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RIGHT PHRENIC NERVE INJURY IN ORTHOTOPIC LIVER TRANSPLANTATION¹

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Right hemidiaphragm paralysis has been previously documented in patients after orthotopic liver transplantation (OLT) and it may contribute to the development of postoperative pulmonary problems. It has been postulated that a crush injury to the right phrenic nerve during OLT is the cause of dysfunction of the right hemidiaphragm. To assess the incidence and effect of right phrenic nerve injury after OLT, we prospectively studied 48 adult liver recipients. Twelve patients who underwent liver resection (LR), in whom the suprahepatic vena cava was not clamped, were used as a comparison group. Diaphragm excursion by ultrasound and pulmonary function were performed preoperatively and postoperatively; transcutaneous phrenic nerve conduction studies were performed postoperatively.

Right phrenic nerve injury and hemidiaphragm paralysis occurred in 79% and 38% of the liver recipients but not after LR. Conduction along the right phrenic nerve was absent in 53% and reduced in another 26%. Left phrenic nerve conduction and left hemidiaphragm excursion were normal in both liver recipients and the patients who had LR. Liver recipients with no conduc-

tion in the right phrenic nerve had a significantly greater decrease in vital capacity in the supine position ($29 \pm 9.8\%$) compared with those with some conduction ($14 \pm 6.9\%$, $P < 0.001$). However, neither the time on the ventilator nor the hospital stay was significantly different in the latter two groups. Complete recovery of phrenic nerve conduction and diaphragm function took until nine months in some patients.

Right phrenic nerve injury is common after OLT and it is the cause of right hemidiaphragm dysfunction.

Respiratory complications occur in 40-78% of patients after orthotopic liver transplantation (OLT) (1, 2). Pleural effusions, atelectasis and pneumonia are common causes of morbidity (3-6). Contributing factors include poor respiratory effort secondary to debilitation, altered consciousness level, and ascites.

Paralysis of the diaphragm is an additional mechanical factor that could potentially exacerbate hypoventilation in patients after OLT but the frequency of this complication has not been carefully studied. Starzl made the first observation of paralysis of the right hemidiaphragm after OLT (7). He documented transient right hemidiaphragm paralysis in four children and postulated that it was due to a crush injury of the right phrenic nerve from the suprahepatic caval clamp. In a series of 100 liver recipients at UCLA a paralyzed diaphragm on the right side was noted on the postoperative chest x-ray in 12 patients (4). In a preliminary study we found ultrasound evidence of reduced excursion of the right hemidiaphragm in 9 of 11 liver recipients (8).

To determine the frequency of right diaphragm dysfunction and the evidence for phrenic nerve injury as the direct cause of

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this complication we prospectively studied 51 patients undergoing liver transplantation. Twelve patients with liver resections (LR)* were used as a comparison group. Their abdominal incisions and subdiaphragmatic dissections were similar to patients with OLT but the suprahepatic vena cava was not clamped during liver resection.

MATERIALS AND METHODS

Fifty-one consecutive adult patients who received liver transplants between January 1991 and December 1991 were prospectively evaluated. Three patients died in the early postoperative period, leaving 48 patients in the study. There were 24 females and 24 males ranging in age from 16 years to 67 years (mean 41 years). The indications for transplantation were primary biliary cirrhosis (16), sclerosing cholangitis (10), alcoholic cirrhosis (8), cancer (4), and other (10). Preoperative tests included ultrasound examination of the diaphragm, routine pulmonary function tests, and chest x-ray. During OLT the suprahepatic vena cava was clamped using an 11-inch 60° Debakey clamp (Codman, USA), the tip of which was secured in a bolt and wingnut similar to that described by Calne (9). Other aspects of the recipient operation have been previously described (10). In the third postoperative week, the diaphragm ultrasound and the pulmonary function tests were repeated, and transcutaneous phrenic nerve conduction studies were done. Patients with abnormal tests were studied again at three, six, and nine months. Twelve patients who had an LR (each had a right hepatic lobectomy) underwent the same postoperative tests and were used for comparison. There were 2 females and 10 males ranging in age from 28 to 63 years. The indications for LR were hepatoma (4), metastatic cancer (5), and benign tumors (3).

