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Vecuronium Neuromuscular Blockade Reflects Liver Function during Hepatic Autotransplantation in Pigs

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Background: **Rapid assessment of hepatic function early after reperfusion of the liver graft is of great importance,because it may allow for prompt detection of incipient hepatic graft failure. The current study was undertaken to determine whether the continuous recording of neuromuscular transmission could be used as an on-line assessment of hepatic function during liver transplantation when a muscle relaxant with high hepatic uptake is used.**

Methods: **We quantified and compared the effect of liver exclusion and graft reperfusion on the level of vecuronium-induced neuromuscular blockade in nine pigs studied twice within 3 days. During the 1st day (control session), an intravenous infusion of vecuronium was administered to maintain a constant 90–95% twitch depression during 180 min. The twitch response was then allowed to recover spontaneously to 75% of its prerelaxant value. Neuromuscular transmission was continuously measured on the right anterior leg using an acceleration transducer. During the same time period, the metabolic rate of ^{14}C-labeled aminopyrine (a well-established quantitative test of the liver microsomal function) was determined by measuring the excretion of $^{14}CO_2$ in expired air after administration of an intravenous bolus of ^{14}C-labeled aminopyrine. Two days later, the pigs underwent a hepatic autotransplantation, during which vecuronium was administered to maintain a constant 90–95% twitch depression. After reperfusion of the liver graft, the vecuronium infusion rate was maintained at its anhepatic level, and the recovery index of the neuromuscular blockade (the time from 25% to 75% recovery of twitch height) was calculated. The aminopyrine breath test was performed during the last 30 min of the anhepatic phase, and during 3 h after reperfusion of the liver graft.**

Results: **During control studies, the mean infusion rate of vecuronium was 1.30 ± 0.33 $mg \cdot kg^{-1} \cdot h^{-1}$ and the recovery index was 3.4 ± 0.5 min. During liver dissection, the infusion rate of vecuronium was similar to the control value (1.18 ± 0.16 $mg \cdot kg^{-1} \cdot h^{-1}$), then considerably decreased to 0.05 ± 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$ during the anhepatic phase. After reperfusion of the liver graft, the recovery index was markedly prolonged to 35.5 ± 15.8 min, indicating a prolongation of the recovery of neuromuscular blockade by a factor of 10.4. Excretion of $^{14}CO_2$ was equal to zero during the anhepatic phase and then increased to 0.19 ± 0.11% during the 1st h after reperfusion of the liver graft, an excretion rate corresponding to 11.2% of control conditions. The relationship between individual changes in the recovery index of the neuromuscular blockade and $^{14}CO_2$ excretion in expired air after reperfusion of the liver graft showed a strong significant correlation ($r^2 = 0.71$).**

Conclusions: **These results indicate that, compared with the control studies, there is a similar decrease in the recovery rate of vecuronium-induced neuromuscular blockade and in the metabolic rate of ^{14}C-labeled aminopyrine during the progressive recovery of hepatic function immediately after unclamping of the liver vessels. Metabolism of ^{14}C-labeled aminopyrine increased progressively during the reperfusion phase. Therefore, recording of neuromuscular transmission during liver transplantation could serve as a continuous and easy to perform assessment of liver graft function provided that a muscle relaxant with a high hepatic uptake is used for neuromuscular blockade. (Key words: Animals: pig. Liver: liver function; transplantation. Monitoring techniques: accelerometry; aminopyrine breath test. Neuromuscular relaxants: vecuronium.)**

RAPID assessment of hepatic function early after reperfusion of the liver graft is of great importance because it may allow for prompt detection of incipient hepatic graft failure. Several hepatic parenchymal metabolic tests have been proposed to estimate the initial function of the transplanted liver.[1–5] Most of them are based on the clearance of exogenous or endogenous

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substances, and the results are not generally available during the liver transplantation.[1] It has been proposed that the increase in whole-body O_2 consumption measured after the recirculation of the liver graft may be used as an indicator of sufficient hepatic blood flow and immediate function of the transplanted liver.[6] Because this change in O_2 uptake is quickly observed after reperfusion of the liver graft, this easy but unspecific test can be used as an on–off indicator of hepatic function.[7] We have observed in pigs undergoing orthotopic liver transplantation that the level of neuromuscular blockade induced by a constant intravenous infusion of a muscle relaxant with high hepatic uptake (pipecuronium) quickly decreased after reperfusion of the liver graft.[8] Because the level of neuromuscular blockade closely reflects the plasma concentrations of muscle relaxants and because the monitoring of neuromuscular function by mechanography, electromyography, or accelerography is routine in the operating room, changes in neuromuscular blockade level at reperfusion of the liver graft could be a valuable estimate of the initial function of the transplanted liver when a muscle relaxant with high hepatic uptake is used. For the current study we used vecuronium rather than pipecuronium as it is available in most of the countries, is widely used in clinical practice and has a well-recognized hepatic metabolism.

