Hypothesis: Intra-abdominal hypertension frequently threatens renal function early after orthotopic liver transplantation (OLT).

Design: A prospective study of consecutive patients who underwent OLT.

Setting: The intensive care unit of a National Health Service teaching hospital.

Patients and Main Outcome Measures: The intra-abdominal pressure (IAP) of 108 consecutive patients who underwent OLT was postoperatively measured 3 times a day for 72 hours using the urinary bladder technique. Intra-abdominal hypertension was defined as an IAP of 25 mm Hg or higher.

Results: Thirty-four patients (31%) had a high IAP. Acute renal failure developed in 17 recipients (16%), 11 (65%) of whom had intra-abdominal hypertension (P<.01), with a mean±SD IAP of 27.9±9.9 mm Hg vs 18.6±5.2 mm Hg in those without acute renal failure (P<.001). The subjects with a high IAP were more frequently administered loop diuretics to maintain adequate diuresis (P<.001) and had a low mean arterial pressure on the day of surgery (P<.01), despite the fact that they were given more intravenous fluids (P<.01) and did not differ in the need for inotropic drugs. Logistic regression analysis showed that intraoperative transfusions of more than 15 U, respiratory failure, and intra-abdominal hypertension (P<.01) were independent risk factors for renal failure. The length of intensive care unit stay was similar in the patients with a normal and a high IAP, but mortality was higher among the latter (P=.02).

Conclusions: Intra-abdominal hypertension is common after OLT and is significantly associated with renal failure, reduced urinary output, and intensive care unit mortality. It is, therefore, worth monitoring IAP in those undergoing OLT.

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This prospective study involved a population of consecutive patients undergoing OLT at our center. The only exclusion criterion was preoperative renal dysfunction (defined as serum creatinine levels of >1.5 mg/dL [>133 µmol/L]).

The anesthesia technique was the same for all patients. The native liver was removed after complete suprapubic and infrahepatic vena cava cross-clamping, and a biopump-driven venovenous bypass was established between the superior vena cava and the portal and inferior vena cava districts. On the completion of surgery, the patients were transferred to the intensive care unit, where they were weaned from ventilatory support as soon as possible, as previously described. Immunosuppression consisted of oral cyclosporine, 10 mg/kg started on the day of surgery and titrated to maintain blood trough levels of 200 to 250 ng/dL; methylprednisolone sodium phosphate, 10 mg/kg intraoperatively, tapered by 50% daily to prednisolone hemisuccinate, 20 mg/d; and azathioprine, 1 mg/kg per day if the platelet count was greater than 60,000. Intrahepatic basiliximab, 20 mg, was administered on the day of surgery and 4 days later. Hemodynamic monitoring included the measurement of arterial pressure, central venous pressure (pulmonary artery and pulmonary capillary wedge pressure), and cardiac output by pulmonary artery catheter (Edwards Lifesciences LLC, Irvine, Calif).

The IAP was measured every 8 hours for at least the first 3 postoperative days using the urinary bladder technique: the urinary bladder is an extraperitoneal intra-abdominal structure with a compliant wall, so changes in intraperitoneal pressure are reflected by parallel changes in intraluminal bladder pressure; intravesical pressure, therefore, equals IAP. The technique of urinary bladder pressure measurement is simple. A 3-way stopcock is inserted between the patient's Foley catheter and the urine drainage bag; after the bladder is emptied and then filled with 100 mL of sterile isotonic sodium chloride solution, the stopcock is turned so that the Foley catheter is closed to the drainage bag but open to run into a standard pressurized monitoring line leading to a pressure transducer that is placed at the level of the symphysis pubis. To our knowledge, no published agreement has yet been reached about the level at which the IAP should be considered high. However, because a range of 10 to 25 mm Hg has recently been used in several clinical studies,7,18-21 we defined IAH as an IAP of 25 mm Hg or higher to be able to identify any deleterious effects more clearly.

The IAP was measured after the patients had been placed in a supine position and disconnected from the ventilator.

After completing the study, the patients were divided into 2 groups: those with a persistently high IAP (≥2 consecutive measurements) (group H) and those with a normal or only a sporadically high IAP (group N).

