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Anesthesia for liver transplantation in patients with arterial hypoxemia

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Abstract. Arterial oxygenation during anesthesia and time of postoperative mechanical ventilation were investigated in 17 patients with chronic liver disease who underwent liver transplantation. Six patients had arterial hypoxemia (PaO_2 64 ± 3 mm Hg) and the other 11 patients had normal PaO_2 (105 ± 5 mm Hg) before transplantation. None of the patients were smokers and all had normal preoperative pulmonary X-ray and spirometry. During transplantation, PaO_2 increased in both groups, but PaO_2 was still approximately 20% lower and PA-aO_2 was 40%–60% higher in the hypoxemic group than in the normoxemic patients ($P < 0.05$). The median postoperative time on mechanical ventilation was three times longer in the hypoxemic group (56 h) than in the normoxemic patients (18 h; P = NS). Number or severity of postoperative complications and outcome did not differ between the two groups. It is therefore suggested that patients with arterial hypoxemia without overt lung disease should also be accepted for liver transplantation.

Key words: Anesthesia, in liver transplantation – Liver transplantation, anesthesia in

Patients with chronic liver disease often have impaired arterial oxygenation [7, 12, 15]. Hypoxemia has been described in as many as 60% of the patients [12]. Several mechanisms for the hypoxemia have been discussed, such as portopulmonary shunting [2], intrapulmonary shunting through arteriovenous fistula [1], diffusion limitations for oxygen [3], and disturbed ventilation-perfusion relationships [11, 14, 17]. A recent study, demonstrating normalization of arterial oxygen tension and ventilation-perfusion disturbances after successful liver transplantation, suggests that the latter may be due to vasodilating substances produced by, or not metabolized by, the diseased liver [5]. On induction of general anesthesia, almost all lung-healthy patients develop atelectasis and intrapulmonary shunting, resulting in impaired gas exchange [4, 8, 9]. A liver transplantation is a very long procedure, the operating time being 10–15 h. It is therefore of clinical importance to analyze changes in arterial oxygenation during anesthesia in these patients, many of whom have low PaO_2 even when they are not under anesthesia. Moreover, it is not known what effect arterial hypoxemia might have on the outcome of transplantation. To investigate this, we have compared arterial blood gases during and after liver transplantation, time of postoperative mechanical ventilation, number and severity of complications, as well as 3-month survival after transplantation in patients with preoperative arterial hypoxemia to those in patients with normal oxygenation.

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Patients and methods

Patients

At our center, 61 liver transplantations have been performed in 50 patients. Six of the patients have been children. In this study we have retrospectively reviewed all adult patients who underwent liver transplantation. Chronic liver failure was the indication for transplantation in 34 adult patients. Seventeen of these patients were excluded, due to moderate to heavy smoking, radiological changes, such as pneumonia or pleural effusions, pathological preoperative spirometry, hepatic coma, or mechanical ventilation prior to transplantation. Of the remaining 17 patients, 6 (3 men and 3 women) had arterial hypoxemia ($PaO_2 \leq 75$ mm Hg) and 11 (4 men and 7 women) had normal arterial oxygen tension. The severity of the liver disease and $PaCO_2$ were similar in the two groups (Table 1). Thus, there were no significant differences in Child-Pugh classification [13], alanine aminotransferase (ALAT), albumin, bilirubin, thrombocytes, or coagulation parameters between the two groups (data not shown). The patients are described in more detail in Table 1.

Before patients with end-stage liver failure were accepted for liver transplantation, they were evaluated with several tests, including arterial blood gases, spirometry, and pulmonary X-ray. After admission to the hospital for liver transplantation, a new arterial blood gas analysis and pulmonary X-ray were performed.

Table 1. Clinical data, arterial blood gases before transplantation, duration of operation, and complications. Numbers in brackets are median values. Tyr, Tyrosinemia; CAH, chronic acute hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; CC, cryptogenic cirrhosis; Esof var, esofageal varices; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; P_A-aO_2, alveoloarterial oxygen tension difference; Postop vent, postoperative mechanical ventilation; MOF, multiple organ failure

