

## Alterations in hemodynamics and hepatic and splanchnic circulation during laparoscopy in rats

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### Abstract

**Background:** There is growing evidence that a pneumoperitoneum with increased intraabdominal pressure exerts adverse cardiovascular and splanchnic circulatory effects, whereby portal blood flow, in particular, is disturbed.

**Methods:** Cardiovascular hemodynamics and the blood flow of hollow viscus and solid organs were evaluated in rats undergoing laparotomy, followed by diagnostic carbon dioxide (CO<sub>2</sub>) laparoscopy with an intraabdominal pressure of either 4 or 10 mmHg and rapid desufflation of the abdominal cavity. The method we employed used  $\gamma$ -labeled microspheres and conventional hemodynamic measurements.

**Results:** During CO<sub>2</sub> laparoscopy, cardiac output and mean arterial pressure were significantly reduced to between 20.5% and 25% and 14.8% and 18% respectively. After rapid desufflation, cardiovascular hemodynamics normalized to baseline values. During laparoscopy, blood flow in the hollow viscus organs was less disturbed than that in the solid organs. Although small and large bowel blood flow was reduced significantly (26.6% and 23.9%, respectively), gastric blood flow remained unchanged. The decreases in the liver, spleen, pancreas, and kidney circulation were 29–37.2%, 37.6–64.6%, 51.2–57.5%, and 34.8–40.6%, respectively. Total hepatic blood flow was influenced predominantly by portal blood flow, which was particularly decreased; hepatic arterial flow remained stable.

**Conclusions:** Severe alterations in cardiovascular hemodynamics, and to hepatic and splanchnic circulation occur rapidly during CO<sub>2</sub> laparoscopy. It can be presumed that both increased intraabdominal pressure and hypercapnia are the main factors underlying these disturbances.

**Key words:** Laparoscopy — Pneumoperitoneum — Carbon dioxide — Rat model — Intestinal blood flow — Microspheres

The intraabdominal insufflation of carbon dioxide (CO<sub>2</sub>) is the most widely used technique for the creation of a pneumoperitoneum. Permanent insufflation under a continuous monitoring of intraabdominal pressure throughout the surgical procedure provides adequate exposure of the operating field. As alternatives, mechanical retracting devices (so-called gasless laparoscopy) and different gases (e.g., helium, argon, nitrous oxide, air) may be used, but they have not been adopted clinically [2, 5, 9, 10, 23, 31].

Impairment of intraabdominal circulation during a pneumoperitoneum—in particular, the portal blood flow—has been shown to be induced by different gases (e.g., carbon dioxide, helium, argon) in different experimental and clinical studies [4, 8, 18, 25, 32]. Several methods are available for determining splanchnic blood flow, such as direct measurement by Doppler flowmetry or indirect measurement using mucosal tonometry and indocyanine green pharmacokinetic [16, 20, 25, 30]. Visceral and hepatic blood flow is reported to be reduced by  $\leq 37$ –60%; the extent of such a flow reduction seems to be predominantly related to the intraabdominal pressure (IAP) [12, 16]. However, the impact of these hemodynamic changes is unknown, since the majority of patients who undergo laparoscopic procedures do not exhibit any adverse clinical effects either in the short- or the long-term course.

The aims of the current study were to investigate splanchnic and portal blood flow by quantitative measurement using  $\gamma$ -labeled microspheres (reference sample method) and to assess hemodynamic changes during laparotomy, laparoscopy, and rapid desufflation of the abdominal cavity in a small-animal model.

### Material and methods

#### Animals

Twelve male Sprague-Dawley rats (BRL, CH-4414 Füllinsdorf, Switzerland) with a mean weight of 332 g (range, 300–365 g) were used for all experiments. Animals were kept under normal laboratory conditions on a 12-h dark/light cycle and fed a standard rat chow (Kliba Futter, Basel,

Switzerland) with tap water ad libitum. The experiments had been approved by the Animal Ethics Board of the state of Berne and were performed according to these guidelines.