Phrenic nerve conduction. Phrenic nerve conduction was examined using the technique described by Markand et al (11). At peak expiration the phrenic nerve was supramaximally stimulated percutaneously in the neck. The compound muscle action potential from the ipsilateral hemidiaphragm was recorded with surface electrodes positioned over the costal margin in the anterior axillary line and over the xiphoid sternum, using the Clark Davis Advantage EMG System (London, Ontario, Canada). Peak-to-peak amplitude and motor terminal latency were recorded.

Diaphragm ultrasound. With the patients supine, each hemidiaphragm was scanned between the posterior and middle axillary lines using a 3.5 MHz probe. The positions of the hemidiaphragm at end-expiration and end-inspiration were marked. The direction of movement on inspiration and on sniffing was recorded. Excursion of the hemidiaphragm was defined as the distance between these two marks. Paralysis of the hemidiaphragm was defined as absence of detectable movement or paradoxical movement on inspiration or sniff.

Pulmonary function studies. Forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were measured in both the erect and supine positions because previous studies have shown that patients with isolated diaphragm weakness have a greater than usual decrease in vital capacity on lying supine (ΔVC) (11, 12).

Statistical analysis. Parametric data were compared using the Mann-Whitney *U* test. Ordinal data were compared using Fisher's exact test. Data are provided as the mean $\pm$ SD, with the exception of days on the ventilator and hospital stay, which are expressed as median time and range.

RESULTS

Phrenic nerve conduction. Five patients after OLT and 6 after LR did not undergo nerve conduction study. Evidence of right phrenic nerve injury was found in 34 patients (79%) after OLT. In twenty-three patients there was no conduction present

(inexcitable) and in another 11 the amplitude of the impulse was less than 80% of that seen on the left. In only 9 patients (21%) was the amplitude of the response on the right 80% or more of that seen on the left. This was interpreted as normal. Left phrenic nerve conduction was normal in all of the liver recipients, and phrenic nerve conduction was normal on both right and left sides in all patients after LR (Table 1). When patients with no conduction in the right phrenic nerve after OLT were excluded, the mean amplitude of the compound muscle action potential of the right phrenic nerve in the remaining 20 liver recipients was still significantly less than that seen on the left ($P < 0.01$). It was also significantly less than the amplitude found in either right or left phrenic nerve conduction in the LR patients ($P < 0.05$). In those OLT patients in whom some conduction was present on the right side, the latency was not significantly different compared with the left side and it was not different from the latency on either right or left side in the LR patients.

Diaphragm ultrasound. Nine patients who had emergency OLT did not undergo preoperative ultrasound testing. All patients completed the ultrasound examination postoperatively. Right hemidiaphragm paralysis was seen in 18 of 48 patients (38%) after OLT, all of whom had no conduction demonstrated in the right phrenic nerve. Diaphragm paralysis was not seen in any LR patient. When patients with right hemidiaphragm paralysis were excluded, the mean excursion of the right hemidiaphragm in the remaining 30 patients after OLT was significantly less than right hemidiaphragm excursion before OLT ($P < 0.01$), significantly less than left hemidiaphragm excursion after OLT ($P < 0.001$), and significantly less than right hemidiaphragm excursion after LR ($P < 0.05$) (Table 2).

Pulmonary function. Seventeen liver recipients did not have preoperative testing because of emergency transplantation, pre-

TABLE 1. Phrenic nerve conduction studies*

	OLT group n = 43	LR group n = 6	P value
No conduction right nerve	23	0	<0.05
No conduction left nerve	0	0	—
Right side: amplitude (mV)	0.4 $\pm$ 0.2 ^b	0.9 $\pm$ 0.4	<0.05
Left side: amplitude (mV)	0.8 $\pm$ 0.3 ^b	0.9 $\pm$ 0.4	NS
Right side: latency (msec)	7.7 $\pm$ 1.8	7.3 $\pm$ 0.2	NS
Left side: latency (msec)	7.5 $\pm$ 1.2	6.8 $\pm$ 0.8	NS

* Amplitude and latency data exclude those patients with inexcitable nerves (mV = millivolts; msec = milliseconds).

^b $P < 0.05$.

