related cirrhosis in 16, hepatitis C virus-related cirrhosis in 38, primary biliary cirrhosis in 5, primary sclerosing cholangitis in 9, biliary atresia in 2, cirrhosis-associated hepatocellular carcinoma in 24, hemochromatosis in 1, autoimmune cirrhosis in 1, and cirrhosis of unknown origin in 11. The proportion of patients with alcoholic cirrhosis was numerically higher in the study population than in the total population of patients evaluated during the study period (35% vs. 17%, respectively).

All these patients underwent transthoracic Doppler echocardiography and transvenous liver biopsy associated with right heart catheterization within the same week as

part of pretransplantation workup. Investigations were performed in stable conditions, and none of the patients had experienced major complications such as upper gastrointestinal bleeding or severe sepsis within 2 weeks before evaluation. In almost all cases, Doppler echocardiography was performed first and right heart catheterization thereafter. Investigators performing either Doppler echocardiography or right heart catheterization were not aware of the previous results of the other investigation.

**Right Heart Catheterization at Time of Pretransplantation Evaluation.** In all patients, a catheter was inserted into the right or left jugular vein under local anesthesia. Hemodynamic measurements including pulmonary artery pressure, right atrial pressure, and pulmonary capillary wedge pressure (PCWP) were performed using a Swan-Ganz catheter. Cardiac output was measured by the thermodilution method (Baxter Healthcare Corporation, Santa Ana, CA). Cardiac output was obtained by the average of 3 consecutive measurements. Arterial pressure was measured using a noninvasive external sphygmomanometer (Dinamap; Critikon, Tampa, FL). Systemic vascular resistance was calculated as follows: systemic vascular resistance ( $\text{dynes.s.cm}^{-5}$ ) = (mean arterial pressure - mean right atrial pressure)  $\times$  80/cardiac output. Pulmonary vascular resistance (PVR) was calculated as follows: pulmonary vascular resistance ( $\text{dynes.s.cm}^{-5}$ ) = (MPAP - PCWP)  $\times$  80/cardiac output. In keeping with previously established criteria, the diagnosis of portopulmonary hypertension was based on the association of a MPAP above 25 mm Hg, a PCWP below 15 mm Hg, and PVR over 120  $\text{dynes.s.cm}^{-5}$ .<sup>4,7,8</sup>

**Splanchnic Hemodynamics at Time of Pretransplantation Evaluation.** Splanchnic hemodynamic measurements were performed immediately after right heart catheterization using the same vascular access. Wedged hepatic venous pressure and free hepatic venous pressure were measured via a catheter inserted into the right hepatic vein. The hepatic venous pressure gradient represented the difference between wedged and free hepatic venous pressures.

**Doppler Echocardiography at Time of Evaluation.** All patients were evaluated with a 2-dimensional Doppler echocardiography on a Sonos 1500 Hewlett-Packard or a Supervision 800 Vingmed machine. Continuous wave Doppler of tricuspid regurgitant jet, when present, was used to calculate right ventricular systolic pulmonary artery pressure with the formula: systolic pulmonary artery pressure = (4  $\times$  maximum velocity of the tricuspid regurgitant jet<sup>2</sup>) + mean right atrial pressure, setting mean right atrial pressure at 5 mm Hg, except when the inferior vena cava was collapsed (0 mm Hg) or clearly enlarged with no collapse during inspiration (10 mm Hg).<sup>9</sup> Pul-

monary hypertension was considered when tricuspid regurgitation was present and calculated systolic pulmonary artery pressure was over 30 mm Hg. No attempt was systematically undertaken to consider between the pre- and postcapillary origin of pulmonary hypertension (for example, by analyzing the flow of the diastolic pulmonary regurgitation, when present, or the mitral valve inflow pattern) or to approach the value of pulmonary vascular resistance, taking into account cardiac output estimated from the velocity time integral of the aortic flow.

**Systemic Hemodynamics at Time of Transplantation.** In patients who underwent transplantation, invasive hemodynamic monitoring was systematically performed using a Swan-Ganz catheter inserted into the right or left jugular vein. Measurements and calculations were performed according to the same protocol as mentioned above after the induction of general anesthesia and before abdominal incision. Measurements were repeated at regular time intervals throughout the procedure.

