Inhibition of liver protein synthesis during laparoscopic surgery

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1Department of Anesthesiology and Intensive Care and 2Department of Surgery, Huddinge University Hospital, Karolinska Institute, S-141 86 Huddinge, Sweden; and 3Department of Surgery, State University of New York at Stony Brook, Stony Brook, New York 11794-8191

Barle, Hans, Björn Nyberg, Stig Ramel, Pia Essén, Margaret A. McNurlan, Jan Wernerman, and Peter J. Garlick. Inhibition of liver protein synthesis during laparoscopic surgery. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E591–E596, 1999.—Previous studies have indicated that laparoscopic surgery is associated with a decline in liver protein synthesis. In this study, the fractional synthesis rate (FSR) of total liver protein and albumin was measured in patients undergoing elective laparoscopic cholecystectomy at different times after commencing the procedure (n = 8 ± 8). Liver biopsy specimens were taken after 15 min of surgery in an “early” group and after 49 min of surgery in a “late” group. The liver FSR was higher in the early group (24.1 ± 4.7%/day) compared with the late group (19.0 ± 2.8%/day, P < 0.02). The fractional and absolute synthesis rates of albumin were similar in the two groups, 6.4 ± 1.5 vs. 6.5 ± 1.0%/day and 97 ± 19 vs. 96 ± 18 mg·kg−1·day−1 for the early and late groups, respectively. It is concluded that laparoscopic surgery was accompanied by a decrease in total liver protein synthesis rate, which developed rapidly during surgery. In contrast, no change in the synthesis rate of albumin was apparent during the course of surgery.

Inhibitory effect of laparoscopic surgery on liver protein synthesis.

TRAUMA AND CRITICAL ILLNESS induce profound changes in protein metabolism, resulting in a negative nitrogen balance (15, 43). The loss of body protein is a consequence of a shift in the balance between protein synthesis and degradation. Whole body protein degradation generally increases in response to a catabolic insult (24, 34), but the effect on protein synthesis is variable, depending on the severity of the insult (9, 10, 13, 14). However, whole body rates of protein turnover reflect averages of all the individual tissues, and individual tissues are known to respond differently to states of protein catabolism, e.g., skeletal muscle and liver (11, 28, 32, 38). In humans, the dynamics of protein metabolism in individual tissues have generally been investigated with stable isotope techniques. The majority of studies have involved skeletal muscle or plasma proteins, samples of which are relatively easily obtained by percutaneous biopsy or blood sampling (3, 25), and only a few investigators have attempted to measure protein synthesis in human liver. These studies have employed both the constant infusion method (21, 41) and the flooding technique (30), followed by liver biopsy during open abdominal surgery. These studies have shown that active inflammation of the bowel is associated with increased liver protein synthesis, whereas colonic malignancy leads either to no change or to a decrease in synthesis, possibly depending on the stage of the disease (21, 30).

The development of laparoscopic surgical techniques has offered an opportunity to obtain human liver tissue for research purposes from healthy subjects. Use of this technique has permitted us to characterize the hepatic free amino acid concentrations (5) and the synthesis rates of total liver protein and albumin in humans (7). In two further studies, the effects of parenteral nutrition and preoperative growth hormone administration on these parameters were also investigated (6, 8). However, liver protein synthesis rates in the control groups of these two studies were lower than those in the original study by 28 and 35%, respectively (7). This appears to have resulted from differences in the experimental protocol in the different studies. Thus the liver protein synthesis rate was measured after 20 min of surgery in the first study, instead of after 45–50 min as in the other two studies. This would indicate lower liver protein synthesis rates with longer times of surgery. However, the two later studies also included an additional liver biopsy specimen before measurement of protein synthesis to permit the analysis of the hepatic free amino acid concentrations in the first biopsy and liver protein synthesis rate in the second, which was taken from an adjacent site. It is possible therefore that local injury to the liver by the first biopsy might have influenced the rate of protein synthesis in the second.

The primary aim of the present study was to determine in a randomized, controlled fashion whether or not total liver protein synthesis remains unaffected during laparoscopic surgery and in addition to investigate the effect of a laparoscopic surgical trauma on albumin synthesis rates.

PATIENTS AND METHODS

Materials. L-[ring-2H5]phenylalanine, 99 atom percent (Mass Trace, Somerville, MA), was dissolved in sterile water together with unlabeled phenylalanine (Ajinomoto, Tokyo, J apan) to a concentration of 20 g/l and an enrichment of 10 mole percent excess (MPE).

