Overcoming Reduced Hepatic and Renal Perfusion Caused by Positive-Pressure Pneumoperitoneum

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Hypothesis: Use of the intermittent sequential pneumatic compression (ISPC) device may improve splanchnic and renal perfusion caused by positive-pressure pneumoperitoneum (PPP) in patients undergoing laparoscopic cholecystectomy.

Design: Prospective controlled study.

Setting: University hospital.

Patients: Twenty-two consecutive patients undergoing elective laparoscopic cholecystectomy whose cardiac output decreased at least 10% on induction of PPP.

Intervention: The ISPC device was activated over the lower limbs 15 minutes after PPP was established for the remainder of surgery.

Main Outcome Measures: Urine output, cardiovascular functions, and hepatic and renal perfusion were measured during the surgical phases; urine output was quantified in a matched control group (n=30).

Results: Induction of PPP significantly decreased cardiac output and stroke volume, while ISPC significantly reversed these changes. Increased systemic vascular resistance during PPP was reversed by ISPC. Activation of the pneumatic sleeves during PPP increased the mean±SD portal venous and hepatic arterial blood flows from 0.86±0.30 to 1.33±0.44 L/min (P<.001) and from 0.26±0.10 to 0.38±0.19 L/min (P=.002), respectively; the mean renal segmental arterial index decreased with ISPC from 0.68±0.05 to 0.63±0.08 (P=.003). During PPP, urine output decreased from 1.10 to 0.28 mL/min per meter squared (P=.001) but improved markedly with ISPC to 0.61 mL/min per meter squared (P=.01). Such improvement was absent in the control group.

Conclusions: Use of ISPC significantly improves hepatic and renal blood flows during PPP. Its application is recommended during prolonged laparoscopic procedures, including laparoscopic live donor nephrectomy.

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The creation of a carbon dioxide positive-pressure pneumoperitoneum (PPP) may result in deranged pathophysiological consequences related to acidosis, hypercarbia, and increased intra-abdominal pressure. Studies1-4 in humans and in animals demonstrate deficits in cardiovascular performance, such as decreased cardiac output and stroke volume and increased systemic vascular resistance, which are associated with decreased venous return and with neurological and endocrine changes. These undesirable changes may be of clinical significance in elderly or cardiac patients undergoing prolonged laparoscopic procedures.

Increased abdominal pressure exerts adverse splanchnic circulatory effects. Studies5-8 using various flow measurement techniques demonstrate deranged macrocirculatory and microcirculatory changes during PPP involving visceral organs like the spleen, liver, stomach, pancreas, and intestines. The consequences of decreased hepatic microcirculation may include modified cellular immune response, abnormal liver energy metabolism, and impaired function of hepatocytes and Kupffer cells.9-12 Studies13-16 using different anesthetic and operational variables have tried to elucidate the mechanism of decreased hepatic and renal blood flows during PPP. The significance of reduced renal perfusion and its pathophysiological sequelae during PPP have been especially stressed with the introduction of laparoscopic donor nephrectomy.9,17-19 Furthermore, decreased visceral perfusion during PPP and its subsequent improvement with deflation are responsible for the creation of an ischemia-reperfusion mechanism that may lead to an increased oxidative stress response.20,21

See Invited Critique at end of article
Various solutions have been proposed to overcome the metabolic, respiratory, and cardiovascular consequences of carbon dioxide PPP, including lowering the insufflation pressure, operating in a gasless environment, and substituting an inert gas for carbon dioxide. Recently, different drugs (papaverine hydrochloride, dopamine hydrochloride, clonidine, ethyl nitrite, calcium channel blockers, aldosterone receptor antagonist, and angiotensin II receptor antagonist) have been tried for reversing the mechanisms putatively responsible for decreased splanchnic and renal perfusion. However, these solutions have not been generally implemented because they remain inconclusive, controversial, or in the experimental stage or are inconvenient for the surgeon.

A mechanical solution using an intermittent sequential pneumatic compression (ISPC) device on the legs was suggested by Bickel in Cuschieri et al. This device was successfully implemented in patients undergoing laparoscopic surgery and markedly improved their cardiovascular performance. This device acts primarily by redistributing blood from the lower extremities and by reversing the adverse hemodynamic effects of PPP. It has no significant adverse effects, does not necessitate titration of drugs, and avoids the possible effects of fluid overload.