### Anesthesia and surgical preparation of animals

All animals were fasted overnight and given free access to water. Anesthesia was induced with intraperitoneal injections of pentobarbital (50 mg/kg) and maintained with intraarterial injections of pentobarbital. Prior to the operative procedure, the skin over the abdominal wall and neck was shaved. Animals were placed in a supine position and attached to a specially designed small-animal operating table [3, 22]. The preparation and hemodynamic measurements were performed using the microsphere technique according to Groszmann et al. [11]. Rectal temperature was measured and kept at  $37.5 \pm 0.5^\circ$  with a heating mattress. Cannulation of the right carotid artery was performed using a PE-50 catheter (Parsippany, NY, USA), which was advanced into the left ventricle for injection of the microspheres. Another catheter was placed into the left femoral artery for continuous arterial blood pressure and heart rate monitoring throughout the experiment and for blood sampling. Both catheters were connected to two disposable Combitrans transducers (B. Braun, Melsungen, Germany). Blood pressure and heart rate were recorded continuously on a commercially available recorder (Servomed SMV 104, Hellige, Germany).

A median 4-cm laparotomy (LP) was performed, and the peritoneal cavity was left open for 30 min. The reference sample was withdrawn from the femoral catheter, which was set at a constant rate of 1 ml/min using a Perfusor pump (B. Braun). Ten seconds after starting the withdrawal of the reference sample, 60,000–90,000 polymeric microspheres measuring  $15 \pm 3 \mu\text{m}$  in diameter and labeled with  $^{113}\text{Sn}$  (specific activity, 5–7 mCi/g) were injected over a 20-sec interval into the left ventricle. Until its use, the microsphere solution was suspended by ultrasonication. The right carotid catheter was flushed and blood loss was replaced with 1 ml Ringer lactate via the femoral catheter. Variations in mean arterial pressure (MAP) were minimized by this fluid replacement. The laparotomy was then closed in anatomical layers.

Diagnostic laparoscopy was performed as described by Berguer et al. and our own group [3, 22]. A small opening in the medio-inferior abdominal wall was created, and the 3-mm camera trocar (K. Storz, Tuttlingen, Germany) was inserted into the peritoneal cavity. The pneumoperitoneum was established with  $\text{CO}_2$  insufflation and maintained at a constant 4 mmHg (LS 4) by a standard surgical  $\text{CO}_2$  insufflator (K. Storz). The 2.7-mm arthroscope (K. Storz) was inserted into the camera trocar and held by a self-retracting device. After an equilibration time of 30 min, a second hemodynamic measurement was performed, as described above, using a  $^{46}\text{Sc}$ -labeled microsphere solution (60,000–90,000 microspheres; diameter,  $15 \pm 3 \mu\text{m}$ ; specific activity, 5–7 mCi/g). After the intraabdominal pressure was increased to 10 mmHg (LS 10) and the equilibration time of 30 min had elapsed, a third hemodynamic measurement was performed using  $^{51}\text{Cr}$ -labeled microsphere solution (60,000–90,000 microspheres; diameter,  $15 \pm 3 \mu\text{m}$ ; specific activity, 5–7 mCi/g). Reversibility of the hemodynamic changes was determined 2 min after desufflation (DF) and removal of all trocars by a fourth measurement using  $^{57}\text{Co}$ -labeled microsphere solution (60,000–90,000 microspheres; diameter,  $15 \pm 3 \mu\text{m}$ ; specific activity, 5–7 mCi/g).

After a period of 3–5 min, all the animals were killed and their intra-abdominal organs were harvested through a large U-shaped incision. Liver, spleen, left and right kidney, pancreas, stomach, small intestine, large intestine, and appendix were separately removed, weighed, and stored until radioactivity was determined.

### Analytical and hemodynamic determination

Prior to determination of radioactivity, the larger organs (liver, small intestine, large intestine, appendix) were cut into pieces and placed in separate vials to obtain a better geometric efficiency of counting. Radioactivity was determined for each type of microsphere with a Packard COBRA-II  $\gamma$ -spectrophotometer with Compuser Software (Canberra Packard, Switzerland); an appropriate correction for isotope spillover was included. The radioactivity of each kidney was measured separately to assess the homogeneous mixing of the microspheres. Only animals with a disparity  $<10\%$  were included in the final analysis.