Renal function was evaluated by measuring daily urinary output per hour and, on the second and fourth postoperative days, serum creatinine levels. Acute renal failure (ARF) was defined as a postoperative serum creatinine concentration of more than 1.47 mg/dL (>130 µmol/L) or an increase of more than 1.33 mg/dL (>115 µmol/L) within 72 hours of surgery. Intra-abdominal hypertension and renal dysfunction were considered to be potentially related if they occurred within 48 hours of each other. Standard definitions were used for sepsis and respiratory and cardiovascular failure.

The statistical analysis was performed with Stata software, release 7.0 (Stata Corp, College Station, Tex), and the data are reported as mean ± SD. The Pearson χ² test, the χ² test with Yates correction, and the t test for unpaired data were used as appropriate; a forward stepwise logistic regression analysis was used to evaluate the effect of predetermined risk factors on renal function. Statistical significance was set at P = .05.

Table 1. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥25</th>
<th>&lt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients</td>
<td>34 (31)</td>
<td>74 (69)</td>
</tr>
<tr>
<td>Child-Pugh class, B/C/NC†</td>
<td>13/20/4</td>
<td>33/36/9</td>
</tr>
<tr>
<td>Cold ischemia time, min</td>
<td>547.3 ± 128.0</td>
<td>519.6 ± 197.3</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>393.8 ± 100.4</td>
<td>369.5 ± 58.8</td>
</tr>
<tr>
<td>SAPS, mean (range)</td>
<td>43 (84-38)</td>
<td>38 (63-34)</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>6.5 ± 7.5</td>
<td>5.0 ± 7.0</td>
</tr>
<tr>
<td>ICU outcome, alive/dead†‡</td>
<td>29/5</td>
<td>72/25</td>
</tr>
</tbody>
</table>

Abbreviations: IAP, intra-abdominal pressure; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥18</th>
<th>19-24</th>
<th>&gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 23)</td>
<td>(n = 51)</td>
<td>(n = 34)</td>
<td></td>
</tr>
<tr>
<td>Patients with renal impairment</td>
<td>1 (4)</td>
<td>5 (10)</td>
<td>11 (32)†‡</td>
</tr>
<tr>
<td>Patients taking diuretics</td>
<td>3 (13)</td>
<td>7 (14)</td>
<td>29 (89)§</td>
</tr>
<tr>
<td>Patients undergoing CRRT</td>
<td>0</td>
<td>0</td>
<td>3 (9)†</td>
</tr>
</tbody>
</table>

Abbreviations: CRRT, continuous renal replacement therapy; IAP, intra-abdominal pressure.

This study population consisted of 108 consecutive patients (80 men and 28 women); their mean age was 53.7 years (25th-75th percentile, 45-58 years). Eighty-eight patients (81%) underwent transplantation for liver cirrhosis due to viral infection, 6 (6%) due to alcoholic cirrhosis, and 14 (13%) due to other causes. Other relevant data about the study population are shown in Table 1. The IAP in the population as a whole was 21.5 ± 8.2 mm Hg (range, 9.5-77 mm Hg). Thirty-four subjects had a persistently high IAP (group H), whereas it was always lower or only occasionally higher than 25 mm Hg in the remaining 74 subjects (group N).

Renal function was impaired in 17 subjects (16%) (11 in group H and 6 in group N, P <.01); 3 of the patients in group H required continuous renal replacement therapy (P <.03). The relative risk for renal failure in the patients with IAH was 3.9 (95% confidence interval, 1.6-9.8). The subjects without renal impairment had an IAP of 18.6 ± 5.2 mm Hg, vs 27.9 ± 9.9 mm Hg in the others (P <.001). The relationship between renal impairment and IAP levels is shown in Table 2.

The serum creatinine level on postoperative day 2 was 1.2 ± 0.8 mg/dL (106 ± 71 µmol/L) (range, 0.4-4.3 mg/dL [35-336 µmol/L]) in group H and 0.7 ± 0.3 mg/dL (62 ± 27 µmol/L) (range, 0.4-3.1 mg/dL [35-274 µmol/L].