**Statistical Analysis.** All results are reported as mean  $\pm$  SD. Student's *t* test, paired *t* test, Mann-Whitney test, Fisher exact test, analysis of variance, Bonferroni test, and linear regression analysis were used when appropriate. *P* values < .05 were considered to be statistically significant.

## Results

**Manifestations and Hemodynamic Investigations at Time of Evaluation for Transplantation.** None of the patients in this series exhibited marked exertional dyspnea or any other manifestations suggesting pulmonary hypertension and/or right ventricular failure at the time of evaluation.

Patients were categorized into 3 groups according to the combined results of echocardiography and right heart catheterization (Fig. 1). Group 1 included 10 patients (patients 1 to 10) who met the criteria for portopulmonary hypertension on echocardiography and for whom this diagnosis was confirmed by right heart catheterization. Six of these 10 patients (patients 1 to 6) had evidence of right ventricular dysfunction with ventricular dilatation on echocardiography. Four patients were not listed because the severity of portopulmonary hypertension as well as their general condition was considered to be a contraindication for transplantation. Two of these 4 patients (patients 1 and 2) died 9 and 1 months, respectively, after evaluation because of end-stage liver insufficiency. Two other patients (patients 3 and 4) are currently alive 10 and 53 months, respectively, after evaluation. The remaining 6 patients were listed for transplantation. None of them received a specific treatment for

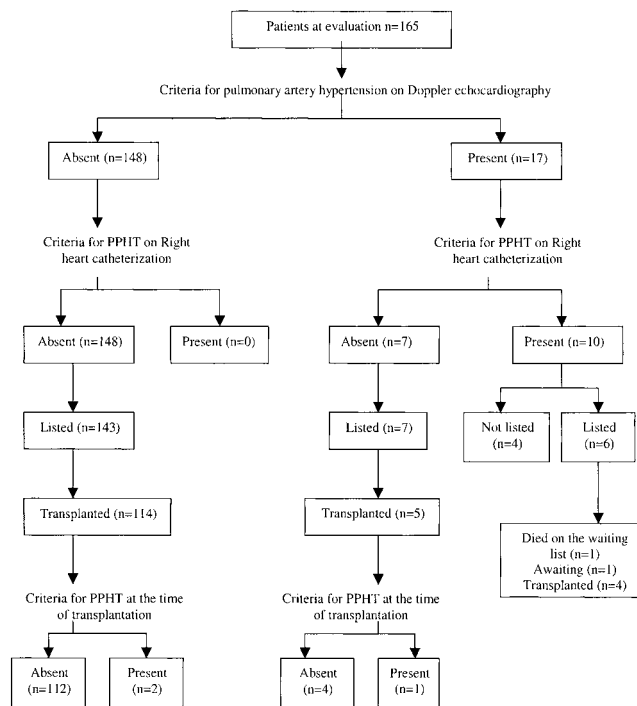


Fig. 1. Distribution of the patients in relation to the results of Doppler echocardiography and right heart catheterization at evaluation, listing for transplantation, and the results of peroperative hemodynamic measurements. PPHT denotes portopulmonary hypertension.

portopulmonary hypertension before transplantation. Patient 5 died before transplantation because of end-stage liver insufficiency. Patient 6 is still on the waiting list. The 4 remaining patients (patients 7 to 10) underwent transplantation, and none of them died during the procedure. Two patients who underwent transplantation died 1 and 4 months after the procedure because of disseminated lymphoma and hemorrhagic shock, respectively, because of ruptured hepatic artery aneurysm. The remaining 2 patients are currently alive 29 and 33 months after transplantation. Individual characteristics of these patients are listed in Table 1.

Group 2 included 7 patients (patients 11 to 17) with pulmonary hypertension on echocardiography but for whom the diagnosis of portopulmonary hypertension was ruled out by right heart catheterization. The 7 patients in group 2 were all listed for transplantation. One patient died before transplantation (7 days after listing) because of end-stage liver insufficiency. One patient is still on the waiting list. The remaining 5 patients have undergone transplantation. Patients 12 and 13, who had mildly elevated PVR but normal MPAP, have undergone transplantation. None of them had pulmonary hypertension at the time of transplantation or developed evidence of portopulmonary hypertension during follow-up. Individual data concerning the patients in group 2 are listed in Table

**Table 1. Individual Characteristics of the 10 Patients (Patients 1-10, Group 1) With Confirmed Portopulmonary Hypertension at Evaluation**