The heart rate and arterial blood pressure were monitored directly via

**Table 1.** Characteristics of the experimental animals

No. of animals	12
Body weight (g)	$332 \pm 18$
Liver weight (g)	$12.83 \pm 1.09$
Spleen weight (g)	$1.06 \pm 0.71$
Kidney weight (g)	$2.49 \pm 0.28$

Values given as mean  $\pm$  standard deviation (SD)

the femoral and right carotid artery catheters and recorded. All other hemodynamic parameters—such as organ blood flow, portal vein flow, hepatic artery flow, total hepatic flow, and cardiac output (CO)—were calculated as described by Groszmann et al. [11]. Cardiac output was expressed as ml/min; as organ blood flow was expressed as ml/min/g organ tissue.

### Statistical analysis

Results are expressed as mean  $\pm$  standard deviation (SD). Means were compared by paired Student *t*-test. A  $p < 0.05$  was considered to be statistically significant.

### Results

The baseline data for the animals, which reveal only minor differences in terms of weight and organ characteristics, are shown in Table 1.

During the equilibration time of 30 min after midline laparotomy, mean CO and arterial blood pressure were 88 ml/min and 128 mmHg, respectively. Diagnostic laparoscopy with 4 mmHg significantly decreased CO to 70 ml/min (–20.5%) and arterial blood pressure to 105 mmHg (–18.0%). Values for CO and arterial blood pressure at 10 mmHg IAP did not decrease any further. Desufflation of the abdominal cavity was followed by a rapid increase of hemodynamic parameters, and baseline values were reached within 2 min (CO, 98 ml/min; arterial blood pressure, 119 mmHg). The course of the hemodynamic changes is summarized in Table 2.

Blood flow in both the hollow viscus and solid organs was reduced by the increased IAP during laparoscopy. The baseline blood flows of the stomach, small bowel, large bowel, and appendix at laparotomy were 1.09 ml/min/g, 15.94 ml/min/g, 2.09 ml/min/g, and 3.18 ml/min/g, respectively. As shown in Table 3, after the pneumoperitoneum was established with 4 mmHg, there was a marked, though not significant, decrease of blood flow in the stomach (–12.8%), small bowel (–26.4%), large bowel (–23.9%), and appendix (–13.5%). Raising the IAP to 10 mmHg caused no further decrease of organ blood flow, but it did cause adaption to the altered IAP increased blood flow rates of all four hollow viscus organs. After desufflation of the abdominal cavity, the blood flow remained below prelaparoscopic values. In contrast to the hollow viscus organs, blood flow in the solid organs was reduced significantly during laparoscopy. During open laparotomy, blood flow rates were 4.11 ml/min/g (total liver), 2.29 ml/min/g (spleen), 1.27 ml/min/g (pancreas), and 13.17 ml/min/g (kidneys). Laparoscopy at 4 mmHg significantly reduced blood flow to 2.58 ml/min/g (–37.2%), 1.43 ml/min/g (–37.6%), 0.54 ml/min/g (–57.5%), and 8.59 ml/min/g for

**Table 2.** Hemodynamic changes during laparotomy, laparoscopy, and rapid desufflation

	LP	LS 4	LS 10	DF
Cardiac output (mmHg)	88 ± 12 (100)	70 ± 11 <sup>a</sup> (79.5)	66 ± 11 <sup>a</sup> (75.0)	98 ± 19 (114.4)
Arterial blood pressure (mmHg)	128 ± 11 (100)	105 ± 12 <sup>a</sup> (82.0)	109 ± 11 <sup>a</sup> (85.2)	119 ± 8 (93.0)

LP, laparotomy; LS 4, laparoscopy 4 mmHg; LS 10, laparoscopy 10 mmHg; DF, desufflation

Values given as mean ± standard deviation (SD); percentages in brackets  
<sup>a</sup>  $p < 0.05$  LS 4 vs LP and LS 10 vs LP

**Table 3.** Effect of the carbon dioxide pneumoperitoneum on hollow visus organ blood flow with different intraabdominal pressures

	LP	LS 4	LS 10	DF
Stomach (ml/min/g)	1.09 ± 0.25 (100)	0.95 ± 0.46 (87.2)	0.97 ± 0.60 (89.0)	0.98 ± 0.47 (89.9)
Small bowel (ml/min/g)	15.94 ± 9.01 (100)	11.70 ± 2.67 <sup>a</sup> (73.4)	18.71 ± 2.98 (117.4)	14.61 ± 5.44 (91.7)
Large bowel (ml/min/g)	2.09 ± 0.57 (100)	1.59 ± 1.20 <sup>a</sup> (76.1)	2.17 ± 0.51 (103.8)	1.87 ± 0.97 (85.5)
Appendix (ml/min/g)	3.18 ± 0.55 (100)	2.75 ± 0.99 <sup>a</sup> (86.5)	3.01 ± 1.47 (94.7)	2.27 ± 0.64 <sup>a</sup> (71.4)