Subjects. Patients (n = 16) undergoing elective laparoscopic cholecystectomy due to cholelithiasis, but otherwise healthy, participated in the study. There was no biochemical evidence of liver disease (alanine and aspartate transaminase and bilirubin) in any of the patients at the time of the study, and those who were smokers had stopped smoking for at least 3 weeks before surgery.
aminotransferases, alkaline phosphatase, γ-glutamyltransferase, and bilirubin were all within normal ranges of values). The patients were randomized into two groups to be investigated early or late during surgery (“early” and “late” groups, respectively). The groups were comparable regarding age, weight, and body mass index (Table 1). The nature, purposes, and potential risks of the experimental procedures were explained to the patients before obtaining their voluntary consent. The study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki and had been approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

Experimental protocol. The general protocol has been used previously (5, 6, 7), but modifications were made for the purpose of this study. Thus, preoperatively, antecubital venous lines were inserted bilaterally and the patients were given Ringer solution (Ringeracetat, Pharmacia Upjohn, Stockholm, Sweden) in the left arm (300–600 ml/h). The line in the right arm was used for blood sampling. The patients were anesthetized in a standardized manner with sodium thiopentone 5–7 mg/kg, fentanyl 2.5–5.0 µg/kg, and atracurium 0.5 mg/kg intravenously at the induction. The anesthesia was maintained by isoflurane in a mixture of oxygen/air, with intermittent doses of fentanyl and atracurium when needed. Carbon dioxide was insufflated into the abdomen, with intermittent doses of fentanyl and atracurium when anesthesia was maintained by isoflurane in a mixture of oxygen/air.

The patients in the early group received an injection of [2H5]phenylalanine (45 mg/kg, 10% enriched) intravenously over 10 min in the left arm at the time of induction of anesthesia. In these patients, a total of three liver biopsy specimens was obtained. The first liver biopsy specimen was taken after ∼15 min of surgery (i.e., after the insertion of the first trocar into the abdomen) and ∼29 min after the injection of phenylalanine, from the edge of the right liver lobe with laparoscopic scissors (Fig. 1). In order to investigate if proximity to the first biopsy site affects the results of liver protein synthesis rate in forthcoming liver biopsies, two more specimens were obtained ∼60 min after the injection of phenylalanine. One of these was taken close to the first biopsy site (within 1 cm) and the other further away (more than 4 cm from the first biopsy site). The patients in the late group received the injection of phenylalanine after 15–20 min of surgery, and the only liver biopsy specimen obtained in these patients was taken ∼33 min later, after ∼49 min of surgery (Fig. 1). Biopsy sites were coagulated diathermally to prevent bleeding. No complications due to bleeding were observed. Blood samples were also drawn at the following intervals: 0, 5, 10, 15, 30, 50, 70, and 90 min after the injection of phenylalanine for the determination of the isotopic enrichment of phenylalanine in plasma and albumin. All the blood samples were centrifuged at 2,000 rpm for 20 min and stored in a −80°C freezer pending analysis.

### Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>3M/5F</td>
<td>3M/5F</td>
</tr>
<tr>
<td>Age, yr</td>
<td>45.6 ± 8.4</td>
<td>43.4 ± 13.0</td>
</tr>
<tr>
<td>Length, m</td>
<td>1.71 ± 0.10</td>
<td>1.69 ± 0.10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.1 ± 11.1</td>
<td>71.6 ± 13.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 ± 2.5</td>
<td>24.8 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8 in each group. Biopsies were taken after 15 (Early) or 49 (Late) min of surgery. BMI, body mass index; M, male; F, female.

Fig. 1. Study protocols for two groups of patients (early (A) and late (B)) investigating association between duration of laparoscopic surgery (cholecystectomy) and liver protein synthesis, as assessed by flooding technique. X, induction of anesthesia; Y, start of intravenous phenylalanine injection (for 10 min); LB, acquisition of liver biopsy specimens. Small arrows, blood samples for precursor pool and albumin enrichments. Thin lines, ongoing anesthesia; bold lines, anesthesia and surgery. Please note temporal relationships between these events in the 2 groups.

Measurements of plasma volume were made with 125I-labeled albumin (100 kBq, Institut for Energiteknikk, Kjeller, Norway), beginning 30 min after the the injection of phenylalanine. Blood samples were taken at 0, 20, 30, 40, and 45 min to assess isotope dilution.