The first objective of our study was to study splanchnic and renal perfusion during PPP in patients undergoing elective laparoscopic surgery. The second objective was to improve these variables with use of an ISPC device.

**METHODS**

**STUDY POPULATION**

Twenty-five consecutive patients undergoing elective laparoscopic cholecystectomy for symptomatic cholecystolithiasis were enrolled in this prospective study. The patients were all in good health (American Society of Anesthesiologists class I or II). The study was approved by the institutional ethics committee, and written informed consent was obtained from each patient.

Only patients who developed a significant (≥10%) decrease in cardiac output during induction of PPP were included; therefore, 3 enrolled patients were excluded. The investigation was designed as a repeated-measures study, with each patient’s baseline readings serving as a control. Because of the great variability associated with urine output during surgery, a separate matched group of 30 patients served as a comparison group for this variable during the stages of surgery. Selection of this group was determined according to the availability of the Doppler ultrasound unit and radiologists in the operating room at the time of surgery.

**ANESTHESIA AND PNEUMOPERITONEUM**

The same senior surgeon (A.B.) operated on all patients. General anesthesia was administered to all patients according to an identical protocol. Patients were premedicated with 10 mg of diazepam. Intravenous first-generation cephalosporin (1 g of cefonicid sodium [Monocel; Teva, Jerusalem]) together with a 4-mL/kg isotonic crystalloid fluid bolus was administered before surgery. Following 2 minutes of preoxygenation by mask, anesthesia was induced using fentanyl citrate (3 µg/kg), midazolam hydrochloride (1 mg), propofol (2 mg/kg), or thiopentone (4 mg/kg), as well as atracurium besylate (or rocuronium) for muscle relaxation. Anesthesia was maintained with fentanyl, isoflurane (0.8-1.2 vol%), and oxygen in air mixture (0.40 ratio). Ventilation was mechanically controlled at a frequency and tidal volume sufficient to maintain normocapnia (end-tidal carbon dioxide, 35-38 mm Hg). Intraoperative crystalloid infusion was maintained at 8 mL/kg per hour.

Carbon dioxide PPP was maintained automatically at 14 mm Hg at an infusion rate of 1 to 1.5 L/min. This is the pressure we generally use in laparoscopic surgery and is the pressure widely referred to in the literature. A nasogastric tube and an indwelling urinary drainage catheter were inserted. Patient monitoring included capnography, pulse oximetry, electrocardiography, continuous quantification of urine output, peripheral nerve stimulation (for assessment of depth of anesthesia), and noninvasive mean arterial pressure measurements (recorded at 5-minute intervals).

**ISPC DEVICE OPERATION**

In the study group patients, each leg was wrapped with a pneumatic sleeve from the foot to the groin. Each sleeve contained 10 pneumatic cells (Lymphatia Press; Mego Afek, Kibbutz Afek, Israel) individually connected to a pneumatic compressor that was set to a maximum of 50 mm Hg of air and was sequentially progressed, in a 24-second cycle, from the distal to the proximal air compartments to create a milking effect on veins of the lower limbs. The ISPC device was activated 15 to 20 minutes after establishment of PPP and remained so until the end of surgery. In the control group (30 patients), the ISPC device was not used.

**HEMODYNAMIC VARIABLES**

Cardiac output and stroke volume were measured every 3 minutes by a transesophageal Doppler ultrasonographic apparatus (ODM II Cardio Q Doppler Monitor; Deltex Medical, Chichester, England) with single-use 4-MHz sterile probes (Deltex Medical). Peripheral venous pressure was measured through the brachial vein instead of by invasive central venous pressure monitoring. Systemic vascular resistance was calculated according to standard physiological equations (using peripheral venous pressure for derivation). All hemodynamic variables were recorded from the induction of anesthesia, through establishment of PPP and manipulation of the pneumatic sleeves, until the end of the surgical procedure.