LP, laparotomy; LS 4, laparoscopy 4 mmHg; LS 10, laparoscopy 10 mmHg; DF, desufflation

Values given as mean ± standard deviation (SD); percentages in brackets  
<sup>a</sup>  $p < 0.05$  LS 4 vs LP and LS 10 vs LP

<sup>b</sup>  $p < 0.001$  LS 4 vs LP and LS 10 vs LP

liver, spleen, pancreas, and -34.8% kidneys, respectively. Further increasing the IAP to 10 mmHg could not be compensated for, and blood flow remained at decreased levels. In all solid organs except for the liver, blood flow was only partially restored (72.5–82.4% of baseline values) after rapid desufflation of the abdominal cavity. Hemodynamic changes to the solid organs are summarized in Table 4.

The hepatic artery and portal vein both contribute to total hepatic blood flow. However, as shown in Fig. 1, total hepatic blood flow was predominantly influenced by disturbances to the portal venous flow. Establishing the pneumoperitoneum at 4 mmHg was associated with a significant reduction of portal venous flow to 53.8%. An IAP of 10 mmHg did not further decrease portal blood flow. After decompression of the abdominal cavity, portal blood flow was only partially restored after 2 min to 75.2%, while total hepatic blood flow was almost normalized.

## Discussion

The aim of this study was to assess intraabdominal organ blood flow and, in addition, hemodynamic changes during laparotomy, laparoscopy with different IAP, and rapid desufflation. The CO<sub>2</sub> pneumoperitoneum caused a significant decrease of both CO and arterial blood pressure, although these reductions were rapidly reversible after desufflation of the abdominal cavity. Whereas the hollow viscus organs showed only minor changes in blood flow, there was a significant reduction of blood flow in the solid organs. Nor-

malization of organ blood flow was delayed after emptying the peritoneal cavity.

Of all the different methods used to assess organ blood flow, the  $\gamma$ -labeled microsphere technique, as described by Groszmann et al., has been the one most widely used in animal studies [6, 11]. Although only a limited number of flow measurements can be performed, different intraabdominal organs can be investigated simultaneously in a given animal under equal experimental conditions. More recently, Doppler flowmetry and transit-time ultrasound have been used for the direct determination of splanchnic and, in particular, portal blood flow in human and animal studies [12, 26]. In contrast to the microsphere technique, direct measurement of blood flow can be achieved by positioning the flow probe onto the corresponding vessel, but compression should be avoided. D'Almeida et al. compared ultrasound to the microsphere technique and found only minor differences concerning the validity of both techniques [6]. Therefore, the theoretical objection that the repeated use of microspheres can cause an obstruction of the capillary system that impairs hemodynamic measurements has no impact on the accuracy of the microsphere technique.

There was a significant decrease in CO (-25%) and arterial blood pressure (-18%) during CO<sub>2</sub> laparoscopy, followed by a rapid normalization of both parameters after desufflation of the abdominal cavity. Our results are in agreement with earlier reports in the literature concerning the reduction of CO, but the changes in arterial blood pressure showed a larger disparity. Various studies—some in healthy patients undergoing various laparoscopic procedures, others in different animal models—found a marked decrease in CO of between 18% and 28% [7, 14, 17]. Only slight differences in CO were reported by Andersson et al., Knolmayer et al., and Windberger et al. [1, 20, 32]. In addition, Klopfenstein et al. stressed the importance of the patient's position on the operating table [19]. In fact, the management of ventilation and fluid replacement during anesthesia, as well as the head-up position, greatly influence intrathoracic pressure, venous backflow, and filling of the vascular system. Some recently published animal studies comparing the effects of CO<sub>2</sub> and helium pneumoperitoneum found a similar decrease in CO for both gases [25, 27]. Therefore, the mechanical effect of increased IAP may be at least partially responsible for the impaired CO.

