The effect of liver transplantation on circulating levels of estradiol and progesterone in male patients: Parallelism with hepatopulmonary syndrome and systemic hyperdynamic circulation improvement

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ABSTRACT. The correction of hepatopulmonary syndrome (HPS) after liver transplantation (LT) remains controversial. The aims of our study were to: 1) analyze whether LT reverses HPS; 2) note any relationship between HPS and the systemic hemodynamic disturbance; and 3) note changes in circulating sex hormones and the possible association with pulmonary and systemic hemodynamic changes. Systemic hemodynamic parameters, cardiac output and systemic vascular resistance (SVR), sex hormones, and intrapulmonary vasodilatation assessed by contrast transesophageal echocardiography, and gas exchange abnormalities were investigated in 19 patients with advanced cirrhosis prior to and 6 months (176.8±30 days) after LT. LT was followed by a marked reduction in cardiac output (6.6±1.7 *vs* 3.5±0.5 l/min; $p<0.001$) and SVR (1039±460 *vs* 1978±294 dyn·sec·cm^{-5}; $p<0.005$). Before LT, circulating estradiol and progesterone levels were invariably elevated (66±22 pg/ml and 1.8±1.1 ng/ml, respectively, normal values <31 pg/ml and 0.35 ng/ml, respectively), and dropped after LT (28±12 pg/ml $p<0.001$ and 0.38±0.2 ng/ml; $p<0.001$, respectively). Seventeen of 19 patients had intrapulmonary vasodilatation and increased alveolar-arterial oxygen difference, thereby fulfilling diagnostic criteria for HPS. Patients with HPS presented higher cardiac output ($p<0.05$), lower SVR ($p<0.01$), and higher progesterone and estradiol levels than patients without HPS ($p<0.05$). LT produced normalization of intrapulmonary vasodilatation in all patients. LT normalized hyperdynamic circulation and is a useful therapeutic option in patients with HPS. Normalization of sex hormone levels after LT suggests that they could play a pathogenic role in the development of HPS.

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INTRODUCTION

Intrapulmonary vasodilatation, abnormal gas exchange and the presence of advanced liver disease are accepted criteria for hepatopulmonary syndrome (HPS). This syndrome is associated with a high mortality rate (1-5). While severe hypoxemia due to HPS was considered an absolute contraindication to liver transplantation (LT) (6), this view has been recently challenged (7-9). Reasons for abnormal gas exchange in patients with liver disease are the following: pulmonary vasodilatation (PV), anatomical intrapulmonary shunts, decreased DLco (diffusion of co), ventilation perfusion mismatching, and restrictive-obstructive defects (10).

Pathogenesis of HPS is unclear. Thus far, some studies have evaluated hypoxemia and hyperdynamic circulation in cirrhosis (11), but little is known about a possible relationship between pulmonary and systemic hyperdynamic circulation. Overactivity of vasodilating factors, including endothelial-derived factors (12) and humoral agents (13), is a possible contributor to peripheral vasodilatation and PV in cirrhotic patients. Estradiol and progesterone are

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increased in liver cirrhosis (14-16) and have shown vasodilating action (17). It has also been documented that increased values of estradiol and progesterone levels return to normal range after LT (14-16).
The aim of this prospective longitudinal study was to analyze a possible relationship between parameters of hyperdynamic circulation, plasma levels of sex hormones and HPS.

SUBJECTS AND METHODS

Subjects

Nineteen patients with cirrhosis admitted to the Liver Transplantation Unit of Hospital Ramon y Cajal for LT evaluation were included in the study. All patients had histologically proven cirrhosis (mean age 48±7 yr). Causes of cirrhosis were alcohol abuse in 8 patients, chronic hepatitis C in 6, chronic hepatitis B in 4, and autoimmune hepatitis in 1 patient. Sixteen patients had ascites at entry into the study, 16 had esophageal varices and 6 had bled from the varices. Eleven patients (58%) were classified as Child-Turcotte class B (18), and the remaining (42%) as class C. All measurements performed on these 19 patients were repeated 6 months (176.8±30 days) after LT. Patients with a history of chronic bronchopulmonary disease, abnormal chest X-ray and electrocardiographic evidence of right ventricular hypertrophy, cardiac complications, recently ruptured esophageal varices or pre-menopausal women were not included. None of the patients received treatment with vasoactive drugs. All patients were afebrile. Informed written consent was obtained from all patients and the study was approved by the Hospital Ethics Committee.