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L]) in group N (P<.01); on postoperative day 4, it was again significantly higher in the subjects with an increased IAP (1.8±1.1 mg/dL [159±97 µmol/L] vs 0.8±0.7 mg/dL [71±62 µmol/L]; P<.01). There was no difference in the serum creatinine levels of the patients in group H on the second and fourth postoperative days (P=.20). The hourly urinary output was not different between the 2 groups (99±39.5 mL in group N vs 112±51.9 mL in group H; P=.20), but the patients with IAH were more frequently administered loop diuretics to maintain adequate diuresis (29 vs 10 patients; P<.001).

In the subjects with IAH, the odds ratio (95% confidence interval) was 5.4 (1.8-16.3) for renal failure, 16.5 (0.8-330.0) for continuous renal replacement therapy, and 37.1 (11.6-118.4) for the need for loop diuretics.

The patients with IAH did not differ from those with a normal IAP in hemodynamic variables (central venous, pulmonary artery, and pulmonary capillary wedge pressures and cardiac output), but had a significantly lower mean arterial pressure (P<.01 during the first 24 hours after surgery, P<.001 on day 2, and P=.01 on day 3). However, the values were never critical in terms of tissue and renal perfusion, being 91.8±11.1 mm Hg on postoperative day 1, 93.3±13.6 mm Hg on postoperative day 2, and 99±4±16.9 mm Hg on postoperative day 3. Three patients in group H needed inotropic drugs vs 1 in group N (P=.06).

The patients with IAH needed a significantly higher amount of intravenous fluids than those with a normal IAP: 5420±1073 mL/d vs 2852±905 mL/d (P<.01). However, no difference was found for the patients with IAH who did and did not have ARF (P=.20).

Bivariate analysis showed that renal impairment significantly correlated with relaparotomy (P=.01), the use of abdominal packs (P=.01), intraoperative blood transfusions of more than 15 U (P<.01), IAH (P<.01), sepsis (P=.02), and respiratory failure (P<.01), but not with cardiac failure (P=.05), the postoperative use of aminoglycosides (P=.05), or classification in Child-Pugh class C, indicating severe pre-OLT liver disease (P=.20).

A forward stepwise logistic regression model showed that renal impairment significantly and independently correlated with intraoperative blood transfusions of more than 15 U, respiratory failure, and IAH (P<.01).

The length of intensive care unit stay was similar in both groups (P=.02), but the patients with IAH had a worse intensive care unit outcome (P=.02) and an odds ratio (95% confidence interval) for death of 6.2 (1.1-33.8).

**COMMENT**

The abdominal cavity can be considered a single compartment, so any change in its content increases the atmospheric or even negative IAP found in normally breathing subjects; consequently, an increase in the volume of abdominal or retroperitoneal content can lead to an increase in IAP that, at the bedside, is best measured via a urinary bladder catheter connected to a pressure transducer.

Intra-abdominal hypertension adversely influences visceral perfusion, and a close correlation has been found between the increase in IAP and impaired splanchnic blood flow; thus, when the IAP increases, renal function is threatened. However, the pathophysiological mechanism underlying this injury is still unclear, although, since the first demonstration that effective renal plasma blood flow and the glomerular filtration rate are reduced by IAH, there have been claims that many factors may be implicated. Recent reports tend to consider the cause of renal impairment in patients with IAH as multifactorial. Diminished renal arterial blood flow (due to decreased cardiac output), the shunting of blood from the cortex into the medulla, direct compression of kidney and renal veins, high renal venous pressure, and high levels of antidiuretic hormone, renin, and aldosterone have been advocated as possible cofactors, whereas ureteral occlusion and consequent postrenal azotemia have been excluded as major causal factors because the placement of ureteral stents did not improve renal function in subjects with IAH.

Only a few recent articles have described IAP monitoring after surgery, and none have addressed this issue in patients undergoing OLT. The rate of abdominal hypertension in our patients was similar to that found by Sugrue et al in 2 populations of patients who have undergone laparotomy, but they defined IAH as 18 and 20 mm Hg in the 2 studies vs the 25 mm Hg used by us. What actually constitutes high IAP is still under debate: some researchers have described IAH as an IAP of 10 mm Hg or higher, whereas others have suggested 14 mm Hg or higher, 18 mm Hg or higher, or even 20 to 25 mm Hg.