Synthesis rates of total liver protein and albumin. The details of the preparation and analysis of liver, plasma, and albumin samples for the enrichment of [2H5]phenylalanine have been described elsewhere (7, 12, 35). We have previously demonstrated that plasma phenylalanine enrichment closely approximates the enrichment within the liver when a flooding amount of [2H5]phenylalanine is given (6, 8). For preparation, the liver tissue specimens were homogenized in cold 3% perchloric acid (PCA) on ice and centrifuged for 5 min at 8,000 rpm at 4°C. After being repeatedly washed in order to remove traces of free phenylalanine, the protein precipitate was suspended in 0.3 M NaOH and reprecipitated in 5% PCA. After further washing, proteins were hydrolyzed in 6 M HCl for 24 h at 110°C. The HCl was removed by evaporation in vacuo, and the hydrolysate was used for the measurement of isotopic enrichment.

Albumin in plasma samples was extracted from 9% trichloroacetic acid–precipitated protein fraction by differential solubility in absolute ethanol (33). The purity of the albumin fraction was checked with matrix-assisted laser desorption time of flight mass spectrometry (Finnigan Laser mat 2000, Finnigan, Hemmelp Hempstead, England) showing that a single peak with a molecular mass 67,450 kDa had been isolated. Thereafter, the protein precipitate was suspended in 0.3 M NaOH and reprecipitated in 5% PCA. After being washed with 2% PCA, albumin was hydrolyzed in 6 M HCl for 24 h at 110°C. The HCl was removed by evaporation in vacuo, and the hydrolysate was used for the measurement of isotopic enrichment.

Samples of plasma for the determination of free phenylalanine enrichment were treated with 8% sulfosalicylic acid to precipitate protein. The supernatants were purified with cation-exchange columns [Dowex-50, Biorad AG, 50W-X8, (H+)-form, 100–200 mesh], eluted with 4 M NH₄OH, and then dried in vacuo.

The enrichment of [2H5]phenylalanine from liver protein and albumin hydrolysates was determined by measuring the mass-to-charge ratio (m/z) at 106 and 109 of the n-heptafluorobutyryl derivative of phenylethylamine on a Fisons MD 800
mass spectrometer (Fisons, Beverly, MA; Refs. 12, 35). The
\(^{2}H_{3}\) enrichment of free phenylalanine in plasma was mea-
sured by monitoring the ions at \(m/z\) 336 and 341 of the
N-tert-butyldimethylsilyl derivative on an HP 5972 mass
spectrometer (Hewlett-Packard, Palo Alto, CA).

Other analytical procedures. The serum concentration of
albumin was measured with the bromocresol purple method
on a Hitachi 917 automated analyzer (Hitachi, Naka, Japan; Ref. 39).

Calculations and statistics. The fractional synthesis rate of
liver protein (FSR\(_{\text{Liver}}\)), i.e., the the daily amount of protein
synthesized by the liver, both endogenous and secreted
proteins, expressed as a percentage of the total protein
content of the liver, was calculated according to the previously
described formula (25)

\[
\text{FSR}_{\text{Liver}} = \frac{P \times 100}{\text{AUC}}
\]

where \(P\) is the isotopic enrichment of phenylalanine (MPE) in
total liver protein at the time of the second liver biopsy
specimen and AUC is the area under the curve for plasma free
phenylalanine enrichment (MPE) vs. time (days).

The fractional synthesis rate for albumin (FSR\(_{\text{Alb}}\)), i.e., the
percentage of the intravascular albumin pool that is synthe-
sized every day, was calculated with the same formula as
previously described (3)

\[
\text{FSR}_{\text{Alb}} = \left(\frac{P_{2} - P_{1}}{P_{2}}\right) \times \text{AUC}
\]

where \(P_{2}\) and \(P_{1}\) represent the enrichment of phenylalanine
in albumin between 50 and 90 min, after the curve becomes
linear (based on 50-, 70-, and 90-min samples). The AUC for
the enrichment of plasma free phenylalanine is adjusted for
the secretion time, i.e., the temporal lag period before the
appearance of labeled albumin in plasma. The secretion time
was assessed by plotting the individual regression line for the
linear part of the albumin enrichment curve and extrapolat-
ing to the baseline enrichment (3). Absolute synthesis rates
for albumin were calculated as the fractional rate of albumin
synthesis times the intravascular albumin mass, calculated
from the concentration of plasma albumin and the measured
plasma volume.