Patient	Age	SPAP	MPAP	PCWP	CO‡	PVR¶ (dynes · s · cm <sup>-5</sup> )	Listed	OLT#	Time on the Waiting list (mo)	Follow-up (mo)	Outcome
		Echocardiography* (mm Hg)	Catheterization† (mm Hg)	Catheterization‡ (mm Hg)							
1	53	46	60	13	5.7	664	No	No	NA	3	Alive
2	57	65	48	15	5.9	450	No	No	NA	1	Dead
3	48	50	44	12	6.3	405	No	No	NA	39	Alive
4	51	84	38	10	3.2	706	No	No	NA	3	Dead
5	51	60	48	13	5.8	479	Yes	No	1.3	3	Dead
6	46	55	26	12	8.4	133	Yes	No	4.8	7	Alive
7	50	60	38	9	6.2	377	Yes	Yes	5	26	Alive
8	47	35	27	13	7.4	152	Yes	Yes	4	24	Alive
9	47	35	42	12	5.8	413	Yes	Yes	14	12	Dead
10	51	84	38	10	5.8	388	Yes	Yes	2.4	1	Dead

Abbreviations: SPAP echocardiography, calculated systolic pulmonary artery pressure on echocardiography; MPAP catheterization, mean pulmonary artery pressure measure by catheterization; PCWP catheterization, pulmonary capillary wedge pressure measured by catheterization; CO, cardiac output; PVR, pulmonary vascular resistance; OLT, orthotopic liver transplantation; NA, not applicable.

2. All patients in groups 1 and 2 had adequate tricuspid regurgitant jet on Doppler echocardiography.

Group 3 included the remaining 148 patients who did not meet the criteria for portopulmonary hypertension on either echocardiography or right heart catheterization. Five of these 148 patients were not listed because they were found to have contraindications other than portopulmonary hypertension during evaluation. The remaining 143 patients were listed. At the end of the study, 114 of these 143 patients (80%) had undergone transplantation, 15 (10%) had died before transplantation, 5 (4%) had been delisted because of significant improvement, and 9 (6%) were still on the waiting list. Forty-six patients had adequate tricuspid regurgitant jet on Doppler echocardiography and calculated systolic pulmonary artery pressure below 30 mm Hg. In the remaining 102 patients, tricuspid regurgitant jet was absent or inadequate, and systolic pulmonary artery pressure could not be calculated. The comparison of the results of systemic and splanchnic hemodynamic investigations in these 3 groups is shown in Table 3. MPAP, PCWP, and pulmonary vas-

cular resistance differed significantly among the 3 groups. MPAP, systemic vascular resistance, and pulmonary vascular resistance were significantly higher in group 1 than in group 2. PCWP was lower in group 1 than in group 2, but the difference did not reach a significant level. Mean age, sex ratio, and Child-Pugh score were not significantly different in the groups 1 and 2. The proportion of patients receiving  $\beta$ -blockers at the time of pretransplantation workup was not significantly different among groups 1, 2, and 3 (60%, 60%, and 71%, respectively). In group 1 patients,  $\beta$ -blockers were discontinued once the diagnosis of portopulmonary hypertension was established.

None of the patients without evidence of pulmonary hypertension on echocardiography were found to have portopulmonary hypertension on right heart catheterization. In this series, the prevalence of portopulmonary hypertension at evaluation for transplantation was 6.1%. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of Doppler echocardiography for the diagnosis of portopulmonary hypertension at the time of evaluation were 100%, 96%, 59%, 100%, and

**Table 2. Individual Characteristics of the 7 Patients With Suspected Portopulmonary Hypertension on Echocardiography Not Confirmed by Right Heart Catheterization (Group 2)**

Patient	Age	SPAP	LV Dysfunction	RV Dilatation	MPAP	PCWP	CO (L/min)	PVR (dynes · s · cm <sup>-5</sup> )	OLT	Follow-up (mo)	Outcome
		Echocardiography* (mm Hg)			Catheterization (mm Hg)	Catheterization (mm Hg)					
11	49	42	No	Yes	20	15	13.3	30	No	1	Dead
12	61	40	No	No	13	4	4.6	156	No	5	Alive
13	55	35	No	No	21	12	4.3	166	Yes	50	Dead
14	62	42	No	Yes	30	23	9.2	61	Yes	70	Alive
15	53	43	No	Yes	32	26	9.8	49	Yes	16	Alive
16	23	40	No	No	13	9	8.9	36	Yes	6	Alive
17	45	48	Yes	Yes	34	29	11.8	34	Yes	3	Dead

Abbreviations: SPAP echocardiography, calculated systolic pulmonary artery pressure on echocardiography; LV, left ventricle; RV, right ventricle; MPAP catheterization, mean pulmonary artery pressure measure by catheterization; PCWP catheterization, pulmonary capillary wedge pressure measured by catheterization; CO, cardiac output; PVR, pulmonary vascular resistance; OLT, orthotopic liver transplantation.

