Intravascular Volume Depletion in a 24-Hour Porcine Model of Intra-abdominal Hypertension

Alexander Schachtrupp, MD, Juergen Graf, MD, Christian Tons, MD, Joerg Hoer, MD, Volker Fackeldey, and Volker Schumpelick, MD

Background: The purpose of the study was to examine hemodynamic parameters and intravascular volume in a porcine model in the presence of intra-abdominal hypertension (IAH) lasting for 24 hours.

Methods: Twelve pigs (52.5 ± 4.9 kg) were studied over a period of 24 hours. In six animals, the intra-abdominal pressure was increased to 30 mm Hg via carbon dioxide-pneumoperitoneum. The others served as controls. Using the double-indicator dilution technique, intrathoracic blood volume (ITBV), total circulating blood volume, and cardiac output (CO) were measured. Standard parameters (e.g., central venous pressure [CVP]), were also recorded.

Results: In the presence of IAH, ITBV and total circulating blood volume were significantly reduced to 55% and 67% of control values. CO decreased to 27% and CVP increased fourfold.

Conclusion: IAH leads to significant intravascular volume depletion that is not reflected by the CVP. Assessment of CO and ITBV in the presence of a critically increased intra-abdominal pressure is therefore recommended.

Key Words: Abdominal, Compartment syndromes, Animal model, Dye dilution, Intrathoracic blood volume (ITBV), Total circulating blood volume (TBV).

Intra-abdominal hypertension (IAH) (i.e., an intra-abdominal pressure exceeding 15 mm Hg) occurs in up to 41% of surgical patients and can result from various incidents, such as trauma, intra-abdominal bleeding, mechanical obstruction, or peritonitis. Without intervention, the abdominal compartment syndrome (ACS) may develop, a life-threatening condition that leads to renal, pulmonary, and circulatory failure. The treatment of IAH without concomitant organ dysfunction is nevertheless still under discussion. Moreover, randomized, controlled, clinical studies are not available yet, and controlled studies in humans and in animals did not exceed investigation periods of 8 hours, neglecting the fact that elevated intra-abdominal pressure may persist.

In various clinical and experimental observations, an increased IAP resulted in reduced cardiac output and raised the so-called cardiac filling pressures, such as central venous pressure (CVP) and pulmonary artery occlusion pressure. Both phenomena have been attributed, though divergently, to changes of the intravascular volume. Whether pulmonary artery occlusion pressure or CVP really reflects the intravascular volume status remains a matter of controversy. Therefore, the effect of long-term IAH on the intravascular volume status is unknown.

The purpose of this study was to investigate systemic hemodynamic changes in the presence of an IAP increased to 30 mm Hg in a 24-hour porcine model. Applying the double-indicator dilution technique, we furthermore aimed to evaluate the intravascular volume and its relationship to cardiac output and central venous pressure under this condition.

Materials and Methods

Twelve domestic male pigs with a mean body weight of 52.5 ± 4.9 kg (mean ± SD) were examined. The research protocol was approved by the regional animal welfare committee. The animals were fasted for 24 hours before the intervention period with free access to water. General anesthesia was induced and maintained with ketamine and pentobarbital. The animals were placed in supine position. Volume-controlled ventilation with an inspiratory oxygen concentration of 25% and a positive end-expiratory pressure of 2 cm H2O was used (Servo 900 C ventilator, Siemens, Solna, Sweden). At a constant respiratory rate of 15 breaths/min, the ventilatory setting was adjusted to maintain a PCO2 of 35 to 40 mm Hg. These settings remained unchanged throughout the experiment. Heart rate was recorded continuously with a three-channel electrocardiograph. Normal saline was infused at a constant rate of 1.5 mL/kg/h throughout the examination, using an automatic infusion device (Braun, Melsungen, Germany). A core temperature of 36° to 38°C was maintained by the application of heating lamps. Urine output was recorded via a suprapubic catheterization. A 3-French thermistor-tipped fiberoptic catheter (PV 2023 Pulmonary...
Intravascular Volume Depletion under IAH