Diagnosis of HPS

All patients with HPS had the following criteria:
1) demonstration of PV;
2) presence of gas exchange abnormalities defined by an upper limit-widened age-corrected alveolar-arterial oxygen difference ($AaPO_2$) >15 breathing room air, in sitting position, in rest, and with local anesthesia;
3) absence of primary cardiopulmonary disease demonstrated by normal pulmonary function test (1-5).

Arterial blood gas analysis

Arterial blood gas analysis included the determination of the pH, PaO_2, $PaCO_2$, by mean of selective electrodes and with IL 16/40 pH/blood gas analyzer equipment (Milano, Italy), in supine and breathing room air. Hypoxemia was defined by PaO_2<70 mmHg, and hypocapnia by a $PaCO_2$<35 mmHg. $AaPO_2$ was calculated following the equation: {[(BP-47)x0,2093] - (1,15x$PaCO_2$)} - PaO_2 (BP: barometric pressure).

Description of study of intrapulmonary vasodilatation

Contrast transesophageal echocardiography (CTEE) was performed with 5 MHz transesophageal probe (ATL Ultramarck 9 equipment, UK) and an integrated video-recording system to register the studies. After introducing the probe, a four-cameral plane was selected in order to visualize the 2 atrial cavities, and simultaneous bi-dimensional images and images in M mode through both atria were recorded. Five cc of 0.9% saline previously agitated was injected through a three-way stopcock connected to two syringes of 10 cc. A few seconds after injection an increased echogenicity was observed in the right atrium due to the arrival of the injected substance. Five or 6 heartbeats were observed to detect the passing of microbubbles to the left chambers, in order to exclude permeable foramen ovale or intracardiac shunts. The injection was repeated twice, once the contrast had been cleared in both chambers, accepting as definitive the largest pass of microbubbles. All studies were recorded on videotape.
Grading: In order to objectively grade and make the procedure reproducible (the pass of microbubbles to the left atrium), a semiquantitative scale was made (19): grade 1, absence of passing; grade 2, passing of few isolated microbubbles (approximately <15 bubbles); grade 3, passing of numerous isolated microbubbles; grade 4, passing of numerous microbubbles that obtain an increase in background echogenicity; grade 5, opacification of the left atrium, but less extent than the right atrium; grade 6, opacification of left atrium similar to right atrium. Given the excellent image quality of CTEE, passing of isolated microbubbles was considered as normal. Therefore, grades 1 and 2 were considered as no PV, grade 3 as mild PV, and >4 as significant PV.

Hormone assays

Estradiol and progesterone levels were measured by Immulite chemiluminescent enzyme immunoassays (Diagnosis Products Corporation, Los Angeles, CA, USA). For the estradiol assay, the intra-assay coefficient of variation (CV) was 6.3%, the inter-assay CV was 10.5%. The assay has a working range of 20 to 2000 pg/ml. For the progesterone assay, the intra-assay CV was 9.2% and the inter-assay CV was 10.2% with a range of 0.2 to 40 ng/ml. All determinations were done on the same day. The

Table 1 - *Arterial blood gases before and after liver transplantation (no.=19). Data X (SD). The table shows improvement in blood gas parameters after liver transplantation (LT).*

	Pre-LT (SD)	Post-LT (SD)	*p*-value
PaO_2 (mmHg)	70.9 (14.5)	86.8 (6.9)	<0.001
PaO_2<70 mmHg (n)	12	2	<0.05
PaO_2 (mmHg)	32.8 (4)	36.4 (1.3)	<0.001
PaO_2<35 mmHg (n)	16	1	<0.001
$AaPO_2$ (mmHg)	30.2 (13.4)	12.8 (6.3)	<0.001
Increased $AaPO_2$ (n) (age-corrected)	12	2	<0.05

Table 2 - *Gas exchange abnormalities in patients with and without hepatopulmonary syndrome (HPS). Data X (SD). The table shows low PaO_2 and high PCO_2 levels in patients with HPS.*

	HPS (SD)	No HPS (SD)	*p*-value
PaO_2 (mmHg)	63.5 (12)	77.7 (13.6)	<0.05
PaO_2 (mmHg)	32.4 (4)	33.4 (4.2)	NS
$AaPO_2$ (mmHg)	37.3 (8.7)	23.7 (13.9)	<0.05

mean progesterone and estradiol levels of healthy patients in our own reference group were 0.35 ng/ml and <31 pg/ml, respectively.