Data are presented as means ± SD. Student's t-test was
used for comparison, and repeated-measures ANOVA was
used for comparisons within the early group.

RESULTS

The fractional rate of liver protein synthesis was
24.1 ± 4.7%/day (\(n = 8\)) when measured early during
surgery. This was higher than the value in the late
group (\(n = 8\)), which was 19.0 ± 2.8%/day (\(P = 0.019\;
Table 2). The fractional rates of liver protein synthesis
calculated for the second (close to the first biopsy site) and
third (>4 cm from the first biopsy site) liver biopsy
specimens in the early group were not significantly
different from each other (17.6 ± 3.4 and 18.2 ±
4.6%/day, respectively; Table 2). However, a significant
depression was observed when comparing these two to
the value obtained in the first measurement 30 min
earlier (\(P < 0.001\)).

The rate of liver protein synthesis calculated from
biopsy 1 in the early group correlated significantly with
rates calculated from biopsy 2 (\(r = 0.77, P = 0.043\)) and
biopsy 3 (\(r = 0.95, P < 0.01\)). The rates from biopsies 2
and 3 were also correlated (\(r = 0.82, P = 0.024\)).

| Time of
<p>| Surgery Before | FSR, Total |</p>
<table>
<thead>
<tr>
<th>Liver</th>
<th>Liver Protein</th>
<th>Liver Protein</th>
<th>Liver Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy 1</td>
<td>(Biopsy 1)</td>
<td>(Biopsy 2)</td>
<td>(Biopsy 3)</td>
</tr>
<tr>
<td>Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>29.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>28.2</td>
<td>22.7</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>18.8</td>
<td>17.1</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>23.9</td>
<td>14.0</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>23.3</td>
<td>17.5</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>25.7</td>
<td>17.4</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>28.2</td>
<td>21.3</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>16.2</td>
<td>13.5</td>
</tr>
<tr>
<td>14.8 ± 3.6</td>
<td>24.1 ± 4.7</td>
<td>17.6 ± 3.4 †</td>
<td>18.2 ± 4.6 †</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51</td>
<td>21.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>48.8 ± 3.6 †</td>
<td>19.0 ± 2.8 *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n = 8\) in each group. FSR, fractional
synthesis rate. FSR is measured in %/day. * \(P < 0.05\) and † \(P < 0.001\)
vs. early group, biopsy 1.

The FSR of albumin was similar in the two groups:
6.4 ± 1.5%/day in the early group and 6.5 ± 1.0%/day
in the late group. The absolute synthesis rates were also
similar (97 ± 19 vs. 96 ± 18 mg·kg\(^{-1}\)·day\(^{-1}\); Table 3).
Furthermore, no differences between the groups regard-
ing plasma albumin concentration (36.1 ± 2.3 vs. 35.1 ± 3.1 g/l)
or plasma volume (3.4 ± 0.6 vs. 3.0 ± 0.5 l) were
observed.

The first liver biopsy specimen in the early group was
taken 35.5 ± 1.9 min after the induction of anesthesia,
14.8 ± 4.5 min after the start of the operation, and
29.4 ± 2.2 min after the injection of phenylalanine.
The second and third liver biopsy specimens in this
group were taken after 47.2 ± 6.2 min of surgery. The liver
biopsy specimen in the late group was taken 72.5 ± 8.4
min after the induction of anesthesia, 48.8 ± 3.6 min
after surgery was started, and 32.8 ± 1.8 min after the
phenylalanine injection (Fig. 1 and Table 2).

DISCUSSION

In this study, we have demonstrated that laparo-
scopic cholecystectomy depresses liver protein synthe-
sis. This is consistent with results from our previous
studies showing discrepant rates of liver protein synthe-
sis, which we hypothesized might result from varia-
tions in the time between the measurement and the
start of surgery. The results from the present and
previous studies are summarized in Fig. 2. Thus mea-
surements beginning 45–50 min after starting surgery
are lower than those after 20 min of surgery (6–8). This
indicates that the surgical trauma or associated proce-
imens, that is, a calculated value based on the analysis of
plasma albumin concentration and plasma volume, factors
which may change rapidly during the surgical procedure.
Although of interest for further comparison between
the groups, these results should be interpreted with
cautions.