**HEPATIC AND RENAL PERFUSION**

Peak and mean portal venous and hepatic arterial blood flows were measured directly by an ultrasound Doppler scanner (2102 XDI; B-K Medical A/S, Mileparken, Denmark) with a laparoscopic transducer (frequencies, 3.0, 6.5, and 7.5 MHz). Additional measurements of the averaged hepatic arterial blood flows were determined by calculation of the area under the velocity curve (graphically produced by the apparatus) multiplied by the vessel cross-sectional area and divided by the interval. Although portal and hepatic flows were significantly changed by activation of the pneumatic sleeves, they did not change with cycling of the device. Flow was recorded 3 times during PPP and after activation of ISPC, following 10 minutes of equilibration time for each period.

The renal segmental arterial resistive index (percentage reduction of the end-diastolic flow compared with the systolic flow) was measured by laparoscopic Doppler sonography dur-
of hemodynamic changes in the study group during induction of anesthesia, establishment of PPP, and activation of the ISPC device.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anesthesia</th>
<th>PPP</th>
<th>Δ (%)</th>
<th>P Value†</th>
<th>ISPC</th>
<th>Δ (%)</th>
<th>P Value†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate, beats/min (n = 22)</td>
<td>69.1 ± 13.2 (50-95)</td>
<td>71.7 ± 13.4 (56-110)</td>
<td>104 .29</td>
<td>72.5 ± 10.8 (55-91)</td>
<td>105 .23</td>
<td>.69</td>
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<tr>
<td>Cardiac output, L/min (n = 22)</td>
<td>6.9 ± 2.1 (4.0-12.0)</td>
<td>4.5 ± 1.5 (2.4-8.1)</td>
<td>65 &lt;.001</td>
<td>6.5 ± 2.2 (3.3-12.8)</td>
<td>94 .27</td>
<td>&lt;.001</td>
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<tr>
<td>Systemic vascular resistance, dynes-s-cm⁻² (n = 14)</td>
<td>930.2 ± 274.7 (466-1400)</td>
<td>1642.4 ± 654.7 (661-2770)</td>
<td>177 &lt;.001</td>
<td>1177.4 ± 515.2 (419-2330)</td>
<td>127 .07</td>
<td>&lt;.002</td>
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<td>Stroke volume, L/min (n = 20)</td>
<td>92.8 ± 26.3 (54-150.0)</td>
<td>65.9 ± 21.4 (36-110.0)</td>
<td>71 &lt;.001</td>
<td>86.8 ± 27.0 (50.0-146.0)</td>
<td>94 .21</td>
<td>&lt;.001</td>
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<tr>
<td>Mean arterial pressure, mm Hg (n = 22)</td>
<td>80.2 ± 15.8 (55-122)</td>
<td>97.7 ± 14.9 (55-125)</td>
<td>122 &lt;.001</td>
<td>99.7 ± 10.3 (80.0-117.0)</td>
<td>124 .60</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular pressure, mm Hg (n = 14)</td>
<td>8.0 ± 3.6 (1.0-13.0)</td>
<td>15.1 ± 5.8 (5.0-26.0)</td>
<td>188 &lt;.001</td>
<td>16.9 ± 5.9 (10.0-28.0)</td>
<td>212 &lt;.001</td>
<td>.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal venous blood flow, L/min (n = 21)</td>
<td>...</td>
<td>0.86 ± 0.30 (0.4-1.7)</td>
<td>...</td>
<td>1.33 ± 0.44 (0.7-2.3)</td>
<td>...</td>
<td>... &lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic arterial blood flow, L/min (n = 15)</td>
<td>...</td>
<td>0.26 ± 0.10 (0.1-0.5)</td>
<td>...</td>
<td>0.38 ± 0.19 (0.2-0.9)</td>
<td>...</td>
<td>... &lt;.002</td>
<td></td>
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<tr>
<td>Renal index (n = 19)</td>
<td>...</td>
<td>0.68 ± 0.05 (0.6-0.8)</td>
<td>...</td>
<td>0.63 ± 0.08 (0.4-0.7)</td>
<td>...</td>
<td>... &lt;.003</td>
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</table>

Abbreviations: ISPC, intermittent sequential pneumatic compression; PPP, positive-pressure pneumoperitoneum; ellipses, not applicable.