TABLE 2. Diaphragm excursion as measured by ultrasound*

	OLT preoperative n = 39	OLT postoperative n = 48	LR postoperative n = 12
Right side paralysis	0	18 ^b	0 ^b
Left side paralysis	0	0	0
Right side (cm)	3.2 $\pm$ 0.9 ^c	1.9 $\pm$ 0.9 ^{c,d,e}	2.8 $\pm$ 1.0 ^c
Left side (cm)	3.4 $\pm$ 1.0	3.0 $\pm$ 1.0 ^d	2.8 $\pm$ 0.9

* The postoperative time was approximately 3 weeks after surgery. Diaphragm excursion data exclude those patients with diaphragm paralysis (no movement).

^b $P < 0.01$.

^c $P < 0.01$.

^d $P < 0.001$.

^e $P < 0.05$.

* Abbreviations: ΔVC , percentage decrease in vital capacity on lying supine; FEV1, forced expired volume in the first second; FVC, forced vital capacity; LR, liver resection.

operative coma, or an inability to cooperate. Postoperatively, 11 liver recipients and 5 LR patients failed to complete pulmonary function testing because of mechanical ventilation, pain, confusion, or distance from the hospital. FVC and FEV1 were reduced postoperatively after OLT compared with preoperative values (Table 3). The postoperative Δ VC was significantly greater than the preoperative Δ VC in the patients who had OLT ($P<0.01$) and it was also significantly greater than the Δ VC seen in the patients after LR ($P<0.005$). In liver recipients with no phrenic nerve conduction, the Δ VC was significantly greater than in patients who had some phrenic nerve response ($29\pm 9.8\%$ versus $14\pm 6.9\%$, respectively [$P<0.001$]) but no significant differences in days on the ventilator and hospital stays were seen between those two groups (Table 4). No LR patient required postoperative ventilation and the median hospital stay after LR was 13 days (range 8–32 days).

As shown in Table 4, not every patient with absent conduction in the right phrenic nerve had a paralyzed diaphragm. There were 5 patients in whom no nerve conduction was present yet they demonstrated movement of the right hemidiaphragm on ultrasound examination. This finding is specifically addressed in the discussion below.

Follow-up studies. Of 23 patients with no nerve conduction at 3 weeks, eight lived nearby and were available for serial testing and long-term follow-up. At three months four patients had normal right hemidiaphragm excursion with low amplitude right phrenic nerve impulses. No improvement was seen in the other four patients. At six months two more patients had recovery of phrenic nerve conduction and right hemidiaphragm

movement, and by nine months the remaining two patients also demonstrated the return of phrenic nerve conduction and diaphragm function to normal.

DISCUSSION

This study has shown that right phrenic nerve injury is common after OLT and in the majority it resulted in abnormal movement of the right hemidiaphragm. Evidence of impaired nerve function ranged from moderate reduction in conduction to no response, and evidence of impaired diaphragm dysfunction ranged from significantly reduced excursion to complete paralysis. The absence of nerve conduction abnormalities or diaphragm paralysis in the group of LR patients rules out the subdiaphragmatic dissection as a possible cause of nerve injury or diaphragm dysfunction. Therefore, as suggested by Starzl many years ago, diaphragmatic paralysis is the result of a crush injury to the phrenic nerve from the suprahepatic caval clamp (7). During OLT, the proximity of the phrenic nerve as it pierces the diaphragm either with or just lateral to the inferior vena cava makes it easy to include it in the bite of tissue taken with the clamp. Small sensory twigs to the parietal pleura are given off above the diaphragm. The three motor branches that supply the muscular portion of the diaphragm are given off as the nerve passes through the muscle (14). Taking a generous portion of the diaphragm in the clamp increases the security of the grip but it makes the nerve more vulnerable to incorporation in the tissue between the jaws. Dissection of the diaphragm off the lateral border of the vena cava may allow placement of the clamp without including the nerve. Also, extra length of the caval cuff may be achieved by isolating the orifices of the hepatic veins in the caval opening permitting application of the clamp without a large bite of the diaphragm (15). The piggyback technique of liver replacement should help to avoid phrenic nerve injury by side-clamping rather than cross-clamping the vena cava (16).