Study of cardiac output and peripheral vascular resistance

Study of cardiac output and peripheral vascular resistance was performed using a Ultramarck 9 ultrasonographer (ATL) equipped with a 3.5 mHz combined imaging and Doppler transducer. Patients were studied in left lateral decubitus. Two-dimensional guided M-mode tracings were recorded at 50 $mm*sg^{-1}$, with the transducer placed in the third to fifth left intercostal space. Left ventricular internal dimensions were measured at end-diastole and end-systole, according to the American Society of Echocardiography Guidelines (20).

The left ventricular outflow tract diameter was measured through the paraesternal long-axis view, just below the insertion of the anterior and posterior aortic valve leaflet during early systole. Diameter was measured between the two inner echocardiographic edges. An average of three measurements was made. Cross-sectional area was calculated as $(3.14 \cdot diameter^2)/4$. For the velocity recording at the left ventricular outflow tract, pulsed-Doppler echocardiography was used. The apical window was used and the sample volume was placed into the valve leaflet and gradually moved backward until the first clear ventricular outflow velocity was obtained. The area under the velocity curves or time-velocity integral was derived by planimetry. An average of three cardiac cycles was made. Stroke volume was determined as (cross-sectional area · time-velocity integral). Cardiac output was determined as (stroke volume·cardiac rate). Peripheral vascular resistance was assessed as [(mean arterial blood pressure·80)/cardiac output]. Blood pressure measurements were taken with a cuttmercury sphygmomanometer at the time of echocardiography with the patient in supine position.

Statistical analysis

Data are expressed as the mean±SD. Statistical analysis was carried out using two-tailed paired or unpaired Student's *t*-test, as needed, and analysis of variance (ANOVA). Ordinal variables were evaluated by the χ^2 test. Correlation between variables were determined by Pearson test. $P<0.05$ was considered significant. For analysis purposes, SPSS Statistic pack were used.

RESULTS

The mean time of follow-up after LT in this series was 176.8±30 days. Hepatic function remained normal throughout the follow-up period.

Gas exchange before and after LT

Arterial blood gas analysis pre- and post-LT is presented in Table 1. Before LT, 16 of 19 patients (84.2%) had evidence of alveolar hyperventilation ($PaCO_2$<35 mmHg). Twelve patients were hypoxemic (PaO_2<70 mmHg) and showed a widened $AaPO_2$. There was not association between etiolo-

Table 3 - *Sex hormones data for 19 patients before and after liver transplantation (LT), and for patients with hepatopulmonary syndrome (HPS) (no.=10) and without HPS (no.=9). Data X (SD). The table shows high estradiol and progesterone levels in patients with pre-LT and with HPS.*

	Pre-LT	Post-LT(SD)	*p*	HPS	No HPS	*p*
Estradiol (pg/ml)	66 (22)	28 (12)	<0.001	79.5 (27.9)	61.2 (20.2)	0.05
Progesterone (ng/ml)	1.8 (1.1)	0.38 (0.2)	<0.001	2.4 (1.2)	1.4 (0.8)	<0.05