The first objective of the current study was to determine the effect of the anhepatic phase on dose requirements of vecuronium to obtain a constant neuromuscular blockade. We found that, compared with control, the dose requirement of vecuronium was considerably decreased by the removal of liver and the recovery rate of the neuromuscular blockade was significantly prolonged after recirculation of the liver graft. Thus, we proceeded to the second objective of these studies, to measure the effect of liver graft reperfusion on the metabolic rate of ^{14}C-labeled aminopyrine, a well-established quantitative test of the microsomal function of the liver (the aminopyrine breath test [ABT]),[9] and to compare it with the changes in neuromuscular blockade secondary to graft reperfusion during liver autotransplantation in pigs.

Materials and Methods

Experimental Procedure

Nine landrace pigs (*Sus scrofa domesticus*, 22–25 kg) were included in the current study, after approval by the Ethical Committee on Animal Research of our institution. Each animal was studied twice within an interval of 3 days. Each pig first served as its own control and then underwent a hepatic autotransplantation.

Control Experiment

Pigs received the neuroleptic azaperon 6 mg/kg (Stresnil, Janssen Pharmaceutica, Belgium), midazolam 0.3 mg/kg, and atropine 0.01 mg/kg intramuscularly, and 15 min later, anesthesia was induced with isoflurane 2–3% in O_2. The trachea was intubated without using a muscle relaxant. Isoflurane was discontinued and anesthesia was maintained by an intravenous bolus of etomidate (6 mg/kg), azaperon (2 mg/kg), and fentanyl (8 μg/kg) followed by continuous intravenous infusions of etomidate (8 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (4 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Ventilation was controlled to maintain arterial CO_2 tension at 35–40 mmHg at an inspired O_2 fraction of 0.5 in air. Isotonic saline solution was infused intravenously at 4 $ml \cdot kg^{-1} \cdot h^{-1}$. Mean systemic arterial and central venous pressures were continuously measured using a carotid arterial cannula and a central venous catheter, respectively, connected to calibrated pressure transducers (156-PC-06-GW2, Honeywell, Zürich, Switzerland), positioned at the midaxillary line, and recorded on a 6-channel recorder (8000 S, Gould Electronics, Zürich, Switzerland). A standard three-lead electrocardiogram was continuously displayed on a Hewlett-Packard monitor with digital readout of heart rate by means of subcutaneous electrodes. Rectal temperature was continuously monitored using an electronic thermometer and maintained at 35.0–39.0°C with thermoblankets. ^{14}C-Labeled aminopyrine was injected through the venous catheter placed in the internal jugular vein 30 min after a stable anesthetic level was obtained. Expiratory breath samples were collected, from 30 min before to 180 min after administration of the intravenous bolus of ^{14}C-labeled aminopyrine. Muscle relaxation, measured with an acceleration transducer (see below), was obtained by a single intravenous bolus injection of vecuronium of 1 mg/kg followed five min later by an intravenous infusion of vecuronium continuously adjusted to maintain a constant 90–95% twitch depression during 180 min. The intravenous infusion of vecuronium was stopped and the value of the initial twitch response was allowed to recover spontaneously to 75% of its baseline value. The time from 25% to 75% recovery of twitch height was defined as recovery index. The study was ended when the twitch recovered to 75% of the control level. Then,

spontaneous or neostigmine-induced (20 μg/kg) twitch height recovery to control values was obtained and the animals awakened and the trachea extubated. All pigs recovered uneventfully from the control experiments.