Patient number/ Diagnosis	Clinical findings	Sex M/F	Age (years)	Child score	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	P_A-aO_2 (mm Hg)	Operation time (h)	Postop vent (h)	Complications
Hypoxemic patients										
1 Tyr	Esof var, ascites, cyanosis, clubbing of fingers	F	17	9	52	35	52	14	88	-
2 CAH	Esof var, ascites	M	31	13	75	29	38	16	9	MOF, died after 2 months
3 CAH	Esof var, ascites, cyanosis, clubbing of fingers	F	36	12	62	30	49	15	88	Cardiac and cerebral infarction, seizures
4 PSC	Ascites	M	51	11	75	16	52	11	23	-
5 PBC	Esof var, ascites	F	46	8	65	35	40	9	7	-
6 CC	Esof var, ascites, cyanosis, clubbing of fingers	M	44	9	53	37	51	11	96	-
Mean			38	(10)	64	30	48	12.5	(56)	
SE			±5.0		±3	±3	±3	±1.3		
Normoxemic patients										
7 PSC	Esof var, ascites	M	54	10	119	29	2	12	8	Septicemia, died after 2 months
8 PBC	Ascites	F	55	10	89	29	24	13	28	Massive pleural effusion
9 PBC	-	F	44	9	104	30	7	15	-	Cardiovascular collapse, died day 1
10 PBC	Esof var, ascites	F	47	9	93	36	11	11	14	Primary nonfunction, died day 7
11 PBC	Ascites	M	24	13	130	27	12	13	20	Retransplanted day 7
12 PBC	-	M	41	9	92	36	12	11	19	-
13 PBC	Esof var, ascites	F	52	9	145	22	2	11	17	-
14 PBC	Esof var, ascites	F	41	10	117	30	2	11	59	-
15 PBC	Esof var, ascites	F	37	11	94	25	24	12	>100	-
16 CAH	Ascites	M	19	10	97	32	15	10	17	-
17 PSC	Esof var, ascites	F	38	13	98	29	11	11	14	-
Mean			41	(10)	105	30	10	11.7	(18)	
SE			±3.5		±5	±1	±3	±0.5		

Anesthesia

After premedication with 5–10 mg oxycone and 0.2–0.4 mg scopolamine subcutaneously, the patients were transferred to the operating theater. Anesthesia was induced with the rapid sequence technique, since few of the patients were fasting. Induction of anesthesia was done with 100–250 mg thiopental IV, followed by 75–100 mg suxamethonium IV to facilitate endotracheal intubation. Anesthesia was maintained with 0.5%–2% isoflurane inspired concentration in oxygen/air, supplemented with 0.1 mg fentanyl IV, and 1–2 mg midazolam IV or 5 mg diazepam IV intermittently. Muscle paralysis was prolonged with pancuronium bromide, loading dose 6–8 mg IV, and maintained with 1 mg supplementary doses when needed. Inspired oxygen fraction (FiO_2) was 0.4 after induction of anesthesia (preanhepatic period). During the anhepatic state, FiO_2 was 1.0. Venovenous bypass (Biomedicus, Minnetonka, Minn) was used in all patients during the anhepatic period. After insertion of the new liver (postanhepatic period), FiO_2 was reduced to 0.3–0.5, to provide a PaO_2 in excess of 120 mm Hg. Inspired oxygen fraction was measured using the polarographic technique (Capnomac, Datex, Helsinki, Finland). During the anesthesia, the patients were ventilated mechanically (Servo 900 C, Siemens Elema, Solna, Sweden) at a respiratory rate of 14 breaths/min. Minute volume was set to maintain an end-expiratory CO_2 concentration of approximately 4%. Carbon dioxide concentration was measured with an infrared analyzer (Capnomac).

Perioperative management

During anesthesia and before commencing surgery, an arterial line, a central venous and a pulmonary artery catheter were inserted for pressure recordings and blood sampling. Arterial blood gases were assessed hourly before and after the anhepatic period, during which blood gases were sampled every 15 min. During the operation the patients received 5% glucose and acetated Ringer's solution as basal fluid replacement. Plasma (fresh-frozen or stored) was used for volume replacement and to substitute for deficient coagulation factors, in combination with specific concentrates of factors VII, VIII, and IX, when needed. Blood lost was replaced with packed erythrocytes in Sagman solution and plasma.

After transplantation, the patients were transferred to the intensive care unit for postoperative observation. The patients were

Table 2. Arterial blood gases before and during anesthesia and at extubation. FIO_2, Inspired oxygen fraction; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; $PA\text{-}aO_2$, alveolar-arterial oxygen tension difference

	Normoxemic patients				Hypoxemic patients			
	FIO_2	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	$Pa\text{-}aO_2$ (mm Hg)	FIO_2	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	$PA\text{-}aO_2$ (mm Hg)
Awake before transplantation	0.21 ± 0.0	105 ± 5	30 ± 2	10 ± 3	0.21 ± 0.0	64 ± 3[d]	30 ± 3	48 ± 3[d]
Anesthesia								
Preanhepatic period	0.37 ± 0.01	128 ± 10	30 ± 1	102 ± 13	0.42 ± 0.04	99 ± 5	30 ± 1	161 ± 25[b]
Anhepatic period	1.00 ± 0.0	496 ± 17	30 ± 1	185 ± 14	1.00 ± 0	410 ± 30[b]	32 ± 1	262 ± 30[b]
Postanhepatic period	0.45 ± 0.06	190 ± 20	35 ± 2	109 ± 35	0.48 ± 0.02	137 ± 21[b]	35 ± 2	156 ± 33
In the intensive care unit								
Before extubation (1 h before)	0.31 ± 0.01	125 ± 8	36 ± 2	22 ± 1[e]	0.45 ± 0.03	82 ± 1[c]	38 ± 1	180 ± 12[d, f]
After extubation (1 h after)	3.4 ± 0.3[a]	122 ± 10	42 ± 2	–	4.6 ± 0.3[a]	79 ± 1[b]	42	–