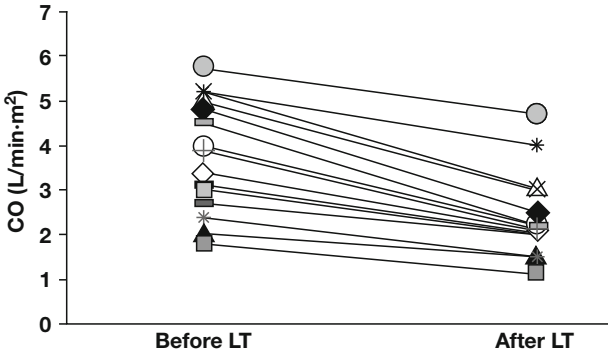

Fig. 1 - *High cardiac output (CO) before liver transplantation (LT) in 19 patients (p<0.001).*

gy of liver disease and hypoxemia, hypocapnia or abnormal $AaPO_2$. After 6 months of LT, 10 of 12 patients with hypoxemia or widened $AaPO_2$ before LT returned to normal situation. One patient continued hypoxemic, due to interstitial pneumonia associated to CMV infection; persistent hypoxemia could not be explained in the remaining transplanted. Fifteen of 16 patients exhibiting alveolar hyperventilation before LT, presented normal $PaCO_2$ after LT.

Intrapulmonary vasodilatation and hepatopulmonary syndrome

None of 19 patients presented intracardiac shunt or right ventricular hypertrophy. All patients underwent CTEE. PV was demonstrated in 10 of 19 patients (52.6%). All these patients presented gas exchange abnormalities, thus fulfilling diagnostic criteria of HPS. Table 2 shows gas exchange abnormalities in patients with and without HPS. Patients with HPS presented significant lower mean PaO_2 levels, and higher mean $AaPO_2$ levels. However there was not significant difference between the two groups in mean $PaCO_2$ levels.

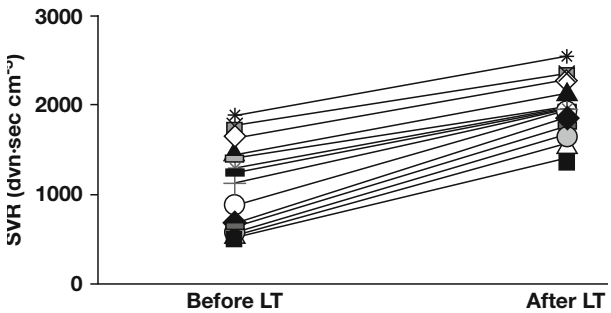

Fig. 2 - *Low systemic vascular resistance (SVR) before liver transplantation (LT) in 19 patients (p<0.005).*

Sex hormones data

Table 3 shows estradiol and progesterone levels before and 6 months after LT and levels of these hormones in function of HPS status. As shown, prior to LT, significant increase in estradiol and progesterone levels were observed in all patients. Patients with HPS manifested higher estradiol ($p<0.05$) and progesterone levels ($p<0.05$) than patients without HPS.

Cardiac output and systemic vascular resistance

Figures 1 and 2 show cardiac output and peripheral vascular resistance in patients before and after LT. Cirrhotic patients had hyperdynamic circulation, with high cardiac output and low peripheral vascular resistance. LT was followed by marked changes in these parameters at 6 months, with significant reductions in cardiac output (6.6±1.7 *vs* 3.5±0.5 l/min; $p<0.001$) and significant increases in systemic vascular resistance (SVR) (1039±460 *vs* 1978±294 dyn·sec·cm^{-5}; $p<0.005$). As Figure 3 shows, patients with HPS had significant higher cardiac output and lower SVR than patients without HPS. Figure 4 shows the correlation between estradiol and progesterone levels and parameters of hyperdynamic circulation.