Hepatic Autotransplantation

Each animal underwent a hepatic autotransplantation 2 days after the control experiment; this technique was used to avoid to kill a second animal to donate a liver, and to avoid phenomenon of acute rejection in the early postoperative period. Anesthetic technique and monitoring were identical to that used during the control experiment. However, the infusion rate of etomidate and fentanyl were reduced to 2 $mg \cdot kg^{-1} \cdot h^{-1}$ and 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively, during the anhepatic phase. The surgical procedure consisted of three phases.[10] The first phase corresponded to the removal of the spleen to place a passive splenojugular venovenous bypass, to the dissection of hepatic vessels and the biliary duct, and to the section of the hepatic ligaments. The liver was then removed, placed on ice, flushed with Ringer's lactate solution at 4°C, and kept on ice for 44 ± 9 min. For reimplantation the vascular anastomosis were: suprahepatic and infrahepatic, posterior vena cava, and portal vein. The reperfusion of the liver graft started after the completion of the vena cava and portal vein anastomosis. The hepatic artery anastomosis was completed within 30 min after reperfusion of the liver graft. The third phase consisted of the period of venous recirculation of the graft during which end-to-end anastomosis of hepatic artery and bile duct were performed. Isotonic saline solution was infused intravenously at 7 ± 2.5 $ml \cdot kg^{-1} \cdot h^{-1}$. Arterial *p*H was maintained at 7.32–7.50 with sodium bicarbonate. Blood losses were compensated with plasma expander, or blood, when available. Urine output was maintained at more than 1 $ml \cdot kg^{-1} \cdot h^{-1}$ during the investigation.

^{14}C-Labeled aminopyrine was injected intravenously 30 min before recirculation of the liver graft. Breath samples were collected during the last 30 min of the anhepatic phase, and during 180 min after recirculation of the liver graft. Muscle relaxation was measured with an acceleration transducer (see below) on a similar manner as in the control experiment. After a stable anesthetic level was established for at least 15 min, a single intravenous bolus injection of vecuronium of 1 mg/kg was administered, followed 5 min later by an intravenous infusion of vecuronium continuously adjusted to maintain a constant 90–95% twitch depression to the end of the anhepatic phase. After recirculation of the liver graft, the infusion rate of vecuronium was maintained at its anhepatic value, and the recovery rate of the neuromuscular blockade was measured. The study was ended when the twitch recovered to 75% of the prerelaxant control level.

Recording of Neuromuscular Transmission

Neuromuscular transmission was continuously measured on the right anterior leg of the pig using an acceleration transducer (Accelograph, Biometer International, Odense, Denmark).[11,12] A small piezoelectric ceramic wafer was fastened on the leg with adhesive tape. After stimulation of the radialis nerve by two transcutaneous electrodes delivering supramaximal train-of-four stimulation at 2 Hz with 0.2 ms duration every 20 s, the transducer was set in motion, the developed voltage being proportional to the acceleration. The resulting electrical signal was continuously recorded by the Accelograph monitor and recorder. The first of the four evoked responses was considered the twitch height. The Accelograph was recalibrated 2–3 min before the administration of vecuronium, when a stable anesthetic level was established for at least 15 min. To calculate the degree of neuromuscular blockade in percent, all twitch heights were referred to those measured before the first injection of vecuronium.

Measurement of Metabolic Rate of ^{14}C-Labeled Aminopyrine

^{14}C-Labeled aminopyrine (CEA, Gif-sur-Yvette, France) with a specific activity of 126 mCi/mmol was divided in aliquots of 15 μCi diluted in 5 ml of isotonic saline solution. Thirty min before and 3 h after the administration of an intravenous bolus of ^{14}C-labeled aminopyrine, the expired gases were collected by continuous suction at 800 ml per min, dried in a cylinder containing calcium chloride, and saturated in a gas wash bottle containing methanol. Expiratory gases were then bubbled through a CO_2-trapping solution, which consisted of 10 ml of a mixture of methanol and ethanolamine (vol:vol 80:20). A 3-ml aliquot of this solution was transferred in a liquid scintillation vial containing 10 ml scintillation cocktail. All samples were counted for 10 min in a liquid scintillation counter (LS 200, Beckman, Fullerton, CA).

Statistics

Mean ± SD values of hemodynamic and biochemical data at the different time intervals were calculated. During each experimental day, comparison of the re-

Table 1. Time Course, Hemodynamic Variables, Arterial *p*H, and Rectal Temperature during Control and Hepatic Autotransplantation Experiments

Variable	Control Session	Hepatic Autotransplantation		
		Before Clamping Liver Vessels	Anhepatic Phase	After Liver Recirculation
Duration (min)	180	108 ± 32	137 ± 36	180 ± 10
Heart rate (beats/min)	95 ± 33	81 ± 15	144 ± 36*	127 ± 37
MAP (mmHg)	84 ± 14	81 ± 8	63 ± 13*	65 ± 13*
CVP (mmHg)	6 ± 3	5 ± 1	2 ± 1	4 ± 1
Arterial *p*H (units)	7.48 ± 0.02	7.50 ± 0.03	7.39 ± 0.05*	7.32 ± 0.04*
Rectal temperature (°C)	38.2 ± 1.2	37.5 ± 0.4	36.0 ± 0.9*	36.0 ± 1.0*

MAP = mean systemic arterial pressure; CVP = central venous pressure.