Hemodynamic Parameters

In the present study, the integrated hemodynamic monitoring COLD Z-201 (PULSION Medical Systems, Munich, Germany) was used, with 20 mg indocyanine green (ICG-PULSION, PULSION Medical Systems) dissolved in 10 mL iced dextrose 5% solution for double-indicator (thermal and dye) dilution measurements. The double-indicator dilution technique is based on different transport functions of cold and dye during their transpulmonary passage. After injection into the superior vena cava, the dye binds immediately to plasma proteins and stays intravascularly, whereas the cold diffuses also into the extravascular space. The dilution curves of the dye and the cold are recorded simultaneously in the descending aorta. Analysis of the dilution curves yields cardiac output (CO) and mean transit time and exponential downslope time of both indicators. These parameters are used to calculate intrathoracic blood volume (ITBV), total circulating blood volume (TBV), and extravascular lung water (EVLW) as described by others.\textsuperscript{12,14–17}

The ITBV, TBV, and EVLW have been evaluated in animals and humans. The ITBV correlates well with changes of the CO, and this suggests a superior parameter of preload compared with the commonly used “filling pressures.”\textsuperscript{12,14,18} The TBV closely correlates with the circulating blood volume,\textsuperscript{18} and the EVLW provides a reliable estimate of the free lung water measured gravimetrically.\textsuperscript{19,20}

Additional hemodynamic parameters (i.e., heart rate, mean arterial pressure [MAP], CVP, peak inspiratory pressure [PIP], and urine output) were recorded hourly. The systemic vascular resistance was calculated using the following equation: systemic vascular resistance index = (MAP – CVP) × 79.9 × CI (unit: mm Hg/kg/min/mL, with cardiac index [CI] as mL/min/kg). Blood samples were taken, and arterial PO$_2$, PCO$_2$, and hematocrit were measured every 4 hours. Double-indicator dilution measurements were also performed every 4 hours.

Statistical Analysis

Values were indexed to body weight where appropriate and results presented as mean ± SD. Statistical analysis was carried out with an analysis of variance (ANOVA) for repeated measurements combined with a post hoc test according to Bonferroni. Within each group, a paired $t$ test was performed between values of the baseline and the following measurements beginning with values taken after 24 hours. Furthermore, unpaired $t$ tests were performed between the IAP-30 and the controls at corresponding points of time, again beginning with the values taken after 24 hours. The $t$ test was performed when normal distribution of the values was confirmed ($F$ test). A value of $p < 0.05$ was considered significant. In the case of repeated (n) $t$ tests, the level of significance was adjusted to $p < 0.05/n$. Furthermore, Pearson’s coefficient of correlation was calculated ($r$).

RESULTS

All animals survived the examination period. Elevation of intra-abdominal pressure significantly raised the central venous pressure within 2 hours from 5.2 ± 2.0 mm Hg (baseline) to 10.4 ± 3.0 mm Hg compared with control values. This parameter further ranged between 11.5 and 13.0 mm Hg (Fig. 1). The mean arterial pressure in the study group was significantly reduced to 57.5 ± 18.9 mm Hg or 65% of control values after 16 hours, whereas the values in the control group remained unchanged. Heart rate in both groups ranged between 108.2 ± 12.6 and 99.3 ± 19.1 beats/min without significant differences. The systemic vascular resis-
tance in the study group was significantly increased in both groups after 24 hours. Table 1 depicts MAP and systemic vascular resistance index at intervals of 4 hours, with a significantly decreased MAP after 16 hours compared with the control group.

Under the condition of elevated intra-abdominal pressure, the urine output significantly decreased, and all animals were anuric after 24 hours. In contrast, the urine output of the control group significantly increased by 84% after 24 hours compared with baseline values (Fig. 2). Mean body weight of the study group increased significantly after 24 hours when compared with the control group by 2.9 ± 0.2 kg versus 1.2 ± 0.1 kg (p < 0.05), respectively. Elevation of the intra-abdominal pressure significantly increased the peak inspiratory pressure within 1 hour by 109%, whereas in the control group this parameter remained constant, as shown in Figure 3.

Arterial Po2 in the study group decreased substantially (range, 137.3 ± 30.8–105.31 ± 31.0 mm Hg) but remained unchanged in the control group (range, 131.5 ± 20.8–130.4 ± 14.2 mm Hg). The arterial PcO2 in both groups also remained stable over the whole study period (31.5 ± 13.4–41.6 ± 3.6 mm Hg in the study group and from 33.5 ± 6.3–38.4 ± 5.8 mm Hg in the control group).