**Table 3. Comparison of the Results of Systemic and Splanchnic Hemodynamic Variables in Groups 1, 2, and 3**

	Group 1 (n = 10)	Group 2 (n = 7)	Group 3 (n = 148)	P Value*
Mean arterial pressure (mm Hg)	86 ± 12	89 ± 12†	81 ± 11	NS
Cardiac index (L/min/m <sup>2</sup> )	3.3 ± 0.8	4.6 ± 1.4†	4.1 ± 1.2	NS
Mean pulmonary artery pressure (mm Hg)	42 ± 10	23 ± 9‡	17 ± 4	<.0001
Pulmonary capillary wedge pressure (mm Hg)	12 ± 2	17 ± 9‡	12 ± 4	.008
Systemic vascular resistance (dynes · s · cm <sup>-5</sup> )	993 ± 256	719 ± 515§	856 ± 353	NS
Pulmonary vascular resistance (dynes · s · cm <sup>-5</sup> )	414 ± 185	76 ± 59¶	68 ± 34	<.0001
Wedged hepatic venous pressure (mm Hg)	27 ± 4	28 ± 11†	29 ± 7	NS
Hepatic venous pressure gradient (mm Hg)	15 ± 4	14 ± 5†	18 ± 6	NS

NOTE. Group 1, patients who met the criteria for portopulmonary hypertension on both echocardiography and right heart catheterization; Group 2, patients who met the criteria for portopulmonary hypertension on echocardiography but not on right heart catheterization; Group 3, patients who did not meet the criteria for portopulmonary hypertension either on echocardiography or right heart catheterization.

\*P values refer to the comparison among the 3 groups.

†No statistically significant difference between groups 1 and 2.

‡P = .003 between groups 1 and 2.

§P = .04 between groups 1 and 2.

¶P = .001 between groups 1 and 2.

96%, respectively. Using a cut-off value of 40 mm Hg instead of 30 mm Hg for Doppler echocardiography, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of this technique were 80%, 96%, 60%, 98%, and 95%, respectively.

In groups 2 and 3, MPAP and PCWP were significantly correlated ( $r^2 = 0.83$ ,  $P < .001$  for both groups). Noteworthy, 11 of 155 patients in groups 2 and 3 had MPAP over 25 mm Hg, although they did not meet the criteria for portopulmonary hypertension because PCWP was above 15 mm Hg. All of these patients had normal PVR, except one who had mild elevation of PVR (186 dynes.s.cm<sup>-5</sup>). This latter patient did not have evidence of portopulmonary hypertension, either at the time of transplantation or during posttransplantation follow-up. No significant correlation was found between splanchnic hemodynamics and pulmonary vascular measurements among groups. In the whole population, no significant correlation was found between mean pulmonary artery pressure and hepatic venous pressure gradient. In group 1, no statistically significant correlation was found between systolic pulmonary artery pressure estimated by Doppler echocardiography and MPAP measured by right heart catheterization.

**Comparison of Hemodynamic Variables at Time of Evaluation and at Time of Transplantation.** One hundred twenty-three of 165 patients underwent transplantation and had invasive systemic hemodynamic investigations at the time of transplantation. The values of MPAP in the 4 patients who had portopulmonary hypertension at the time of evaluation and who underwent transplantation are shown in Fig. 2. Two of these 4 patients had an increase in MPAP (12 and 4 mm Hg) between evaluation and the initial phase of transplantation.