As those studies in which we previously obtained low
rates of liver protein synthesis also included a liver
biopsy before isotope injection (6, 8), an alternative
explanation would be that the removal of the first liver
biopsy specimen may have influenced the rate of pro-
tein synthesis measured in the second biopsy. However,
the results from this study do not support this notion.
First, the late group showed a low rate of liver protein
synthesis, even though only one liver biopsy was taken.
Second, in the early group two extra biopsy specimens
were taken (6, 8). An alternative explanation might be
that the removal of the first liver biopsy before isotope
injection (6, 8) and one some distance away (4 cm). There
was no difference between the liver biopsy locations of
the liver (Table 2), showing that proximity to the inju-
ry caused by the first biopsy specimen had no apparent
effect.

Values are means ± SD; n = 8 in each group. ASR, absolute
synthesis rate. Secretion time is temporal lag period from injection
of isotope until appearance of labeled albumin in plasma.

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Table 3. FSR and ASR of albumin measured early and
late during surgery in 2 groups of patients undergoing
elective laparoscopic cholecystectomy

<table>
<thead>
<tr>
<th>Secretion Time, min</th>
<th>FSR Albumin, %/day</th>
<th>ASR Albumin, mg kg⁻¹·day⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31.6</td>
<td>3.8</td>
</tr>
<tr>
<td>2</td>
<td>30.6</td>
<td>6.8</td>
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<tr>
<td>3</td>
<td>33.8</td>
<td>5.7</td>
</tr>
<tr>
<td>4</td>
<td>31.0</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>29.1</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>33.0</td>
<td>5.6</td>
</tr>
<tr>
<td>7</td>
<td>31.7</td>
<td>9.2</td>
</tr>
<tr>
<td>8</td>
<td>35.0</td>
<td>6.4</td>
</tr>
<tr>
<td>32.0 ± 1.9</td>
<td>6.4 ± 1.5</td>
<td>97 ± 19</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32.4</td>
<td>7.3</td>
</tr>
<tr>
<td>2</td>
<td>33.1</td>
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</tr>
<tr>
<td>8</td>
<td>33.9</td>
<td>5.2</td>
</tr>
<tr>
<td>33.1 ± 0.8</td>
<td>6.5 ± 1.0</td>
<td>96 ± 18</td>
</tr>
</tbody>
</table>

By contrast, no differences in albumin synthesis
between the two groups were observed (Table 3). This
may indicate that albumin synthesis rates were actu-
ally preserved during surgery, despite the decrease in
the synthesis rates of total liver protein. However, the
time period over which albumin synthesis was mea-
sured differs in some respects from that for total liver
protein synthesis. Albumin synthesis rates were deter-
mined from the increase in albumin enrichment in
blood samples taken between 50 and 90 min after the
injection of [2H5]phenylalanine (Fig. 1). As the secretion
time of albumin is ∼32 min in the early group (Table 3),
this means that albumin synthesis rates were effec-
tively measured between 18 and 58 min after the
injection of isotope and between 4 and 44 min of
surgery. Similarly, in the late group, the period of
measurement was between 35 and 75 min of surgery.
Thus albumin synthesis is measured later in the course
of surgery than liver protein synthesis, so it is possible
that the effect of the surgical trauma on albumin
synthesis may already have been established in the
ey group by the time of measurement. If that is the
case, the depressive effect on albumin synthesis does
not appear to be progressive, because the value in the
late group is not different. However, given the results
from this study, it is not possible to distinguish between
these two interpretations (i.e., preserved vs. rapidly
decreased albumin synthesis). Moreover, the albumin
FSR found in this study, although low compared with
rates in healthy subjects, still falls within the range of
mean values obtained previously when the same tech-
nique was employed (2, 31). Regarding the absolute
synthesis rate of albumin, it needs to be pointed out
that it is a calculated value based on the analysis of
plasma albumin concentration and plasma volume,
factors which may change rapidly during the surgical
procedure. Although of interest for further comparison
between the groups, these results should be interpreted
with caution.