Values are mean ± SD, measured every 15 min in eight animals.

* $P < 0.05$ *versus* "before clamping liver vessels."

corded variables over time was conducted by a one-way analysis of variance for repeated measurements followed by Duncan's multiple comparisons test. Between experimental days, comparison of recorded variables was conducted by a two-tailed paired Student's *t* test. The Pearson's least-squares correlation coefficient was used to detect a significant association between recovery rate of the neuromuscular transmission and the rate of $^{14}CO_2$ elimination. For all statistical comparisons, differences were considered significant if $P < 0.05$.

Results

Systemic hemodynamics, arterial *p*H, and rectal temperature measured during the control session and the hepatic autotransplantation are reported in table 1. The animals received 200 ± 50 ml of blood during the liver transplantation, and the mean value of hematocrit measured every 15 min was 28 ± 2%. There were no statistical differences between control experiments and the first period of the liver transplantation. In contrast, removing the liver resulted in a significant decrease of mean arterial pressure, associated with a significant increase in heart rate and a small but significant decrease in arterial *p*H and rectal temperature. These hemodynamic and metabolic changes persisted after reperfusion of the liver graft (table 1).

The first objective of the current study was to determine the influence of absence of liver circulation on a constant level of vecuronium-induced neuromuscular blockade during liver autotransplantation in pigs. The doses of vecuronium necessary to maintain a constant 90–95% neuromuscular blockade in control animals and during liver autotransplantation are reported in table 2. There was no difference in the infusion rate of vecuronium between the control experiment and the first phase of liver transplantation, *i.e.*, before the clamping of liver vessels. In contrast, during the anhepatic phase, a greater than 95% decrease in the infusion rate of vecuronium necessary to maintain a constant 90–95% neuromuscular blockade was observed (from 1.18 ± 0.16 to 0.05 ± 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$, $P < 0.05$). The onset of recovery of the neuromuscular blockade was observed before the reperfusion of the hepatic artery, indicating that the liver started to remove vecuronium from plasma immediately after reperfusion of the portal vein. The recovery index of neuromuscular blockade measured at the end of control experiments and during the first 60 min after liver reperfusion are reported in table 3. Compared with control, the recovery index was prolonged by a factor of 10.4 after liver graft reperfusion.

Table 2. Vecuronium Infusion Rate in Control and Hepatic Autotransplantation Experiments

	Control Session	Hepatic Autotransplantation	
		Before Clamping Liver Vessels	Anhepatic Phase and after Liver Recirculation
Vecuronium infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	1.30 ± 0.33	1.18 ± 0.16	0.05 ± 0.03*

Values are mean ± SD, measured every 15 min in eight animals.

* $P < 0.05$ *versus* "before clamping liver vessels."

Table 3. Recovery Index of the Vecuronium-induced Neuromuscular Blockade and $^{14}CO_2$ Excretion Rate in Expired Air during Control and Hepatic Autotransplantation Experiments

Condition	Recovery Index (min)	Excretion Rate of $^{14}CO_2$ (%/h)
Control session	3.4 ± 0.5	1.69 ± 1.04
First hour of liver graft reperfusion	35.5 ± 15.8*	0.19 ± 0.11*

Values are mean ± SD; n = 8.

* $P < 0.05$ *versus* controls.