In addition to the 4 patients who had portopulmonary hypertension at evaluation, 3 patients met the criteria for portopulmonary hypertension based on the values recorded at the time of transplantation. During the first phase of transplantation, these 3 patients (patients 17, 18,

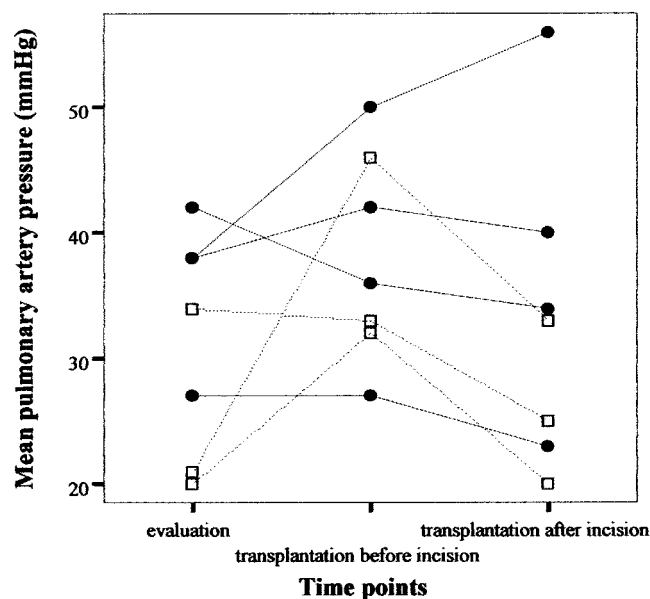


Fig. 2. Individual values of mean pulmonary artery pressure in the 4 patients who had portopulmonary hypertension at evaluation and who underwent transplantation and in the 3 patients with an acquired portopulmonary hypertension profile. Values have been recorded at the time of evaluation, during the first phase of transplantation, (transplantation before incision), and during the second phase of transplantation (transplantation after incision). The 4 patients who had portopulmonary hypertension at evaluation are marked by **circles** and **solid lines**. The 3 patients who did not meet the criteria for portopulmonary hypertension at the time of evaluation but who had an acquired portopulmonary hypertension profile at the time of transplantation are marked by **squares** and **dotted lines**.

**Table 4. Individual Hemodynamic Data in the 3 Patients With an Acquired Portopulmonary Hypertension Profile (Patients 17, 18, and 19) at Different Time Points**

		Patient 17	Patient 18	Patient 19
Evaluation	MPAP (mm Hg)	34	20	21
	PCWP (mm Hg)	29	11	15
	CO (L/min)	11.8	10.9	5.9
	PVR (dynes · s · cm <sup>-5</sup> )	34	66	81
	SVR (dynes · s · cm <sup>-5</sup> )	378	457	1,076
Transplantation before incision	MPAP (mm Hg)	33	32	46
	PCWP (mm Hg)	15	13	15
	CO (L/min)	12	8.5	5.5
	PVR (dynes · s · cm <sup>-5</sup> )	120	178	451
	SVR (dynes · s · cm <sup>-5</sup> )	480	912	995
Transplantation after incision	MPAP (mm Hg)	25	20	33
	PCWP (mm Hg)	14	8	13
	CO (L/min)	16	6.8	6.1
	PVR (dynes · s · cm <sup>-5</sup> )	55	141	262
	SVR (dynes · s · cm <sup>-5</sup> )	395	1,107	1,180
Posttransplantation day 1*	MPAP (mm Hg)	33	27	30
	PCWP (mm Hg)	15	12	11
	CO (L/min)	12.4	7.2	5.6
	PVR (dynes · s · cm <sup>-5</sup> )	116	166	271
	SVR (dynes · s · cm <sup>-5</sup> )	405	882	986

Abbreviations: MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

\*Patients were sedated.

and 19) had MPAP values of 33, 32, and 46 mm Hg, all of which exceeded the upper limit of the 95% confidence interval of MPAP in those without pulmonary hypertension (group 3) at the same time point (9.6 to 31.6 mm Hg). Two of these 3 patients showed a marked increase in MPAP between evaluation and the first phase of transplantation (12 and 25 mm Hg in patients 18 and 19, respectively). In the third patient (patient 17) who had a hyperdynamic profile and was categorized in group 2 at evaluation, MPAP was almost unchanged (34 vs. 33 mm Hg) at the time of transplantation. However, there was a marked increase in pulmonary vascular resistance during the first phase of transplantation as compared with evaluation (120 vs. 38 dynes.s.cm<sup>-5</sup>). Noteworthy, in the 3 patients with an acquired portopulmonary hypertension profile, time intervals between evaluation and transplantation were 2.5, 3, and 5 months. In these 3 patients, PCWP during the first phase of transplantation was 15, 13, and 15 mm Hg, respectively. PVR values were 120, 178, and 451 dynes.s.cm<sup>-5</sup>, respectively. Cardiac output values were 12, 8.5, and 5.5 L/min. Individual values at different time points in these patients are shown in Table 4 and in Fig. 2.