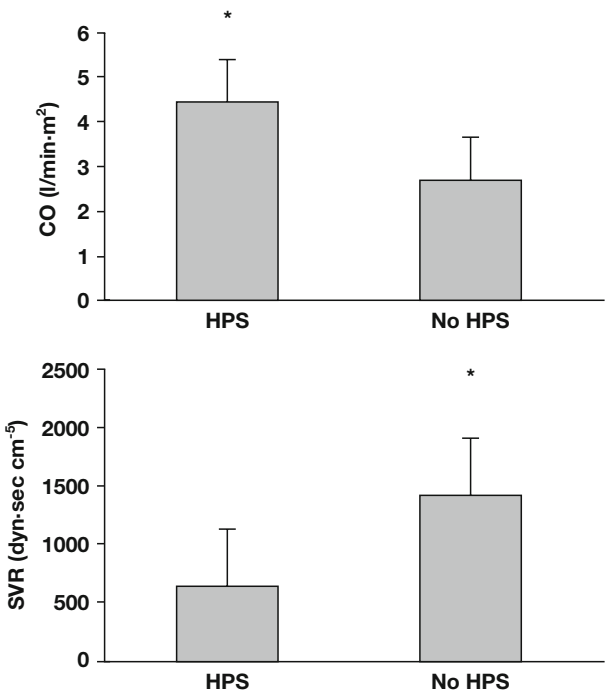

Fig. 3 - *High cardiac output (CO) and low systemic vascular resistance (SVR) in cirrhotic patients before liver transplantation (LT) with and without hepatopulmonary syndrome (HPS) (no.=19). *p<0.001.*