The second objective of these studies was to measure the effect of liver graft reperfusion on the metabolic rate of ^{14}C-labeled aminopyrine in the ABT, a well-established quantitative test of microsomal function of the liver and to compare it with the changes in neuromuscular blockade secondary to graft reperfusion during liver autotransplantation in pigs. The cumulative excretion of $^{14}CO_2$ over 3 h in control and autotransplantation experiments is shown in figure 1 and table 2. During the anhepatic phase, there was no excretion of $^{14}CO_2$. After declamping liver vessels, the mean cumulative excretion of $^{14}CO_2$ reached 0.19 ± 0.11%/h during the 1st h after recirculation of the liver graft, corresponding to 11.2% of values measured during the last hour of the control session (table 3). Then, the excretion rate of $^{14}CO_2$ increased to reach a value of 0.63 ± 0.57%/h for the last 60 min of the study ($P < 0.05$ from the 1st h after reperfusion of the liver graft). Interestingly, there was no sign of decrease in neuromuscular block after liver graft reperfusion in the one animal which had a primary graft failure. Finally, there was a significant positive correlation ($r^2 = 0.71$) between individual changes of $^{14}CO_2$ excretion in expired air and the recovery rate of vecuronium-induced neuromuscular blockade secondary to the reperfusion of the liver graft, expressed as a fraction of the values measured during the control studies (fig. 2).

Discussion

The results of our previous studies have suggested that, using a muscle relaxant with high hepatic uptake, changes in the neuromuscular blockade secondary to the reperfusion of the liver graft could be an early and easy to perform estimate of the transplanted liver function.[8,13] Therefore, the first objective of this study was

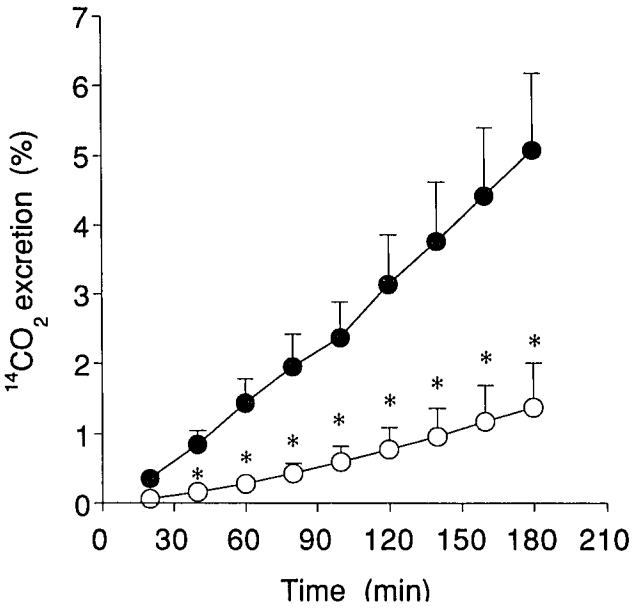

Fig. 1. Cumulative excretion of $^{14}CO_2$ in expired air over 3 h in the control session (closed circles) and immediately after liver recirculation in the liver autotransplantation experiments (open circles). Data points measured every 20 min represent the mean value ± SE of eight pigs. *$P < 0.05$ from the corresponding values of control experiments.

to determine the effect of removal of the liver and the effect of graft reperfusion on the level of vecuronium-induced neuromuscular blockade during hepatic autotransplantation in pigs.

The well-known similarities of the pig liver and the human one justified the choice of this animal for the

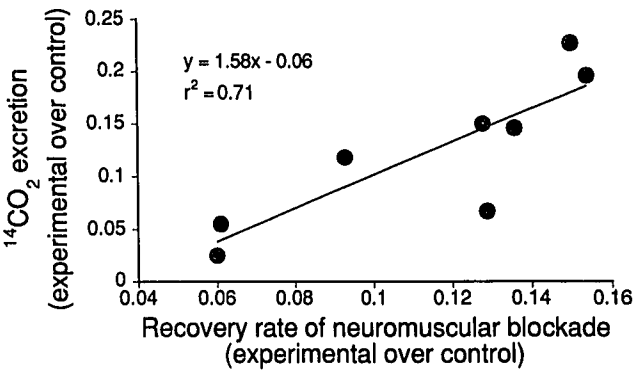

Fig. 2. Correlation between individual values of $^{14}CO_2$ excretion in expired air and of the recovery rate (1/recovery index) of the vecuronium-induced neuromuscular blockade, both measured during the 1st h after the reperfusion of the liver graft and expressed as the fraction of the values measured in the same animals during the control studies.

current studies. In fact, although the dose-requirement for vecuronium is three times greater in pigs than humans, the pig has been shown to be a more suitable animal than the rat and the cat for studying the time-course data for neuromuscular blockade and the hepatic uptake of muscle relaxants.[14] A high bolus dose of vecuronium (3 × the 95% effective dose for pigs) was given at the beginning of the control studies and of the liver transplantation in order to achieve more rapidly a 90–95% steady-state neuromuscular blockade.