*Data are given as mean ± SD (range) unless otherwise indicated.
†Compared with anesthesia stage.
‡Compared with PPP stage.


ing PPP and after activation of ISPC. Intrarenal Doppler signals were obtained, peak systolic and end diastolic velocities were determined, and the index was calculated accordingly (peak systolic velocity minus end diastolic velocity and divided by peak systolic velocity). Urine output was measured every 15 minutes and was expressed in milliliters per minute per meter squared of body surface area (determined from each patient’s height and weight).

Each of the physiological measurements was performed by a different physician to avoid bias. These measures included urine collection, cardiovascular variables, and laparoscopic visceral data and interpretation.

### Statistical Analysis

Data were analyzed using SPSS version 11.5 (SPSS Inc, Chicago, Ill). Paired t tests were used to compare value changes in urine output and in renal, hepatic, and cardiovascular hemodynamic variables during the stages of surgery, with each patient serving as his or her own control. The sign test was applied to assess the significance of variation in the numbers of patients who underwent significant hemodynamic changes (≥10% or ≥20%) between consecutive stages of the procedure.

The Wilcoxon rank sum test and the Fisher exact test were used to compare the characteristics of the study and control groups, applying 2-tailed statistics. The χ² test was applied to compare frequencies of patients in both groups having significant changes in urine output during the stages of surgery. Data are expressed as mean ± SD, and the significance level was set at P < .05.

### Results

Of the hemodynamic variables evaluated in the study group, pulse rate remained almost stable throughout the surgical stages (Table 1). The induction of PPP caused a significant decrease of cardiac output (from 6.9 ± 2.1 L/min to 4.5 ± 1.5 L/min, P < .001), while activation of ISPC significantly reversed these changes (to 6.5 ± 2.2 L/min) and significantly increased cardiac output, approximating the pre-PPP levels. Similarly significant, yet opposite, changes were observed in systemic vascular resistance, increasing from a baseline of 930.2 ± 274.7 dynes-s-cm⁻² to 1642.4 ± 654.7 dynes-s-cm⁻² during PPP and back to 1177.4 ± 515.2 dynes-s-cm⁻² with ISPC.

The stroke volume, which decreased significantly during PPP, was reversed with external pressure of the ISPC sleeves, as summarized in Table 1. The mean arterial pressure and peripheral venous pressure (reflecting central venous pressure) increased significantly during PPP and remained elevated with activation of ISPC.

Activation of the pneumatic sleeves during PPP significantly increased portal venous and hepatic arterial blood flows from 0.86 ± 0.30 L/min to 1.33 ± 0.44 L/min (P < .001) and from 0.26 ± 0.10 L/min to 0.38 ± 0.19 L/min (P = .002), respectively, as summarized in Table 1. Substantial increases in portal venous blood flow were seen in most patients, and similar numbers of patients experienced significant changes of their hepatic arterial blood flows (≥10% increase in 20 patients and ≥20% increase in 18 patients, P < .001).

Demographic and clinical data regarding the study and control groups are given in Table 2. The groups were similar in age, sex, medication use, comorbidities, and initial pulse rate and differed slightly in total body surface area and in baseline mean arterial pressure. Cardiac output was not measured in the control group, as we thought it to be irrelevant (see the “Comment” section).
The renal segmental arterial resistive index decreased significantly following activation of ISPC in the study group from 0.68±0.05 to 0.63±0.08 (P=.003) (Table 1). Likewise, urine output decreased significantly during PPP from 1.10 to 0.28 mL/min per meter squared (P=.001), but it improved markedly with activation of ISPC to 0.61 mL/min per meter squared (P=.01), as shown in the Figure. Such improvement was absent in the control group, in which urine output decreased from 1.12 to 0.37 mL/min per meter squared during PPP and further decreased to 0.14 mL/min per meter squared as PPP continued (P=.03). The numbers of patients who exhibited significant urine output increases between PPP and ISPC of at least 10% and at least 20% were 12 and 5, respectively, in the study group; the corresponding numbers of patients demonstrating decreased urine output were 5 and 5, respectively, in the study group and 11 and 11, respectively, in the control group. These proportions differed significantly between the groups (P=.005 for ≥10% change and P=.03 for ≥20% change).