We decided to set our threshold for IAH at the highest value reported in the literature to highlight the pathophysiological relationship between IAH and ARF in a short-term situation such as the post-OLT period. However, when the threshold is set at lower levels (as in the studies by Sugrue et al), IAH is more frequent (40.7% vs 31% in our study), but the incidence of renal dysfunction remains similar (32.7% vs 32% in our study). This suggests that factors other than absolute IAP levels should be considered in the pathogenesis of the renal dysfunction occurring in postsurgical patients with IAH. Our experience seems to indicate not only that renal impairment is dose dependent (ARF significantly increases with the increase in IAH) but also that the duration of IAH may play an important role in this setting; ARF was more frequent in group H patients, who had IAH for at least 12 consecutive hours, than in those in group N, whose mean IAP was normal (but higher than in previous studies) or only occasionally higher than 25 mm Hg.

Other factors could influence renal function in the presence of a high IAP (eg, a low level of intravascular filling can play a major role in increasing the risk of ARF in patients with IAH). Loading patients with intravenous fluids may prevent the deleterious effects of IAH by counteracting the reduced cardiac output due to the diminished preload, caused by the fact that venous return to the heart is hampered by IAH-induced compression of the inferior and superior vena cava compartment (because of increased abdominal and thoracic pressures). However, our experience indicates that, although this approach can successfully maintain a stable hemodynamic state, it does not prevent renal failure because, despite that our patients with IAH received significantly more fluids than the normotensive subjects and their hemodynamic data were never critical in terms of systemic and renal perfusion, they were more frequently affected by ARF. This may have been...
due to the action of local factors, such as the shunting of blood from the cortex to the medulla, the direct compression of kidney and renal veins, or high renal venous pressure, that play a major role in causing ARF in the presence of IAH.\textsuperscript{7,13,18} However, fluid therapy was helpful in containing the severity of ARF, as is shown by the slight, although significant, increase in serum creatinine levels in the group H patients.

This observation also explains why we decided to adopt a conservative attitude toward the patients with IAH. Abdominal decompression by repeated laparotomy is an appealing way of reducing the risks associated with IAH, but although there have been reports of the prompt reversal of ARF after decompression, they are few\textsuperscript{20} and even controversial; furthermore, although decompressive de-lioty can lead to a significant reduction in IAP and bethlar signs of extremity compartment syndrome.\textsuperscript{7} Once again, and muscle ischemia begins long before the neuromuscular changes taking place in the early period after such a procedure. In any case, it has been suggested that the detrimental physiological effects of IAH take place long before its clinical manifestation, just as nerve and muscle ischemia begins long before the neuromuscular signs of extremity compartment syndrome.\textsuperscript{7} Once again, the duration of IAH and not just the absolute level of IAP may be a key factor. It is also difficult to determine the temporal relationship between IAH and renal dysfunction, although the effect of IAH is progressive rather than immediate and requires about 2 days to occur.\textsuperscript{20}

Regarding the correlation between high IAP and intensive care unit outcome, we found that the survival of the patients with a normal IAP was significantly better, thus confirming a previous report.\textsuperscript{3} However, IAH can threaten many other systems and functions, as well as renal function,\textsuperscript{7,18,19} and an association between increased IAP and sepsis and/or multiorgan dysfunction has been reported.\textsuperscript{10} The increased mortality may, therefore, not be related to renal dysfunction alone. In the absence of large-scale clinical trials analyzing the possible direct causal relationship between IAH and mortality in postoperative patients, it seems advisable to consider high IAP a major, but not decisive, risk factor in such patients, whose outcome can also be affected by severe comorbidities.

In conclusion, our findings show that attending clinicians need to be aware that a high IAP may be a serious risk factor for renal dysfunction during the early postoperative course of subjects undergoing OLT. In our experience, extra intravenous fluid loading, with stable and adequate hemodynamic variables, failed to prevent renal failure but did help to limit its severity.

Frequent IAP monitoring should be considered in subjects undergoing OLT because it may help transplantation specialists to understand better the basic physiological changes taking place in the early period after such a complex procedure. Whether IAH is a marker of critical illness or significant comorbidity still has to be elucidated.

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Corresponding author and reprints: Gianni Biancofiore, MD, Post-surgical and Transplant Intensive Care Unit, Azienda Ospedaliera Pisana, Ospedale di Cisanello, Via Paradisa 2, 56100 Pisa, Italy (e-mail: g.biancofiore@med.unipi.it).

REFERENCES