The hematocrit of the study group increased significantly from 30.2 ± 3.1% (baseline) to 36.5 ± 5.1% and 36.2 ± 4.9% after 12 hours and 24 hours, respectively. This was also significantly higher (p < 0.006 and p < 0.01, according to unpaired t test) than the control values, which tended to decrease from 31.5 ± 2.0% (baseline) to 29.8 ± 1.2% and 30.0 ± 3.1% after 12 hours and 24 hours, respectively.

In the presence of an IAP increased to 30 mm Hg, the ITBV significantly decreased to 55% of corresponding con-

Table 1 Mean Arterial Pressure and Systemic Vascular Resistance Index during 24 H of 30 mm Hg IAP and in Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>0 H</th>
<th>4 H</th>
<th>8 H</th>
<th>12 H</th>
<th>16 H</th>
<th>20 H</th>
<th>24 H</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP†</td>
<td>IAP-30 (mm Hg)</td>
<td>72.6 ± 8.1</td>
<td>76.3 ± 11.2</td>
<td>66.3 ± 13.0</td>
<td>60.8 ± 17.8</td>
<td>57.5 ± 18.9†</td>
<td>52.7 ± 14.6†</td>
<td>45.0 ± 14.6†</td>
</tr>
<tr>
<td>Control (mm Hg)</td>
<td>71.5 ± 12.9</td>
<td>67.8 ± 5.1</td>
<td>72.4 ± 10.8</td>
<td>80.4 ± 14.1</td>
<td>83.8 ± 9.6</td>
<td>81.7 ± 10.2</td>
<td>83.6 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>SVRI</td>
<td>IAP-30 (mm Hg/kg/min/mL)</td>
<td>51.0 ± 16.5</td>
<td>78.1 ± 26.0</td>
<td>106.0 ± 87.6</td>
<td>112.6 ± 93.8</td>
<td>108.2 ± 104.5</td>
<td>126.5 ± 81.5</td>
<td>127.0 ± 60.0*</td>
</tr>
<tr>
<td>Control (mm Hg/kg/min/mL)</td>
<td>50.5 ± 15.2</td>
<td>48.8 ± 5.9</td>
<td>69.2 ± 18.8</td>
<td>84.6 ± 21.8</td>
<td>94.6 ± 16.4</td>
<td>82.1 ± 18.4</td>
<td>80.0 ± 17.1*</td>
<td></td>
</tr>
</tbody>
</table>

* Significant difference to baseline according to paired t test: MAP (20 h), p < 0.01; SVRI (24 h), p < 0.04 (control and IAP-30).
† Significant difference to corresponding control according to unpaired t test: MAP (16 h), p < 0.006.
‡ Significant change during 24 h according to ANOVA and post hoc analysis (MAP, p < 0.037).

Fig. 2. Urine output (UO) (mean ± SD) of pigs with normal (control) and elevated intra-abdominal pressure (IAP-30). All animals of the study group developed renal failure. Time intervals changed from 1 to 4 hours after a break at 4 hours. † Significant difference compared with baseline value according to paired t test, p < 0.001 (IAP-30 after 3 hours) and p < 0.008 (control after 24 hours). ‡ Significant difference compared with baseline value according to unpaired t test, p < 0.001 after 3 hours. ANOVA and post hoc analysis: p < 0.0001.

Fig. 3. Peak inspiratory pressure (PIP) (mean ± SD) of pigs with normal (control) and elevated intra-abdominal pressure (IAP-30). PIP was significantly increased with the increase of IAP. Time intervals changed from 1 to 4 hours after a break at 4 hours. † Significant difference compared with baseline value according to paired t test, p < 0.001 (IAP-30 after 1 hour) and p < 0.0061 (control after 24 hours). ‡ Significant difference compared with baseline value according to unpaired t test, p < 0.001 after 1 hour. ANOVA and post hoc analysis: p < 0.0001.
control values after 20 hours and 24 hours (Fig. 4). Moreover, the total circulating blood volume declined to 67% of control values after 20 and 24 hours (Fig. 5). In contrast, the EVLW increased twofold compared with control values after 24 hours under the condition of an increased IAP (Fig. 6). In the controls, ITBV, TBV, and EVLW remained unchanged.

The cardiac output in the study group significantly reduced to 59% of the control values after 12 hours. It further decreased to 27% of control values after 24 hours. In the control group, the cardiac output also decreased significantly but did not fall beyond 74% of baseline values after 24 hours of observation (Fig. 7).