**COMMENT**

Studies14 in humans and in animals demonstrate the negative effects of PPP on cardiovascular and visceral perfusion. Although unfavorable hemodynamic consequences are not expected during most common elective laparoscopic operations in healthy patients, PPP may have significant clinical implications for elderly or cardiac patients undergoing prolonged laparoscopic procedures.1-8,13,15 Most investigations do not demonstrate hemodynamic adaptation during laparoscopic procedures; these findings were recently confirmed in the setting of laparoscopic cholecystectomy.35 Because the deranged hemodynamic changes are not spontaneously reversed in most cases, various methods have been suggested for controlling them.35 Most surgeons continue to operate using a mean PPP pressure of 14 mm Hg and do not use an abdominal wall lifter because of its inconvenience.

Diverse pharmacological means have been experimented with primarily in animals.22-26 However, hepatic perfusion was not analyzed, and the outcomes were often inconclusive. Furthermore, drugs may have undesirable adverse effects, and their use requires precise individualized titration. Increased fluid administration has been suggested to improve survival of renal grafts following laparoscopic live donor nephrectomy or to optimize urine output, cardiac preload, and hormonal stress response.27,28,36 However, excessive fluid administration is not applicable to all patients, and it may unfa-

| Table 2. Demographic and Clinical Variables of the Study Group and the Control Group |
|---------------------------------|-------------------------------|---------------------------------|------------------|
| Variable                        | Study Group (n = 22)          | Control Group (n = 30)          | P Value          |
| Female-male ratio, No. (%)      | 20/2 (91/9)                   | 24/6 (80/20)                    | .28*             |
| Age, mean ± SD (range), y       | 52.1 ± 18.1 (21-76)          | 47.2 ± 16.6 (18-80)            | .30*             |
| Total body surface, m²          |                               |                                |                  |
| Mean ± SD (range)               | 1.8 ± 0.2 (1.6-2.4)          | 1.9 ± 0.19 (1.5-2.3)           | .07*             |
| Median                          | 1.76                          | 1.85                           | .15†             |
| Pulse rate, mean ± SD (range), beats/min | 71.7 ± 13.4 (56-110) | 74.3 ± 10.6 (60-105) | .25*             |
| Mean arterial pressure, mean ± SD (range), mm Hg | 97.7 ± 14.9 (55-125) | 90.2 ± 9.0 (73-107) | .01*             |
| Comorbidities, No.              |                               |                                |                  |
| Type 2 diabetes mellitus        | 2                             | 1                              | .38              |
| Ischemic heart disease          | 1                             | 0                              | .24              |
| Hypertension                    | 3                             | 5                              | .73              |
| Pancreatitis                    | 1                             | 2                              | .75              |
| Relevant medications, No.       | 4                             | 4                              | .63              |
| β-Blockers                      | 2                             | 0                              | .09              |
| Angiotensin-converting enzyme inhibitors | 3                        | 3                              | .69              |
| Calcium antagonists             | 0                             | 2                              | .22              |
| Nitrates                        | 1                             | 0                              | .24              |
| Central α-agonists              | 0                             | 1                              | .39              |

*Wilcoxon rank sum test (2-tailed). †Independent t test (2-tailed).
Vorably affect the renal, cardiovascular, and gastrointestinal systems.

In recent years, 2 mechanical solutions based on different concepts have been proposed. The first used pressure equilibration to eliminate the pressure gradient between the abdominal cavity and the lower extremities during PPP.35 The second applied the ISPC device to improve cardiovascular performance and to affect cardiac autonomic nervous system control during PPP.29,30,40 Its use is feasible, it is not associated with the drawbacks already mentioned, and its underlying mechanism can be reasonably explained.

Indeed, the results of our study demonstrate that, in patients in whom PPP decreased cardiac output by at least 10%, activation of the ISPC device may lead to a significant increase in hepatic and renal perfusion, with improved cardiovascular functionality. This was indicated by the following 2 phenomena: (1) the increase in portal venous and hepatic arterial blood flows and the decrease in the renal segmental arterial resistive index as detected by the Doppler ultrasound and (2) the increase in urine output compared with the steady decrease in the control group during PPP. Cardiac output was not measured in the control group. Although most patients exhibit reduced cardiac output during PPP, unchanged cardiac output in some patients in this group cannot be excluded (ie, theoretically fewer splanchnic effects). Therefore, continued reduced urine output during PPP in this group supports our assumption that the improved urine output in the study group does not reflect physiological adaptation but rather the effect of ISPC on renal perfusion. We considered measuring the hepatic blood flow during PPP, but we assume (because of studies7-8 that demonstrate decreased visceral perfusion during PPP) that it was higher during wakefulness and before PPP anesthesia. With ISPC, the portal venous and hepatic arterial blood flows increased measurably from the values during PPP. This implies improved splanchnic perfusion because the portal vein drains the spleen, pancreas, and gastrointestinal tract.