Most clinical and experimental studies have shown that arterial blood pressure increases by  $\leq 40\%$  after the CO<sub>2</sub> pneumoperitoneum was established [7, 17]. Only minor changes in arterial blood pressure were observed by Andersson et al. and Diebel et al. [1, 8]. In our series, there was a marked decrease in arterial blood pressure during laparoscopy. Arterial blood pressure depends particularly on CO, systemic vascular resistance, and the extent of hypercapnia (not determined); thus, temporary disturbances of these factors may cause different changes in blood pressure. Hypercapnia may partially explain the reduced arterial blood pressure in the current study, since all animals were not mechanically ventilated and thus hypercapnia could not be minimized. Furthermore, patient position and different pharmacological agents may induce deteriorations in arterial blood pressure [18, 19].

In the present study, portal blood flow was significantly reduced by CO<sub>2</sub> laparoscopy, although the amount of flow

**Table 4.** Effect of the carbon dioxide pneumoperitoneum on solid organ blood flow with different intraabdominal pressures

	LP	LS 4	LS 10	DF
Liver (total hepatic flow) (ml/min/g)	4.11 ± 0.45 (100)	2.58 ± 0.45 <sup>a</sup> (62.8)	2.92 ± 0.21 <sup>a</sup> (71.0)	4.03 ± 0.25 (98.1)
Spleen (ml/min/g)	2.29 ± 0.41 (100)	1.43 ± 0.31 <sup>b</sup> (62.4)	0.81 ± 0.35 <sup>b</sup> (35.4)	1.66 ± 0.71 <sup>c</sup> (72.5)
Pancreas (ml/min/g)	1.27 ± 0.26 (100)	0.54 ± 0.26 <sup>b</sup> (42.5)	0.62 ± 0.35 <sup>b</sup> (48.8)	0.65 ± 0.27 <sup>c</sup> (51.2)
Kidneys (ml/min/g)	13.17 ± 2.87 (100)	8.59 ± 1.54 <sup>a</sup> (65.2)	7.82 ± 2.48 <sup>a</sup> (59.4)	10.85 ± 1.44 <sup>c</sup> (82.4)

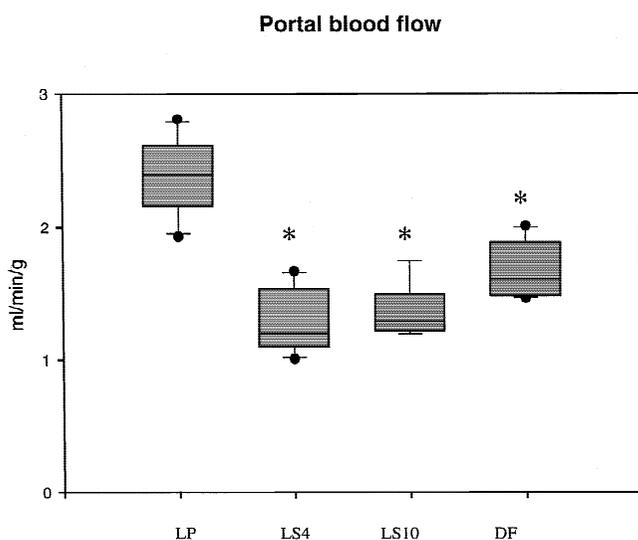
LP, laparotomy; LS 4, laparoscopy 4 mmHg; LS 10, laparoscopy 10 mmHg; DF; desufflation

Values given as mean ± standard deviation (SD); percentages in brackets

<sup>a</sup>  $p < 0.05$  LS 4 vs LP and LS 10 vs LP

<sup>b</sup>  $p < 0.001$  LS 4 vs LP and LS 10 vs LP

<sup>c</sup>  $p < 0.05$  DF vs LP



**Fig. 1.** Portal venous blood flow in the four different experimental groups (laparotomy, laparoscopy 4 mmHg, laparoscopy 10 mmHg, desufflation). Boxes include values between the 5th and 95th percentile; median values are indicated by a horizontal line. T-bars indicate standard deviations. Values outside the standard deviation are shown as closed circles. Portal blood flow was significantly reduced with a CO<sub>2</sub> pneumoperitoneum of either 4 or 10 mmHg as compared to laparotomy ( $p < 0.05$  paired *t*-test) and did not normalize to baseline values after rapid desufflation.