As those studies in which we previously obtained low
rates of liver protein synthesis also included a liver
biopsy before isotope injection (6, 8), an alternative
explanation would be that the removal of the first liver
biopsy specimen may have influenced the rate of pro-
tein synthesis measured in the second biopsy. However,
the results from this study do not support this notion.
First, the late group showed a low rate of liver protein
synthesis, even though only one liver biopsy was taken.
Second, in the early group two extra biopsy specimens
were taken (∼30 min after the first), one close to the first
biopsy site (within 1 cm) and one some distance away
(4 cm). There was no difference between the liver
protein synthesis rates calculated for these different
locations of the liver (Table 2), showing that proximity
to the injury caused by the first biopsy specimen had no
effects. However, when comparing the results from
either of these two measurements to the first measure-
ment, a decrease in the liver protein synthesis rate was
observed (P < 0.01). The liver FSR in these later
biopsies was lower than that in the late group, but this
was expected. The measurement period of 1 h is longer

Fig. 2. Relation between length of surgery and fractional synthesis
rate of total liver protein. Values for early (▲) and late (●) groups
from this study are compared with control values from previous
studies: ▲, taken after 18 ± 6 min of surgery, n = 9 (Ref. 7); ●, taken
after 45 ± 4 min of surgery, n = 9 (Ref. 6); and ○, taken after 52 ± 10
min of surgery, n = 9 (Ref. 8).
than the secretion time of many plasma proteins (e.g., albumin), so the label is lost from the liver, lowering the apparent liver FSR. The fact that the results from the two extra measurements of liver FSR in the early group correlated strongly with the first measurement and with each other indicates that the flooding technique is a reproducible method to measure the rate of liver protein synthesis under these circumstances.

Although a decrease in liver protein synthesis during laparoscopic surgery was observed in our previous study, as assessed by ribosome analysis in repeated liver biopsy specimens (8), this is the first study where the immediate effect of a surgical trauma per se on human liver protein synthesis has been investigated specifically with a stable isotope technique. In a former study, liver protein synthesis was measured during open abdominal surgery with the flooding technique (30), and the result was 20.7 ± 3.1%/day (n = 5), i.e., intermediate between the results of the two groups of this study. In the other two published studies on human liver protein synthesis, the continuous infusion technique was employed, which renders comparison with this study difficult, because export proteins were included to a lesser extent in the measurements, because much longer time periods of isotope infusion were employed (21, 41). Few studies of the metabolic effects of laparoscopic surgery are available, because the technique is fairly new in clinical practice. There is some evidence that laparoscopic cholecystectomy elicits less pronounced metabolic effects compared with open cholecystectomy, including relatively smaller increases of urea synthesis (26) and insulin resistance (42). However, the decreases in skeletal muscle protein synthesis and glutamine free concentration as well as the nitrogen losses are similar, irrespective of the surgical approach (20, 27). During laparoscopic cholecystectomy, the splanchnic circulation has been shown not to be compromised during pneumoperitoneum, implying that the liver is not hypoxic (37). The possibility that the anesthetic agents used (primarily isoflurane) exert the observed effect on liver protein synthesis must be also taken into consideration. However, even though previous studies in rats have shown that halothane depresses liver protein synthesis, such an effect has not been shown for the main anesthetic agent used in this study, isoflurane (22, 29). Furthermore, in human muscle, general anesthesia had no effect on protein synthesis, whereas 90 min of surgery resulted in an inhibition (19).

Previous work on liver protein synthesis has generally shown that stress or inflammation causes an increase, rather than the decrease observed here. In human subjects with ulcerative colitis, liver protein synthesis was elevated (30). Similarly in animals, liver protein synthesis is stimulated by a variety of stressful interventions, such as surgery (28) and cancer (38), as well as by inflammation due to endotoxemia (32) or injection of turpentine or interleukin-1β (4). However, decreases in liver protein synthesis were observed in rats with malaria (23) and during hypoxia (40). With inflammation induced by turpentine or interleukin-1β, the increase in total liver protein synthesis has been shown to be associated with a decline in albumin synthesis (1). This is consistent with reports of decreased albumin messenger RNA levels during inflammation (36). However, the decline in albumin synthesis as a fraction of total liver protein synthesis takes place after several hours, at which time it is largely offset by the increase in total liver protein synthesis. Such a suppressive effect on the albumin synthesis rate during inflammation has also been demonstrated in humans (36). However, in intensive care unit patients, an extreme variability as well as increased rates of albumin synthesis has been reported (16–18). The results from the present study indicate that the time factor (i.e., when in the course of surgery sampling is performed) must be taken into consideration, when effects on liver protein synthesis are studied in association with a surgical trauma. Furthermore, the effect of the degree of trauma and/or the severity of the systemic inflammatory insult needs to be further investigated in humans.

In conclusion, the FSR of liver protein decreased significantly during laparoscopic surgery. This effect developed rapidly after commencement of surgery but was not reflected by a detectable decline in the rate of albumin synthesis.

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