[a] FIO_2 after extubation signifies given volume of oxygen (l/min) through a nasopharyngeal catheter
[b] Significantly different from the normoxemic patients, $P < 0.05$
[c] Significantly different from the normoxemic patients, $P < 0.01$
[d] Significantly different from the normoxemic patients, $P < 0.001$
[e] Significantly different from awake before transplantation, $P < 0.05$
[f] Significantly different from awake before transplantation, $P < 0.01$

mechanically ventilated until they were hemodynamically stable, body temperature was normalized, and arterial oxygenation was adequate at FIO_2 0.3. The mechanical ventilation was done with a Servo 900 B or C (Siemens-Elema, Solna, Sweden). Ventilatory frequency was 12–14 breaths/min. FIO_2 was adjusted to maintain a PaO_2 above 75 mm Hg and minute ventilation set to result in a $PaCO_2$ within the normal range.

Gas analysis

The arterial blood samples were analyzed for PaO_2 and $PaCO_2$ with standard techniques (ABL-2, Radiometer, Copenhagen, Denmark). Alveolar-arterial oxygen tension difference ($PA\text{-}aO_2$) was calculated as $PIO_2\text{-}PaO_2\text{-}PaCO_2/0.8$, PIO_2 being inspired oxygen tension of the warmed and humidified inspired gas and 0.8 an assumed respiratory gas exchange ratio. Data presented on arterial blood gases during anesthesia are mean values for all samples acquired during the respective period.

Statistical analysis

Data are presented as the mean ± standard error of the mean (SE), except for the times on mechanical ventilation postoperatively, where median values are used, due to the wide range of times spent on the ventilator. Wilcoxon's two-sample test was used to test differences between the hypoxemic and normoxemic patients.

Results

Transplantation procedure

The average operating time for the liver transplantation procedure was 12 h (range 8–16 h), with no differences between the normoxemic and hypoxemic patients. Blood loss during transplantation was highly variable (range 2–20 l); the normoxemic patients had a mean of 8 ± 2 l and the hypoxemic patients one of 11 ± 3 l, a nonsignificant difference. Blood lost was replaced with equal amounts of packed erythrocytes and plasma. In general, two-thirds of the plasma was given as fresh-frozen plasma and the remainder as stored plasma. In patients where hemostasis was difficult to control, a relatively higher proportion of fresh-frozen plasma was used. The normoxemic patients were given 9 ± 1 l of plasma and the hypoxemic patients received 12 ± 2 l during transplantation (P = NS). Platelets were given to eight patients (four in each group). Four patients (three normoxemic and one hypoxemic) were given factor VIII and IX concentrates, due to impaired hemostasis during transplantation. No correlation was found between intraoperative bleeding and operation time or PaO_2.

Perioperative gas exchange

Arterial oxygen tension and $PA\text{-}aO_2$ during the varying conditions are shown in Tables 1 and 2. Before anesthesia, the normoxemic patients had a mean PaO_2 of 105 ± 5 mm Hg and the hypoxemic patients one of 64 ± 4 mm Hg ($P < 0.001$). $PA\text{-}aO_2$ was 10 ± 3 mm Hg in the normoxemic patients and 48 ± 3 mm Hg in the hypoxemic patients ($P < 0.001$). $PaCO_2$ was 30 mm Hg in the two groups, both out of and in the anesthetized state before surgery. During anesthesia, PaO_2 increased in both groups due to increased FIO_2. However, PaO_2 was significantly lower and $PA\text{-}aO_2$ higher in the hypoxemic group before, during, and after the anhepatic period, but not during the preanhepatic period (Table 2). PaO_2 and $PA\text{-}aO_2$ in normoxemic liver patients, before and during anesthesia, did not differ from those previously reported during inhalational anesthesia in subjects with normal heart, lung, and liver function [8, 9].