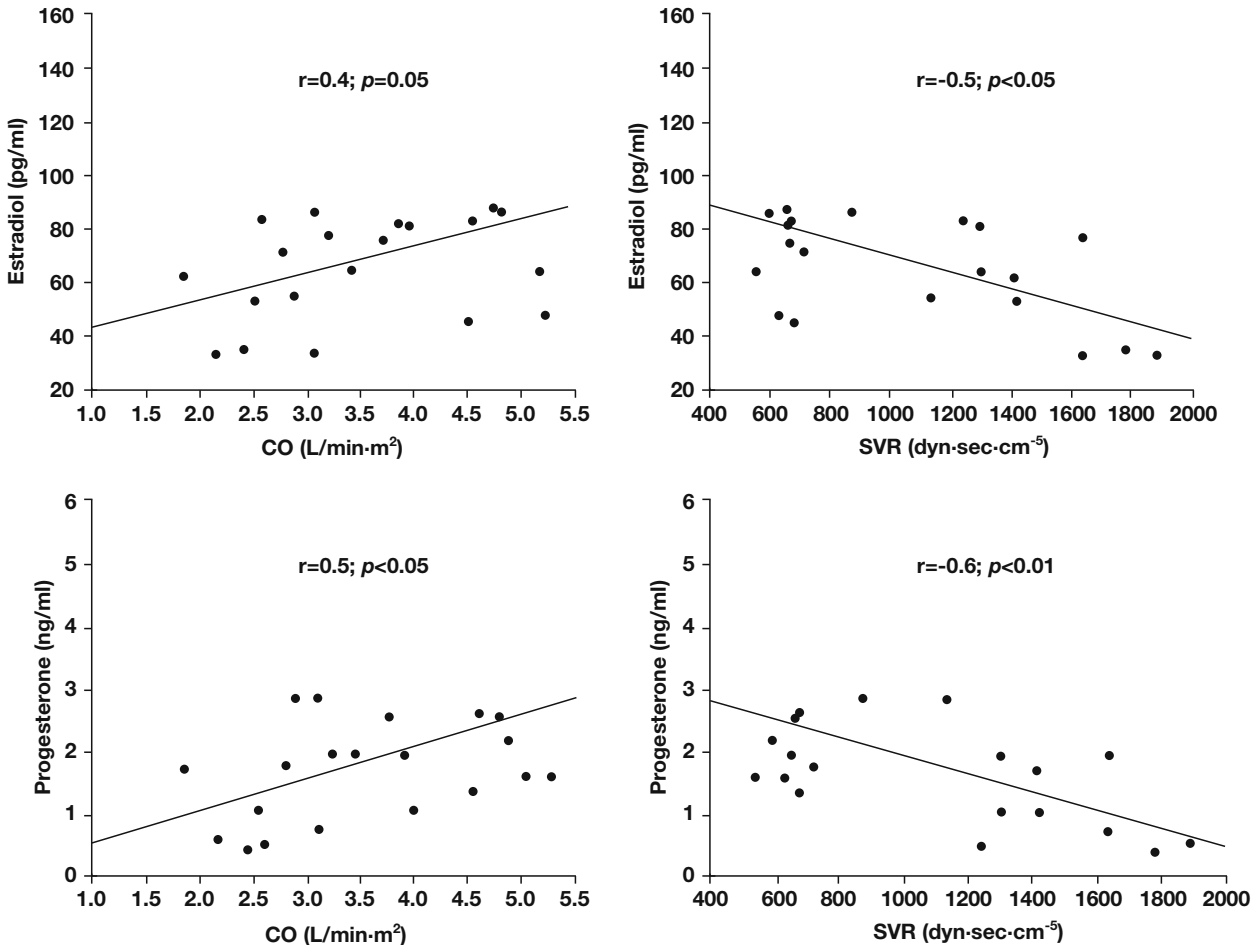

Fig. 4 - *Correlation of estradiol and progesterone levels with cardiac output (CO) and systemic vascular resistance (SVR) in 19 cirrhotic patients prior to liver transplantation (LT).*

DISCUSSION

Our study confirmed the high frequency of gas exchange abnormalities, hyperdynamic circulation (high cardiac output and low peripheral vascular resistance), and elevated levels of plasma sex hormone levels in patients with severe liver disease submitted to evaluation for LT. The most prominent finding of this study was the correction of PV and HPS after LT. These results were in accordance with previous reports (6-10), showing that PV and gas exchange abnormalities ameliorate by LT in patients with cirrhosis. The high prevalence of PV and HPS observed in this study was explained by the use of CTEE in the demonstration of PV. Contrast echocardiography is the most useful screening test for patients with HPS (21). Previous studies have found a better correlation between gas exchange abnormalities and presence of PV, when CTEE is employed (19, 22); the higher sensitivity of this technique and the presence of advanced liver disease in patients of our study (58% had Child's class B and 42% had Child's class C) are possible explanations of the higher prevalence of HPS observed in this study (52.6%). This finding was in keeping with other studies using CTEE, which have demonstrated intrapulmonary shunt in 51% of cirrhotic patients (22).

As previously documented (23-27), significant elevations of progesterone and estradiol levels were found in our cirrhotic patients as compared with the reference values. Although there is a unique study showing correlation between progesterone and estradiol levels and alveolar hyperventilation in patients with liver disease (23), our work was the first study evaluating the association of these hormones to the extent of HPS. In addiction, a significant association between increased progesterone levels and presence of HPS was observed. Progesterone inhibits vascular tone (28). Vasodilatation in pregnant women is well

known, where progesterone concentration markedly increases during pregnancy (29). In addition, the antiprogestin RU486 significantly inhibited the vasorelaxation induced by progesterone (30). Return to normal progesterone levels and resolution of HPS after LT support a contributory role of progesterone on the pathogenesis of this disorder. In our study, estradiol levels were directly correlated with cardiac output and inversely correlated with SVR, being more increased in patients with HPS. It has been demonstrated that estradiol dilates blood vessels in both reproductive and non-reproductive tissues (31). The mechanism of this vasodilatation is believed to involve activation of nitric oxide synthesis (32) or calcium-channel blockade (33). Moreover, estradiol increases the number of progesterone receptors in animals and may facilitate actions of progesterone (34). Increased plasmatic levels of other vasodilating substances may also contribute to the development of intrapulmonary vasodilatation, and normalization of these circulating peptides after restitution of liver function allows an adequate regulation of vascular tone at pulmonary and peripheral level. In support of these findings, increased levels of estradiol and progesterone showed direct correlation with cardiac output and inverse correlation with SVR. Of interest, our results showed a significant association between the presence of HPS and systemic hyperdynamic circulation. These findings support the view that a common pathogenic mechanism could be involved in the pathogenesis of PV and peripheral vasodilatation. In keeping with previous studies (35), our results showed that most hemodynamic and hormonal abnormalities of advanced cirrhosis return to normal or almost-normal range 2 weeks after LT.

In conclusion, LT is a useful therapeutic option for patients with cirrhosis and HPS. PV and systemic vasodilatation could share a common pathogenetic mechanism. Increased levels of sex hormone might play a contributing role in PV and systemic vasodilatation. Reversibility of HPS could be related to improvement of liver function, alleviation of hyperdynamic circulation and return to normal progesterone and estradiol levels.