reduction did not correlate with increasing IAP. This observation can probably be explained by compensatory mechanisms that prevented any further decrease. In contrast, hepatic arterial flow remained stable; thus, total hepatic blood flow was influenced predominantly by the reduction in portal venous flow. These findings are in agreement with numerous other studies that evaluated hepatic and portal blood flow during laparoscopy [15, 18, 28, 32]. The reported reduction in portal blood flow ranged from 35% to 53%. In addition, some studies found a direct correlation between increased IAP and decreased portal blood flow [12, 13, 16]. The intraabdominal insufflation of CO<sub>2</sub> has been used in most studies to increase IAP. Therefore, it has been hypothesized that reduction in portal blood flow is caused either by mechanical compression of the thin-walled portal vein and/or by hypercapnia-induced vasoconstriction, whereas hepatic arterial flow (thick-walled vessel with arterial pres-

sure) may be less compromised by an IAP between 15 and 20 mmHg.

In fact, there is some evidence to show that mechanical compression is a major factor contributing to decreased portal venous flow. Impaired portal blood flow even occurred when hypercapnia was avoided by controlled hyperventilation or increased IAP was created by helium or argon insufflation [18, 25, 27]. In addition, portal blood flow is also dependent on arteriolar resistances in different splanchnic organs.

The data in the literature concerning alterations of hepatic arterial blood flow remain somewhat controversial. It has been shown that hypercapnia, without increased IAP, can reduce hepatic arterial blood flow [24, 29]. In their studies, Windberger et al. [32] and Ishizaki et al. [15] found no changes to hepatic arterial flow during laparoscopy, whereas Diebel et al. [8] reported that hepatic arterial flow was reduced in the presence of increased IAP. In contrast, Klopfenstein et al. noted an increase in hepatic arterial flow with increased IAP [19]. Moreover, total hepatic blood flow may be maintained by a compensatory increase of hepatic arterial blood flow, which is triggered by locally produced adenosine. However, methodological differences must always be kept in mind, and comparisons between different studies may therefore be of limited value.

Reduction in organ blood flow was different for hollow viscus vs solid organs. The decrease in blood flow was less extensive in hollow viscus organs than in solid organs. Nevertheless, circulation in the small and large bowel (including the appendix) was impaired significantly by increased IAP (−26.6% and −23.9%, respectively), whereas gastric blood flow remained unchanged. As with portal blood flow, circulation in other solid organs—such as the spleen, pancreas, and kidneys—was severely reduced during laparoscopy. The amount of reduced blood flow correlated to the magnitude of IAP in solid but not in hollow viscus organs. These results are well confirmed by other reports in the literature, which revealed decreases of intestinal blood flow during laparoscopy with increased IAP [4, 15, 32]. Schilling et al. found a flow reduction of 40–54% in the stomach, 32% in the jejunum, and 44% in the colon, and Shuto et al. observed a decrease of renal blood flow ranging between 9% and 19% [26, 27]. Other authors, who used indirect methods (predominantly intestinal tonometry), only described a re-

duction of pH values and could not exactly quantify the flow reduction [14, 20]. However, the extent of flow reduction and the IAP needed to achieve these negative effects, ranged widely.

The use of various animal models (e.g., pigs, dogs, rats, neonatal lambs), different methods to increase IAP (CO<sub>2</sub>, helium, water, or air-filled bags), and disparate measurement techniques (Doppler flowmetry, tonometry, microsphere technique) may explain this wide range of IAP values and its variable effect on splanchnic circulation. Furthermore, the patient's position on the operating table, the ventilation modus, and the volemic state are all important cofactors that influence hepatic and splanchnic circulation [19]. Despite methodological limitations, there is some evidence that decreased CO and increased vascular resistance are due to increased IAP and hypercapnia, which thus represent main pathophysiological changes that can cause intestinal flow reduction. In fact, when mechanical retractors were used to lift up the abdominal wall (gasless laparoscopy), there was no impairment to the intestinal blood flow [21].

In conclusion, our studies have shown a marked decrease in cardiovascular hemodynamics and splanchnic and portal blood flow during CO<sub>2</sub> laparoscopy. This reduction is presumably related to both increased IAP and hypercapnia-induced changes. However, there are additional factors that also cause hemodynamic and circulatory disturbances (e.g., volemic state, type of ventilation, patient position). The  $\gamma$ -labeled microsphere technique is a valuable method that can be used to investigate hemodynamic and circulatory changes during laparoscopy in a small-animal model.

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