In the liver recipients who demonstrated some conduction in the right phrenic nerve, the mean amplitude of the compound muscle action potential from the right hemidiaphragm was about half that seen on the normal left side, while the latency was normal (Table 1). This pattern suggests a conduction block of some, but not all, of the axons in the nerve, in contrast to the total block seen in those patients with no conduction. When the block is due to a neuropraxia early recovery is expected. When the injury is severe, axonal regeneration must occur from the site of the crush injury to the neuromuscular end plate.

TABLE 3. Pulmonary function tests^a

	OLT preoperative	OLT postoperative	LR postoperative
	n = 31	n = 37	n = 7
FEV1 erect	2.9±0.7	2.4±0.7	2.8±1.3
FEV1 supine	2.6±0.6	2.0±0.6	2.5±1.34
FVC erect	3.8±0.8	2.6±0.9	3.3±1.4
FVC supine	3.5±0.7	2.1±0.9	3.2±1.9
Δ VC	8.8±5.7% ^b	22.5±11.7% ^{b,c}	4.6±4% ^c

^a Postoperative time is approximately 3 weeks after surgery. (FEV1) forced expired volume in first second; (FVC) vital capacity; (Δ VC) decrease in vital capacity between supine and erect position.

^b $P<0.01$.

^c $P<0.005$.

TABLE 4. Effect of right phrenic nerve injury after liver transplantation^a

	No conduction n = 23	Some conduction n = 21	P value
Right hemidiaphragm paralysis	18	0	<0.00001
Left hemidiaphragm paralysis	0	0	
Right hemidiaphragm excursion (cm)	1.5±1.0 ^b	1.9±0.9 ^c	0.4
Left hemidiaphragm excursion (cm)	2.9±0.8 ^b	3.1±1.2 ^c	0.5
Left phrenic nerve amplitude (mV)	0.8±0.3	0.7±0.3	0.3
Left phrenic nerve latency (mSec)	7.7±1.5	7.1±0.9	0.5
Postoperative Δ VC	29%±9.8%	14.6±6.9%	0.001
Postoperative days on ventilator	3 (1–91)	1 (1–19)	0.2
Postoperative days in hospital	35 (13–100)	32 (14–49)	0.5

^a Right diaphragm excursion excludes those patients with diaphragm paralysis. ([Δ VC] decrease in vital capacity on assuming supine from erect position. Numbers in brackets are range).

^b $P<0.001$.

^c $P<0.001$.

This recovery may take many months. It is possible that the design of this study missed some nerve injuries because nerve conduction tests were not performed until three weeks after OLT. Recovery from mild neuropraxias may have occurred during this interval. In the initial observations of Starzl, recovery of diaphragm movement occurred as early as 2 weeks after transplantation (7). The follow-up data on patients with no conduction in this series suggests that most patients with nerve injury should have eventual complete return of motor function.

Of particular note was the fact that ultrasound examination revealed somewhat reduced, but nevertheless appropriate, movement of the right hemidiaphragm in five patients after OLT who also had no conduction measured in the right phrenic nerve. This finding may be explained in one of several ways. Diaphragmatic movement could have been caused by the transmission of increased intraabdominal pressure by contraction of abdominal muscles during expiration. Alternatively, intrinsic movement of the diaphragm could have occurred from peripheral innervation from intercostal nerves, or axons of the phrenic nerve that were spared from injury could have supplied parts of the diaphragm that were not recorded by the electrodes placed over the chest.

The pulmonary function test most severely affected in patients with diaphragm dysfunction was the ΔVC between the supine and erect positions. On assuming the supine position, a reduction in vital capacity of approximately 7.5% can be expected in normal subjects (17). After OLT the ΔVC was reduced by 22.5% in the patients in this series and it was reduced by 29% in those patients in whom right phrenic nerve conduction was absent. It has been shown that paralysis of the right hemidiaphragm causes a greater reduction in supine vital capacity than left hemidiaphragm paralysis (19 versus 10%) (18). Diaphragmatic paralysis results in ventilation and perfusion abnormalities in the lower lobe on the affected side (19). When individuals with isolated diaphragm weakness are otherwise healthy, the effects on respiration are usually minimal. Mild dyspnea and orthopnea are the most common complaints in reported series (12, 13, 19, 20). In a study of patients with unilateral phrenic nerve injury after coronary artery revascularization, only those patients who were malnourished or who had co-existing respiratory problems developed symptoms (21), but diaphragm dysfunction in patients with cirrhosis who are undergoing transplantation has potentially far greater implications for several reasons. The debilitated, malnourished condition of most liver transplant candidates limits their respiratory reserve, making them less able to compensate with increased effort to improve the mechanics of ventilation. If the hepatopulmonary syndrome is present, hypoxemia would be worsened by additional ventilation-perfusion mismatching caused by diaphragm paralysis (22, 23). Perioperative fluid shifts in hypoalbuminemic patients not uncommonly results in degrees of pulmonary edema that further impairs gas exchange. When the mechanics of respiration are already reduced any additional pulmonary problem would be magnified. As a means of optimizing pulmonary function after transplantation nursing recipients in the semi-upright position should help to partially correct the abnormal ventilation resulting from a paralyzed diaphragm. This approach specifically addresses the significantly reduced vital capacity that these patients have when they are in the supine position. Plication of a paralyzed diaphragm results in improved pulmonary function (24). This approach would seem rarely necessary except in those patients