In evaluating hepatic perfusion, several factors should be considered. During laparoscopic surgery, increased sympathetic activity (with the potential participation of humoral factors such as angiotensin II) reduces the hepatic blood flow primarily due to hypercarbia and increased intra-abdominal pressure.41-43 Splanchnic vascular resistance may increase when certain modes of mechanical ventilation are used during anesthesia.43 In addition, anesthetics may decrease cardiac output and proportionally reduce the total hepatic blood flow that is already deranged by cardiovascular effects of PPP.5,13-16,43 Because the measurements in each of the patients were paired and other factors remained unchanged, it is reasonable to conclude that the improvement in hepatic flow was attributable to the hemodynamic and autonomic effects of ISPC.30,40 Nevertheless, further investigations are needed to determine whether hemodynamic improvement may reverse the metabolic and immunological changes associated with PPP.10,12

Renal blood flow, tubular functions, and glomerular filtration rate are affected by numerous multifactorial and complex mechanisms resulting in decreased urine output. Cardiovascular effects of elevated PPP include cardiac preload, decreased cardiac output, impairment of venous return, and eventually reduced renal blood flow.1,4,7-17,37 Another putative mechanism for decreased urine output is mechanical compression of the inferior vena cava and of the renal vasculature and parenchyma.10,44

Positive-pressure pneumoperitoneum also causes increased sympathetic activity, which is regulated through the mechanism of mediated baroreceptors together with the effects of hypercarbia and intraperitoneal pressure, and can lead to renal cortical vasoconstriction and its sequelae.22,41-43 Central and peripheral regulatory mechanisms increase the secretion of antidiuretic hormone, which acts on the collecting ducts and the thick loop of Henle.9,45,46 Reduced renal perfusion together with sympathetic stimulation activates the renin-angiotensin-aldosterone system, inducing its vascular and metabolic effects.9,24,46 Increased levels of catecholamines and endothelin 1 have also been detected.22 All of these factors are in addition to the major effect of surgical stress on renal function. Anesthetic drugs usually decrease glomerular filtration and renal blood flow secondary to their endocrine, sympathetic, and cardiovascular effects.41,45 Other drug interactions and preexisting renal disease contribute to this complex situation. Indeed, positive-pressure ventilation can induce derangement of kidney functions through cardiovascular and neurohumoral mechanisms.45

Urine output increased, the renal index decreased, and several harmful mechanisms were neutralized with ISPC, reflecting increased renal perfusion. This is especially important in the setting of laparoscopic live donor nephrectomy, which is emerging as the favored approach for renal donation.37 We assume that the ISPC device improved renal perfusion by augmenting cardiac output and by decreasing systemic vascular resistance, indirectly affecting the neurohumoral axis and consequently the autonomic nervous system, similar to the mechanisms affecting hepatic perfusion.20,30,40 However, more research is needed in a larger patient group to elucidate the effects of ISPC on renal function, particularly during live donor nephrectomy.

In conclusion, we demonstrate that significantly improved hepatic and renal blood flows during PPP can be achieved using the ISPC device. Additional studies are required to assess other functional advantages related to use of this simple technology. We recommend use of ISPC during prolonged laparoscopic procedures, especially in elderly patients with preexisting cardiovascular diseases.

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Author Contributions: Study concept and design: Bickel and Eitan. Acquisition of data: Bickel, Loberant, Bersudsky, Goldfeld, Ivry, Herskovits, and Eitan. Analysis and interpretation of data: Bickel and Eitan. Drafting of the manuscript: Bickel, Loberant, Bersudsky, Goldfeld, and Herskovits. Critical revision of the manuscript for important intellectual content: Bickel and Eitan. Statistical analy-