In the 116 patients who did not have portopulmonary hypertension either at the time of evaluation or at the time of transplantation, MPAP was, on average, significantly higher during the first phase of transplantation than at evaluation (Table 5). In addition, no significant correlation was found between the values of MPAP at the time of

evaluation and during the first phase of transplantation (Fig. 3). Similarly, no significant correlation was found between the values of MPAP at the time of evaluation and during the second phase of transplantation. In contrast, there was a significant correlation between the values of cardiac output at the time of evaluation and during the first phase of transplantation ( $r^2 = 0.084$ ,  $P = .005$ ).

During the second phase of transplantation (after incision and before hepatectomy), a significant decrease in MPAP and PCWP was observed as compared with values obtained during the initial phase of transplantation (before incision) ( $20.3 \pm 5.5$  mm Hg vs.  $19 \pm 5.3$  mm Hg,  $P = .02$  and  $12.1 \pm 4.2$  vs.  $10.6 \pm 4.5$  mm Hg,  $P = .003$ , respectively). In contrast, mean cardiac output was not

**Table 5. Comparison of the Mean Values of Mean Arterial Pressure, Pulmonary Capillary Wedge Pressure, and Cardiac Output in the 116 Patients Who Did Not Have Portopulmonary Hypertension at 3 Time Points**

	Time Period		P Value
	Evaluation	Transplantation (Before Incision)	
Mean pulmonary artery pressure (mm Hg)	17.8 ± 4.3	20.3 ± 5.5	<.0001
Pulmonary capillary wedge pressure (mm Hg)	11.9 ± 3.9	12.1 ± 4.2	NS
Pulmonary vascular resistance (dynes · s · cm <sup>-5</sup> )	71 ± 35	85 ± 40	.01
Cardiac output (L/min)	7.2 ± 1.9	7.8 ± 2.7	.04