Irrespective of control or study group, the CVP correlated only moderately but negatively with the cardiac output \( r = -0.64 \) (Fig. 8), whereas correlation with the PIP was \( r = 0.86 \). In contrast, the ITBV showed a reliable correlation with cardiac output \( r = 0.86 \) (Fig. 9).

**DISCUSSION**

Mechanical obstruction, peritonitis, pancreatitis, trauma, or intra-abdominal bleeding can lead to intra-abdominal hypertension and may eventually result in the ACS. Although the incidence of the abdominal compartment syndrome ranges between 5% and 15% in trauma and surgical patients, IAH has been observed in up to 41% of surgical patients. Moreover, intra-abdominal hypertension has been identified as an independent risk factor in the development of postoperative renal impairment.

The main finding of this study is that intra-abdominal hypertension results in a reduction of the ITBV and the TBV together with a subsequent increase in hematocrit. This has been correlated positively to a reduced cardiac output.

For the assessment of the intravascular volume status of the investigated animals, transpulmonary double-indicator di-
olution measurements have been performed. The ITBV, TBV, and EVLW have not been evaluated during IAH yet. Nevertheless, the transpulmonary double-indicator dilution technique does not depend on blood pressure measurements, and the ITBV accurately reflects the volume status in patients independent of intrathoracic pressure changes.14 In addition, the significant increase of hematocrit strongly supports the assumed loss of intravascular volume despite a constant volume administration of 1.5 mL/kg/h and the development of anuria in all animals of the study group.

Normal values of ITBV and TBV have not been established for a comparable porcine model yet. Normovolemia, however, must be assumed at the beginning of the experiment, because all animals had free access to water. In addition, the standard infusion has been sufficient to sustain a diuresis above 1.5 mL/kg/h in the control group. In the study group, both ITBV and TBV were significantly reduced toward the end of the investigation period after a substantial decline to 74% within the first 8 hours.

The impact of increased IAP on intravascular volume status as measured by ITBV has been evaluated only once in patients undergoing cholecystectomy. Under these circumstances, ITBV decreased by 16% shortly after the onset of pneumoperitoneum.23

The question of whether an increase of IAP influences intravascular volume status has been addressed in human and animal investigations applying transesophageal echocardiography,24 extracorporal circulation,8 and radioactive microspheres.10 In cases of normo- or hypovolemia, it has been observed that an increase of IAP would decrease venous return and consecutively cardiac output despite increased filling pressures.9 Furthermore, it has been suggested that the increased tissue pressure affects the venous system like a Starling resistor, which results in increased venous outflow resistance and consequently in venous pooling.10

The influence of IAH on volume parameters, however, has not been studied beyond 8 hours of increased IAP yet. Concerning the underlying study, venous pooling might not have been the only factor leading to volume depletion, as one

![Fig. 7. Cardiac output (mean ± SD) of pigs with normal (control) and elevated intra-abdominal pressure (IAP-30). Note that cardiac output was decreased in the presence of an IAP of 30 mm Hg. *Significant difference compared with baseline value according to paired *t* test, *p* < 0.0067 (IAP-30 after 4 hours) and < 0.0058 (control after 12 hours). †Significant difference compared with corresponding control value according to unpaired *t* test, *p* < 0.001 after 12 hours. ANOVA and post hoc analysis: *p* < 0.002.](image1)

![Fig. 8. Correlation between cardiac output and central venous pressure in the control group and under the condition of intra-abdominal hypertension. Note that correlation coefficient was −0.64, indicating a moderate negative correlation between CVP and CO. ●, Values in the presence of increased IAP; ○, control values.](image2)

![Fig. 9. Correlation between cardiac output and intrathoracic blood volume (ITBV) under the condition of intra-abdominal hypertension and under control conditions. Note that the correlation coefficient was 0.86, indicating that a decrease in ITBV correlated with a decrease in cardiac output. ●, Values in the presence of increased IAP; ○, control values.](image3)
In conclusion, IAH leads to intravascular volume depletion measured by ITBV and TBV in this animal model. The CVP, commonly used to assess cardiac preload, did not reflect the volume status under these experimental conditions. Under clinical conditions, IAH and ACS have also been observed to reduce the intravascular volume and the cardiac output. Patients at risk are not clearly defined yet, but a high demand for volume (i.e., > 10 L of crystalloids) and severe acidosis (i.e., a base deficit > 10) were correlated with severe IAH and ACS. 

In these patients, measurement of cardiac output and ITBV may lead to a rational volume management and avoidance of organ dysfunction.

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REFERENCES