The results of the anhepatic phase show that removal of the liver resulted in a dramatic decrease in the dose of vecuronium required to maintain a constant 90–95% neuromuscular blockade (table 2). Previous studies have shown that the liver is of major importance in the pharmacokinetics of vecuronium.[14–17] In particular, Motsch and colleagues showed in a portocaval shunt preparation in pigs that intraportal injection of vecuronium resulted in a significant decrease of the intensity of neuromuscular blockade whereas short hepatic exclusion enhanced the intensity of neuromuscular blockade.[14] Also, it has been reported that removal of the liver significantly reduced the requirement of vecuronium during liver transplantation in humans, confirming that the liver has a major role in the plasma clearance of vecuronium.[18] However, some nonhepatic factors including metabolic acidosis, hypothermia, changes in volume of distribution of vecuronium, bypass technique, variations in systemic hemodynamics and in renal function secondary to the exclusion of the liver could also contribute to the reduction in the dose requirement of vecuronium during the anhepatic phase of liver transplantation. In our studies, arterial *p*H was in the normal range during this phase of liver transplantation (table 1). In contrast, the slight decrease in body temperature secondary to the removal of the liver may have modestly altered the neuromuscular blocker requirement during this phase of liver transplantation. We did not evaluate renal function of the pigs during liver transplantation, but urine output was maintained at values greater than 1 $ml \cdot kg^{-1} \cdot h^{-1}$ during the entire operation. In addition, it has been shown that only moderate amounts of vecuronium are eliminated by the kidneys.[19,20] Changes in receptor sensitivity and in volume of distribution of vecuronium induced by liver exclusion could also be responsible for the decrease in neuromuscular blocker requirement. In previous studies using the same animal model,[13] we have shown that plasma concentrations and the neuromuscular effect of atracurium were not influenced by the absence of hepatic function or circulation, suggesting that it is unlikely that an increased sensitivity of neuromuscular junction or a change in volume of distribution of vecuronium may explain the decrease in vecuronium requirement after removal of the liver. Therefore, exclusion of the liver from the circulation accounts for the reduced requirement of vecuronium during the anhepatic phase of liver transplantation, confirming previous findings that the liver is the most important factor determining the pharmacokinetics of vecuronium.[14–17]

This conclusion is also supported by the finding that the reperfusion of the liver graft was accompanied within 15 min by the onset of spontaneous recovery of the neuromuscular blockade, even though the infusion rate of vecuronium was maintained at its anhepatic level. The onset of recovery was observed before reperfusion of the hepatic artery, indicating that the liver started to remove vecuronium from plasma immediately after reperfusion of the portal vein. Therefore, our results indicate that the measurement of the recovery index may be a fast and easy to perform indicator of hepatic function immediately after reperfusion.

We did not keep the neuromuscular blockade constant after declamping the liver vessels, as we did during the first two phases of liver transplantation, because in pilot experiments it was almost impossible to achieve a steady state of neuromuscular blockade by adjusting the infusion rate of vecuronium during the early phase of reperfusion. This is due to the rapid amelioration of liver function (and thus the hepatic excretion of vecuronium) after hepatic reperfusion, as also demonstrated by the rapid change in the excretion rate of $^{14}CO_2$. Whereas the excretion rate of $^{14}CO_2$ was linear during the 3-h study period in the control session (fig. 1), the excretion rate of $^{14}CO_2$ increased three times during 3 h after reperfusion of the liver in transplanted animals (1st h 0.19 ± 0.11%/h *vs.* 3rd hour 0.63 ± 0.57%/h) (fig. 1).

A second bias of our study design may be our measurement of the recovery rate of neuromuscular blockade while vecuronium infusion was still running. The rationale for the design of these experiments was to change only *one variable*, the reperfusion of the liver. Therefore, we did not stop the infusion of vecuronium after declamping the liver vessels. Indeed, if the vecuronium infusion had been stopped just after the reperfusion of the hepatic graft, the recovery rate of the neuromuscular blockade (and the plasma clearance of