Postoperative ventilation

Several factors influenced the time of mechanical ventilation after the operation. The patients were hypothermic (mean body temperature 35.5 °C) at the end of transplantation, despite the fact that they were placed on a heated water mattress (temperature 40°–42 °C) and covered with heat-insulating dressing. Due to the hypothermia and the time when transplantation was completed (usually late in the afternoon or in the evening), all patients were mechanically ventilated overnight. The normoxemic patients were extubated when PaO_2 was in the normal range with an FIO_2 of approximately 0.3 on mechanical ventilation. The hypoxemic patients were taken off the ventilator when they were judged to be stable and PaO_2 had returned to the preoperative level, even if FIO_2 was as high as 0.5 in the ventilator (Table 2). The time of postoperative mechanical ventilation was highly variable (range 7 h–3 weeks; Table 1). The median time for normoxemic patients was 18 h, as compared to 56 h in hypoxemic ones, a nonsignificant difference.

After extubation the patients received supplemental oxygen through a nasal catheter, 1–6 l/min, until PaO_2 had returned to the preoperative level. The two groups differed significantly in PaO_2 and $PA\text{-}aO_2$ immediately before extubation (Table 2). In the hypoxemic patients, the gas exchange seemed to be improved after termination of mechanical ventilation as compared to before transplantation. Moreover, a major part of the higher PaO_2 at extubation was caused by the supplementary oxygen given (Table 2). No significant differences in PaO_2 in the hypoxemic patients from before transplantation to time of extubation were found.

Patient number 3 was extubated on the morning of the 4th postoperative day, but had to be reintubated in the evening, due to hypoventilation despite vigorous attempts to encourage spontaneous ventilation. The decreased respiratory drive was largely caused by arterial alkalinization after transplantation, and after treatment with hydrochloric acid the patient could successfully be taken off the ventilator. The same patient also developed cerebral and cardiac infarcts, resulting in epileptic seizures despite medication. One patient (number 8) required drainage of excessive pleural effusion before being taken off the ventilator.

Major complications

Four patients (three normoxemic and one hypoxemic) died within the first 3 postoperative months. One patient died in the immediate postoperative period due to cardiovascular collapse, one within a week due to failure of the new liver, one after 2 months of multiple organ failure, and the fourth patient 2 months after transplantation from septicemia. No significant difference was found between normoxemic and hypoxemic patients in 3-month survival. One normoxemic patient was retransplanted 1 week after the primary transplantation. However, that patient had left the intensive care unit with normal arterial oxygen tension several days before the second transplantation.

Discussion

Several studies have demonstrated that patients with cirrhosis of the liver often have impaired arterial oxygenation [7, 12, 15], even if only 5%–8% have severe hypoxemia [12]. In many cases the low PaO_2 could be due to smoking, obstructive lung disease, or intrapulmonary changes, such as pneumonia and atelectasis. In the present study, all smokers and patients with pathological findings in chest X-ray or lung function tests were excluded to eliminate primary lung disorders as the cause of low PaO_2. The reason for hypoxemia in the current six patients could, therefore, be blamed on the liver disease itself. Since severe arterial hypoxemia is regarded as a contraindication to liver transplantation [10], it is important to establish the fate of these patients during anesthesia and in the immediate postoperative period.

During anesthesia $PA\text{-}aO_2$ increased in both the normoxemic and hypoxemic patients, indicating further impairment in gas exchange. As could be expected, this increase was more marked in the patients with hypoxemia. It is noteworthy, however, that the difference between the groups was less marked during than before anesthesia. In patients with liver disease and hypoxemia, the intrapulmonary vascular changes previously observed at autopsy and by radiography, such as precapillary dilation, arteriovenous anastomoses, and spider nevi, have primarily been located in the lower parts of the lung [1, 2, 16, 18]. In the same regions, patients with normal heart, lung, and liver function develop atelectasis and intrapulmonary shunt on induction of anesthesia, due to altered lung mechanics [8, 9]. If these regions were exposed to atelectasis and shunt in cirrhotic and hypoxemic patients, the deterioration in oxygen uptake would be less obvious than in patients without preanesthetic intrapulmonary vascular changes. However, whether this hypothesis could explain the diminished discrepancy between our hypoxemic and normoxemic patients during transplantation is thus far not known.

The current study demonstrates that the outcome of the operation was not influenced by the low PaO_2. Even the patients with severe hypoxemia (patients number 1 and 6) were successfully managed during and after transplantation. Moreover, no significant difference was found in the time on mechanical ventilation after the operation, although the median time on the ventilator was longer in the hypoxemic group. In this context, it has to be realized that the groups investigated were small and that the duration of postoperative mechanical ventilation is influenced by several factors, such as complications during and after transplantation, irrespective of the preoperative PaO_2.

The current findings suggest that hypoxemia per se should not be a contraindication for liver transplantation. This is supported by the results from a previous study on six patients with impaired ventilation-perfusion matching and/or intrapulmonary shunting before liver transplantation [6], demonstrating a normalization of vascular abnor-

malities and low PaO_2 3–6 months after transplantation. Thus, from the present and previous studies, it is suggested that hypoxemia in cirrhotic patients without lung disease is concurrent with the liver disease itself and is reversible when liver function is normalized.

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