REFERENCES

1. Rodriguez-Roisin R.
   Síndrome hepatopulmonar: un nuevo concepto. ¿Un tratamiento nuevo?
   Med. Clin. (Barc.) 1995, *105:* 269-274.
2. Berthelot P., Walker J.G., Sherlock S., Reid L.
   Arterial changes in the lungs in cirrhosis of the liver-lung spider nevi.
   N. Engl. J. Med. 1966, *274:* 291-298.
3. Davis H.H., Schwartz D.J., Lefrak S.S., Susanan N., Schainker B.A.
   Alveolar-capillary oxygen desequilibrium in hepatic cirrhosis.
   Chest 1978, *73:* 507-511.
4. Lange P.A., Stoller J.K.
   The hepatopulmonary syndrome.
   Ann. Intern. Med. 1995, *122:* 521-529.
5. Abrams G.A., Fallon M.B.
   The hepatopulmonary syndrome.
   Clin. Liver Dis. 1997, *1:* 185-200.
6. Van Thiel D.H., Schade R.R., Gavaler J.B., Shaw B.W., Iwatsoki S., Starzl T.E.
   Medical aspects of liver transplantation.
   Hepatology 1984, *4:* 795-835.
7. Krowka M.J., Cortese D.A.
   Hepatopulmonary syndrome: an evolving perspective in the era of liver transplantation.
   Hepatology 1990, *11:* 138-142.
8. Krowka J.M., Porayko M.K., Plevak D.J., Pappas S.C., Steers J.L., Krom R.A.F., Wiesner R.H.
   Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review.
   Mayo Clin. Proc. 1997, *72:* 44-53.
9. Hobeika J., Houssin D., Bernard O., Devictor D., Grimon G., Crapuis Y.
   Orthotopic liver transplantation in children with chronic liver disease and severe hypoxemia.
   Transplantation 1994, *57:* 224-227.
10. Battaglia S.E., Pretto J.J., Irving L.B., Jones R.M., Angus P.W.
    Resolution of gas exchange abnormalities and intrapulmonary shunting following liver transplantation.
    Hepatology 1997, *25:* 1228-1232.
11. Vachiéry F., Moreau R., Hadengue A., Gadano A., Soupison T., Valla D., Lebrec D.
    Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations.
    J. Hepatol. 1997, *26:* 492-495.
12. Clària J., Jimenez W., Ros J., Asbert M., Castro A., Arroyo V., Rivera F., Rodes J.
    Pathogenesis of arterial hypotension in cirrhotic rats with ascites: role of endogenous nitric oxide.
    Hepatology 1992, *15:* 343-349.
13. Benoit J.L., Barrowman J.A., Harper S.L., Kvietys P.R., Granger D.N.
    Role of humoral factors in intestinal hyperemia associated with chronic portal hypertension.
    Am. J. Physiol. Endocrinol. Metab. 1984, *247:* G486-G493.
14. Van Thiel D.H., Kumar S., Gavaler J.S., Tarter R.E.
    Effect of liver transplantation on the hypothalamic-pituitary-gonadal axis of chronic alcoholic men with advanced liver disease.
    Alcohol Clin. Exp. Res. 1990, *14:* 478-481.