vecuronium) would have not only been dependent on the function of the liver but also on that of other organs (*e.g.*, the kidneys). To establish a comparison between changes in neuromuscular blockade and in ABT induced by the reperfusion of the liver graft, it was necessary to determine a baseline value for both tests during a control session. The use of the ratio of experimental over control measurements for the ABT in figure 2 is straightforward because the aminopyrine is metabolized only by the liver. In contrast, the best design for the comparison of the recovery rate of the vecuronium-induced neuromuscular blockade between sessions would have been, not to stop the infusion rate of vecuronium at the end of the control session, but rather to keep the rate similar to that used after reperfusion of the liver (as determined in pilot experiments) while measuring the recovery rate of the neuromuscular blockade. However, because this infusion rate corresponded to only 4% of the infusion rate necessary to maintain the neuromuscular constant during the control session (table 2), it would minimally shorten the recovery rate of the neuromuscular blockade measured at the end of the control session. Therefore, we believe that the study design does not invalidate the comparison between both tests and the general conclusion of the studies.

To explore this issue, we proceeded to the second objective of these studies which was to quantify the effect of removal of liver and liver graft reperfusion on the metabolic rate of ^{14}C-labeled aminopyrine in the ABT, a well-established quantitative test of the microsomal liver function,[9] and to compare it with the changes in the degree of neuromuscular blockade secondary to reperfusion of the liver graft. A number of metabolic tests have been used to evaluate the hepatic function. Among them, breath tests are the simplest and the easier to perform, allowing measurement in the operating room.[9,21] We chose the ABT, a well-established quantitative test of liver function.[9,21] This test measures the intrinsic ability of the liver to demethylate aminopyrine through the cytochrome P450–dependent microsomal enzyme system as aminopyrine has a low hepatic extraction coefficient, its metabolism is independent of flow rate.[22] Also, the ABT is a quantitative test because plasma disappearance of ^{14}C-labeled aminopyrine is highly correlated with the rate of $^{14}CO_2$ production.[22] Our results show a linear production of $^{14}CO_2$ during the 3-h control session (fig. 1). In contrast, there was no excretion of $^{14}CO_2$ during the anhepatic phase of liver transplantation. After reperfusion of the liver graft, $^{14}CO_2$ was detected in the expired air within 45 min, although the cumulative values measured during the 1st h after declamping the liver vessels corresponded to only 10% of that measured for the same period of time during the control studies (fig. 1). During the 2 h after reperfusion of the liver graft, there was an increasing excretion of $^{14}CO_2$ which reached during the 3rd h a value twice as high as the value measured during the first 60 min after declamping the liver vessels. These findings clearly indicate that the liver graft is able to metabolize drugs after its revascularization, and that its intrinsic metabolic capacity is increasing during the first hours after its reperfusion. The ABT has been shown to be a useful predictive test for the outcome of hepatic transplantation in pigs.[23] Although our studies were not designed for this purpose, we found that there was an absence of $^{14}CO_2$ extraction after reperfusion of the liver graft only in the animal which died after 2 h of reperfusion, suggesting that tests measuring the hepatic metabolic function may also be early and sensitive indicators of acute liver graft failure.

Because there was a comparable decrease in the mean rate of recovery of the vecuronium-induced neuromuscular blockade and in the mean excretion of $^{14}CO_2$ after reperfusion of the liver graft compared with the control studies, we measured the relationship between individual changes of $^{14}CO_2$ excretion in expired air and recovery rate of vecuronium-induced neuromuscular blockade secondary to the reperfusion of the liver graft (fig. 2). We found that there was a significant correlation ($r^2 = 0.71$) between individual changes in the ABT and the recovery rate of the neuromuscular blockade expressed as the fraction of the values measured in the control studies, indicating that changes in the level of neuromuscular blockade may be an early and sensitive indicator of metabolic function of the hepatic graft during liver transplantation. These findings indicate that the slow recovery of the vecuronium-induced neuromuscular blockade measured during the 1st h after the revascularization of the liver graft was probably due to a decreased uptake of vecuronium by the freshly transplanted liver, despite the presence of nonhepatic factors such as hypothermia or metabolic acidosis which may also influence the intensity of the neuromuscular blockade.

In conclusion, our results show that the vecuronium dose-requirement was decreased during the anhepatic phase of liver transplantation. Compared with control studies, there was a similar decrease in the recovery

rate of vecuronium-induced neuromuscular blockade and in the metabolic rate of ^{14}C-labeled aminopyrine, a standard test of the liver function during progressive recovery of hepatic function immediately after unclamping of liver vessels. Therefore, recording of the neuromuscular transmission during liver transplantation might be an on-line and sensitive assessment of liver graft function provided that a muscle relaxant with a high hepatic uptake is used.

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