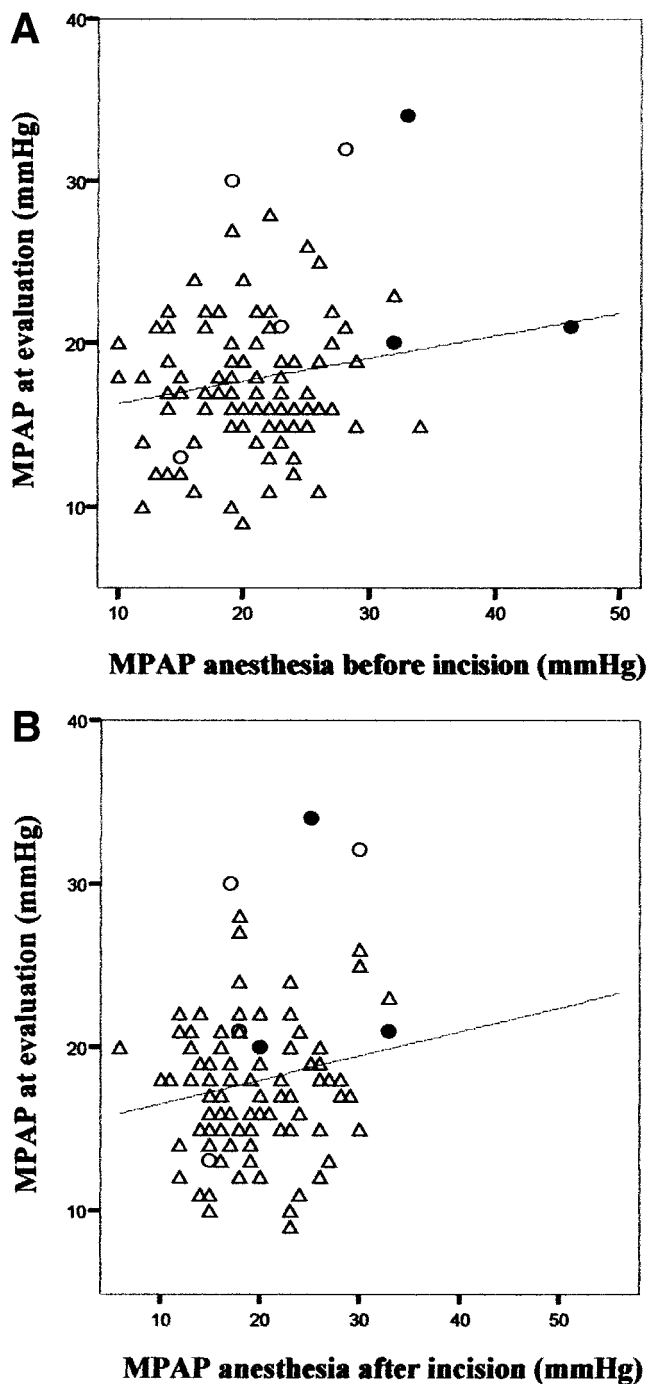


Fig. 3. Relation between mean pulmonary artery pressure at the time of evaluation and during the first phase of transplantation (A; before incision,  $r^2 = 0.031$ ,  $P = .07$ ) and during the second phase of transplantation (B; after incision,  $r^2 = 0.022$ ,  $P = .07$ ). (○) Group 2: patients with pulmonary hypertension on Doppler echocardiography but no portopulmonary hypertension on catheterization at evaluation. (△) Group 3: patients with neither pulmonary hypertension on Doppler echocardiography nor portopulmonary hypertension on catheterization at evaluation. (●) Acquired PPHT profile: patients without portopulmonary hypertension at evaluation but meeting the criteria for portopulmonary hypertension by catheterization during the first phase of transplantation.

significantly different between these 2 time points ( $7.8 \pm 2.9$  vs.  $7.8 \pm 2.7$ , respectively). There was a significant correlation between the values of MPAP, PCWP, and cardiac output during the first and second phase of the transplantation ( $r^2 = 0.19$ ,  $P < .0001$ ;  $r^2 = 0.12$ ,  $P = .005$ ;  $r^2 = 0.7$ ,  $P < .0001$ ; respectively).

Among the 4 patients with portopulmonary hypertension at evaluation who underwent transplantation, 2 had a follow-up longer than 1 year after transplantation (patients 7 and 8). In patient 7, who had the highest MPAP values at the time of transplantation, right heart catheterization was performed 12 months after the procedure, showing MPAP, PCWP, cardiac output, and pulmonary vascular resistance values at 32 mm Hg, 7 mm Hg, 5.13 L/min, and 390 dynes.s.cm<sup>-5</sup>, respectively. The other patient did not have posttransplantation pulmonary vascular investigations.

## Discussion

Even if there is a general consensus on the need for screening for portopulmonary hypertension in candidates for liver transplantation, there is no clear consensus on the most appropriate sequence of investigations for screening. Doppler echocardiography is an attractive technique that has the major advantage over right heart catheterization of being noninvasive. Based on the previous results of studies comparing preoperative and peroperative investigations, it has been suggested that, even if not specific, Doppler echocardiography when performed at evaluation is a reliable tool for detecting pulmonary hypertension.<sup>5,6,10</sup>

An important finding in this study is that no significant correlation was found between preoperative and peroperative values of MPAP when measured by catheterization in patients who had or did not have portopulmonary hypertension. In contrast to what could be expected, MPAP was on average higher during the first phase of transplantation (under general anesthesia and before incision) than at evaluation in patients without portopulmonary hypertension. In this latter group, cardiac output was on average higher during the first phase of transplantation than at evaluation. These findings suggest that several factors, including the positive intrathoracic pressure resulting from mechanical ventilation, anesthesia-induced systemic vasodilatation, increasing cardiac output and, by turn, pulmonary artery pressure, as well as the progression of liver insufficiency and the accompanying circulatory disorders while patients are awaiting for a graft, might to some extent overcome the proper effects of general anesthesia, which were expected to decrease pulmonary artery pressure. It can be suspected that the influence of each of these factors is quite variable from patient to patient and weigh differently according to each case, which could explain, at

least in part, that the values of MPAP at the time of evaluation are not significantly correlated to those observed at the time of transplantation. As a consequence, the results of previous studies in which the accuracy of preoperative Doppler echocardiography was assessed by reference to peroperative right heart catheterization,<sup>5,10</sup> even if determined before abdominal incision, have to be interpreted with caution.