15. Guechot J., Chazouilleres O., Loria A., Hannoun L., Balladur P., Parc R., Giboudeau J., Poupon R.
Effect of liver transplantation on sex-hormone disorders in male patients with alcohol-induced or post-viral hepatitis advanced liver disease.
J. Hepatol. 1994, *20:* 426-430.
16. Madersbacher S., Ludvig G., Stuinig T., Grünberger T., Maler U.
The impact of liver transplantation on endocrine status in men.
Clin. Endocrinol. 1996, *44:* 461-466.
17. Vedernikov Y.P., Liao Q.-P., Jain V., Saade G.R., Chwalisz K., Garfield R.E.
Effect of chronic treatment with 17β-estradiol and progesterone on endothelium-dependent and endothelium-independent relaxation in isolated aortic rings from ovariectomized rats.
Am. J. Obstet. Gynecol. 1997, *176:* 603-608.
18. Pugh R.N.H., Murray-Lyon I.M., Dawson J.L., Pietroni M.C., Willians R.
Transection of the oesophagus for bleeding oesophageal varices.
Br. J. Surg.. 1973, *60:* 646-649.
19. Aller R., Moya J.L., Moreira V., Garcia Lledo A., San Román A.L., Paino C., Boixeda D.
Diagnosis and grading of intrapulmonary vascular dilatation in cirrhotic patients with contrast transesophageal echocardiography.
J. Hepatol. 1999, *31:* 1044-1052.
20. Sahn D.J., DeMaria A., Kisslo J., Weyman A., the Committee on M-mode Standardization of the American Society of Echocardiography.
Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements.
Circulation 1978, *58:* 1072-1083.
21. Abrams G.A., Jaffe C.C., Hoffer P.B., Binder H.J., Fallon M.B.
Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome.
Gastroenterology 1995, *109:* 1283-1288.
22. Vedrine J.M., Duperret S., Bizollon T., Magnin C., Motin J., Trepo C., Ducerf C.
Comparison of transesophageal and transthoracic contrast echocardiography for detection of an intrapulmonary shunt in liver disease.
Chest 1997, *1:* 1236-1240.
23. Lustik S.J., Chubbier A.K., Kolano J.W., Hilmi I.A., Heson L.C., Morris M.C., Bronsther O.
The hyperventilation of cirrhosis: progesterone and estradiol effects.
Hepatology 1997, *25:* 55-58.
24. Caranaugh J., Niewoeber C.B.M., Nutall F.Q.
Gynecomastia and cirrhosis of the liver.
Arch. Intern. Med. 1990, *150:* 568.
25. Madersbacher S., Ludvik G., Stuinigt T., Grünberger T., Maler U.
The impact of liver transplantation on endocrine status in men.
Clin. Endocrinol. 1996, *44:* 461-466.
26. Bell H., Raknerud N., Falch J.A., Haug E.
Inappropriately low levels of gonadotrophins in amenorrhoeic women with alcoholic and non-alcoholic cirrhosis.
Eur. J. Endocrinol. 1995, *132:* 444-449.
27. Gavaler J.S., Van Thiel D.H.
Hormonal status of postmenopausal women with alcohol-induced cirrhosis: further findings and a review of the literature.
Hepatology 1992, *16:* 312-319.
28. Miller V.M., Vanhoutte P.M.
Progesterone and modulation of endothelium-dependent responses in canine coronary arteries.
Am. J. Physiol. Endocrinol. Metab. 1991. *261:* R1022-R1027.
29. White M.M., Zamudio S., Stevens T., Tyler R., Linderfeld J., Leslie K.
Estrogen, progesterone, and vascular reactivity: potential cellular mechanism.
Endocr. Rev. 1995, *16:* 739-751.
30. Philibert D., Moguilewsky M., Mary I.
Pharmacological profile of RU 486 in animal.
In: Beaulieu E.E., Segal S.J. (Eds.), The antiprogestin steroid RU 486 and human fertility control.
Plenum Press, New York, 1985, p. 49.
31. Weiner C.P., Lizasoain I., Baylis S., Knowled R.G., Charles I., Moncada S.
Induction of calcium-dependent nitric oxide synthase by sex hormones.
Proc. Natl. Acad. Sci. USA 1994, *91:* 5212-5216.
32. Bell D.R., Resenberger H.J., Koritnik D.R., Koshy A.
Estrogen pretreatment directly potenciates endothelium-dependent vasorelaxation of porcine coronary arteries.
Am. J. Physiol. Endocrinol. Metab. 1995, *268:* H377-383.
33. Han Shu-Zhong, Karaki H., Ouchi Y., Akishita M.A., Orimo H.
17 beta-estradiol inhibits Ca^{2+} influx and Ca^{2+} release induced by thromboxane A2 in porcine coronary artery.
Circulation 1995, *91:* 2619-2626.
34. McLusky N.J., McEwen B.S.
Oestrogen modulates progestin receptor concentrations in some rat brain regions but not in others.
Nature 1978, *274:* 276-278.
35. Navasa M., Feu F., García-Pagan J.C., Jimenez W., Llach J., Rimola A., Bosch J., Rodés J.
Hemodynamic and humoral changes after liver transplantation in patients with cirrhosis.
Hepatology 1993, *17:* 355-360.