with such severe comorbid conditions that weaning from the ventilator would not be possible unless there was return of diaphragm function.

Although significant changes in pulmonary function were documented after OLT, it is difficult to attribute the changes purely to phrenic nerve injury and the resultant paralyzed diaphragm. Other factors that contribute to disturbed ventilation in sick liver recipients, such as altered sensorium and muscle wasting, make it difficult to isolate the role of diaphragmatic paralysis in the pathogenesis of postoperative respiratory complications. As a measure of morbidity we could not show that patients with absent phrenic nerve conduction required significantly longer time on the ventilator after transplantation compared with those who had some nerve conduction. Nevertheless, this pathophysiological study has identified a common ventilation abnormality in patients after OLT that is due to injury of the right phrenic nerve during surgery. Ultrasound is a reliable method of diagnosing diaphragmatic dysfunction and it allows the easy identification of those patients in whom specific efforts at chest physiotherapy can be directed in the posttransplant period.

PAPER NO. D-6 BY VIVIAN Mc ALISTER,

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DISCUSSION

DR. EDMOND (Chicago, Illinois): As you note, Dr. Starzl made similar observations in the 1960's. The most important group affected by this complication have been children weighing less than 10 kg. Among the 150-200 small children we have transplanted, diaphragm plications have been required about six times, usually to wean patients from the ventilator. Therefore, especially in small babies, it is crucial to keep the clamp down. The piggyback technique may offer an advantage since you don't have to clamp so high to avoid losing your vena cava cuff into the chest.

DR. V. McAlister: We agree.

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HEPATIC LIDOCAINE METABOLISM AND COMPLICATIONS OF CIRRHOSIS

IMPLICATIONS FOR ASSESSING PATIENT PRIORITY FOR HEPATIC TRANSPLANTATION^{1,2}

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The number of patients awaiting hepatic transplantation continues to exceed organ donation. As a result, many liver transplant candidates will develop life-threatening complications of their liver disease and not survive the pretransplant waiting period. Recent studies have demonstrated that hepatic lidocaine metabolism into monoethylglycinexylidide (MEG-X) can predict pretransplant survival. The present study was performed to determine if MEG-X could also predict pretransplant complications and thereby be useful in strat-

ifying persons being evaluated for hepatic transplantation. A total of 57 patients with biopsy-proven cirrhosis underwent MEG-X testing. Of 57 patients, 30 (53%) developed life-threatening complications of their liver disease—i.e., variceal bleeding, grade II hepatic encephalopathy or worse, and spontaneous bacterial peritonitis. MEG-X values were greater in persons without complications of liver disease than in persons with complications (25.7 ± 2.9 versus 14.7 ± 1.4 ng/ml, respectively). No patients with MEG-X greater than 30 ng/ml developed a major complication. No significant difference in any of the standard liver function tests existed between persons who developed complications and patients who did not. In this group of 57 patients, 4 (7%) died from complications of cirrhosis. Mean MEG-X for patients who died (5.5 ± 1.6 ng/ml) was significantly less ($P < 0.05$) than observed for other patient groups. All patients who died had MEG-X values below 10 ng/ml. This suggests that MEG-X testing could be an extremely useful test in the evaluation of patients for hepatic transplantation by identifying persons at increased risk for developing complications of chronic liver disease.

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