Apart from the absence of a significant correlation between preoperative and peroperative values of MPAP, the results of this study support the poor positive predictive value of Doppler echocardiography for the diagnosis of portopulmonary hypertension. Indeed, about 40% of the patients who met the criteria for portopulmonary hypertension on echocardiography were ruled out by catheterization. A significant proportion of these false positives were found to have MPAP values equal to or over 25 mm Hg on catheterization, confirming the reality of pulmonary hypertension. However, as shown in previous studies, echocardiography is unable to differentiate those who had increased pulmonary vascular resistance (such as observed in case of portopulmonary hypertension) from those who had high pulmonary artery pressure with normal pulmonary vascular resistance (such as observed during hyperkinetic states and/or left ventricular dysfunction) if parameters other than systolic arterial pressure are not measured. As a result, right heart catheterization seems to be the only reliable technique to disclose patients with portopulmonary hypertension among those with elevated pulmonary artery pressure. This distinction is crucial because, in contrast to portopulmonary hypertension, elevated pulmonary pressure in the context of hyperkinetic states does not seem to be associated with an increased incidence of adverse events during and after liver transplantation in our series as well as in others.<sup>11</sup> Overall, the diagnosis of portopulmonary hypertension should always be based on invasive hemodynamic measurements.

Even though this study showed that Doppler echocardiography is not specific for the diagnosis of portopulmonary hypertension, it must be emphasized that its negative predictive value is especially high. Indeed, at evaluation, none of the 117 patients who had no evidence of elevated pulmonary pressure on Doppler echocardiography were found to have portopulmonary hypertension on catheterization. Thus, the absence of evidence of elevated pulmonary artery pressure on Doppler echocardiography might lead to exclusion in almost all cases of portopulmonary hypertension without the need for invasive investigations. Obviously, in patients without tricuspid regurgitant jet, it is impossible to calculate pulmonary artery pressure by Doppler echocardiography. However, tricuspid regurgitation is almost constant in patients with significant pul-

monary artery hypertension.<sup>12</sup> Therefore, the risk of missing portopulmonary hypertension because of the absence of tricuspid regurgitant jet might be extremely low.

Another important finding in this study is that 3 of 155 patients who did not have portopulmonary hypertension at evaluation were found to have an acquired portopulmonary hypertension profile at the time of transplantation. Because, as we have shown above, pulmonary vascular investigations performed during the first phase of transplantation should be interpreted with caution, it remains difficult to ascertain definitely that these patients had "de novo" portopulmonary hypertension. However, the rapid increase in MPAP between evaluation and transplantation exceeding the values observed in patients without pulmonary hypertension and/or the increase in pulmonary vascular resistance in the absence of any identifiable precipitating factor all suggest that these patients developed pulmonary vascular changes compatible with portopulmonary hypertension while awaiting a graft. Objective observations concerning the natural history of the initial steps of portopulmonary hypertension are lacking. Indeed, because portopulmonary hypertension remains asymptomatic in most cases until mean pulmonary artery pressure reaches 40 mm Hg or more, it remains impossible to determine the interval of time during which the early pulmonary vascular changes developed in a given patient. This prospective study gave the opportunity to show that pulmonary vascular changes compatible with new onset portopulmonary hypertension may occasionally develop within time periods as short as 2 to 3 months. Even if none of the 3 patients with acquired portopulmonary hypertension profile had MPAP over 50 mm Hg at the time of transplantation, these findings indicate that the initial development of portopulmonary hypertension might be a rapid process.

In conclusion, the results of this study confirm that portopulmonary hypertension has to be detected systematically in candidates for transplantation because this disorder remains asymptomatic until advanced stages and that Doppler echocardiography is a highly sensitive tool for screening. However, this noninvasive technique has 2 limitations. First, Doppler echocardiography is not specific, which means that the diagnosis of portopulmonary hypertension, when suspected, should always be confirmed by right heart catheterization. Second, a small proportion of patients who do not have pulmonary hypertension at the time of evaluation develop an acquired portopulmonary hypertension profile while awaiting a graft. Finally, this study showed that there is no significant correlation between values of pulmonary artery pressure at evaluation and at time of transplantation. Therefore, the results of previous studies should be, at

least in part, revisited. In the future, any investigation aimed at improving the early diagnosis of portopulmonary hypertension in candidates for liver transplantation should be conducted by reference to preoperative rather than peroperative data.

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