The effects of pneumoperitoneum and fluid administration on renal perfusion

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**Ms. Carolina Moriello:** Assisted with analysis for bolus versus maintenance fluid study

**Dr. Gerry Polyhronopoulos:** Assisted with surgical preparation of pigs in targeting individual hemodynamics study

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**Dr. Bernard Unikowsky:** Assisted with development of model for bolus versus maintenance study
Abstract:

Minimally invasive surgeons are performing increasingly complex and time-consuming procedures on increasingly frail patients. Understanding the complex physiologic consequences of pneumoperitoneum is therefore of critical importance. This is especially true in the field of live laparoscopic donor nephrectomy where a thorough understanding of the effects of pneumoperitoneum on renal perfusion and function is mandated. A systematic review of the literature is undertaken and reveals that both renal perfusion and function are decreased during pneumoperitoneum. Next, a porcine model is established and used to compare the effects of aggressive fluid hydration (28cc/kg/h) versus maintenance fluid hydration (5cc/kg/h). We demonstrate that renal perfusion is preserved with aggressive fluid hydration. Finally, a noninvasive fluid administration algorithm based on esophageal Doppler stroke volume measurements is assessed. Using this technique, renal perfusion is preserved during pneumoperitoneum, using less fluid (10cc/kg/h) than a bolus group (25cc/kg/h). Fluid administration via the esophageal Doppler is a noninvasive way to target individual hemodynamics to maintain renal perfusion during pneumoperitoneum.
**Resume:**

Les chirurgiens spécialisés en interventions chirurgicales non effractives doivent effectuer des procédures de plus en plus complexes sur des patients de plus en plus fragiles. Il est donc d'une extrême importance de comprendre les conséquences physiologiques du pneumopéritoine. Ceci est d'autant plus vrai dans le cas de la néphrectomie par laparoscopie à partir de donateur vivant où une connaissance approfondie des effets du pneumopéritoine sur la perfusion et la fonction rénale est requise. Une révision systématique de la littérature révèle que la perfusion et la fonction rénale sont diminuées durant le pneumopéritoine. Ensuite, un modèle porcin est établi et utilisé afin de comparer les effets d'une hydratation agressive (28 cc/kg/h) versus une hydratation de maintenance (5 cc/kg/h). Sur ce modèle, il est démontré que la perfusion rénale est maintenue avec une hydratation agressive. Finalement, nous évaluons un algorithme non invasif pour l'administration des liquides basé sur la mesure du volume d'éjection systolique par Doppler œsophagien. En utilisant cette technique, la perfusion rénale est maintenue durant le pneumopéritoine en administrant moins de liquides (10 cc/kg/h) qu'un groupe recevant un bolus (25 cc/kg/h). L'administration de liquides via le Doppler œsophagien est une technique non invasive qui permet à l'hémodynamique individuelle de maintenir la perfusion rénale durant le pneumopéritoine.
A. Introduction:

“All pigs are equal, but some pigs are more equal than others.”

- George Orwell

Laparoscopic surgeons have made rapid advances in laparoscopic surgery since the first laparoscopic cholecystectomy performed in 1987. As the use of minimally invasive surgery expands to almost all areas of surgery, a clear comprehension of the physiologic consequences of pneumoperitoneum (PP) is required. This is particularly true since procedures are becoming increasingly complex and time-consuming, and patient selection has expanded to include increasingly frail and elderly patients.

While an understanding of the physiologic consequences of PP is required for all laparoscopic surgeons, this is especially true in the field of laparoscopic live donor nephrectomy (LLDN). The first LLDN was performed in 1995, and since then the number of living donors has rapidly increased.(1) Widespread approval of this procedure has occurred because of benefits such as improved cosmesis, shorter length of hospital stay, and faster return to work, as compared to the open approach. (2)

This procedure mandates a thorough understanding of the precise physiologic consequences of PP on renal perfusion and function. It is crucial to maintain the quality of harvested kidneys during LLDN, since any ischemia occurring to the kidney as a result of PP would be detrimental. Despite widespread adoption of this procedure, concerns regarding the potential negative effects of
pneumoperitoneum on the graft persist. In fact, it has been suggested that aggressive intravenous hydration be administered to optimize preload in an effort to maintain renal perfusion. (3) For example, it is recommended that donors receive up to 2 L/h of crystalloids intraoperatively to maintain renal perfusion. (4)

However, administration of aggressive fluid hydration can have negative consequences even in the relatively young and healthy donor population. Overaggressive hydration is known to cause multiple complications including pulmonary edema and ileus as well as delayed wound healing. (5, 6) The evidence supporting this practice of aggressive intravenous hydration during LLDN is somewhat limited and deserves further investigation.

This thesis examines this topic and evaluates fluid strategies to prevent changes in renal perfusion during PP. The objectives are threefold. First of all, a critical examination of the literature is undertaken to determine whether PP affects renal blood flow or function. Secondly, a porcine model is used to compare the effects of bolus versus maintenance fluid hydration on renal perfusion and function. The goal is to verify whether aggressive fluid hydration maintains renal perfusion during PP. Finally, a novel technique to guide fluid administration is assessed. The esophageal Doppler is evaluated in a porcine model as a noninvasive method to individualize fluid therapy in an attempt to decrease the amount of fluid given during PP while still maintaining renal perfusion.
B. The effect of pneumoperitoneum on renal perfusion and function: A systematic review.

Abstract:

Introduction: The precise physiologic consequences of insufflating carbon dioxide into the abdominal cavity during laparoscopy are not yet fully understood. The aim of this systematic review is to investigate whether pneumoperitoneum (PP) results in a decrease in renal blood flow (RBF) or renal function.

Methods: A literature search was conducted electronically using Medline, Embase and the Cochrane libraries on July 1, 2005. Various combinations of the medical subject headings renal blood flow, pneumoperitoneum, renal function and laparoscopy were searched in all three databases. Reference lists from articles fulfilling the search criteria were used to identify additional articles.

Results: 20 articles concerning RBF and 25 articles concerning renal function during PP were retrieved by the literature search. 17 of 20 studies identified a decrease in RBF and 20 of 25 studies identified a decrease in renal function during PP.

Conclusion: There appears to be enough evidence to conclude that both renal function and RBF are decreased during PP. The magnitude of the decrease is dependent on factors such as preoperative renal function, level of hydration, level of pneumoperitoneum, patient positioning and duration of pneumoperitoneum.
1. Introduction

Despite much research, the physiologic consequences of pneumoperitoneum (PP) are not yet fully understood. Since laparoscopic surgery is rapidly replacing the open approach in many fields of surgery, it is even more important to understand the systemic changes that occur during PP. In particular, the surge in the number of laparoscopic live donor nephrectomies (LLDN) being performed has necessitated a critical examination of whether PP affects renal perfusion or function. It is of utmost importance that graft quality be maintained during LLDN. Any damage occurring to kidneys as a result of PP would warrant a reexamination of LLDN.

To our knowledge, there is only one reported case of graft loss thought to be primarily related to PP. (7) The authors concluded that graft loss was attributable to prolonged renal hypoperfusion that was not diagnosed perioperatively. Causative factors included the elevated intra-abdominal pressure, long operative time, inadequate renal preload assessment by central venous pressure and urine output, prolonged vasospasm, and a long delay to deep cooling because of an enlarged fatty kidney with long bench top preparation.

While there is little evidence to suggest that graft function is compromised during LLDN, there appears to be a widespread belief that PP decreases RBF and function acutely. (8, 9) The purpose of this review is to summarize the available human and animal studies examining this phenomenon in order to make some evidence-based conclusions.
2. Methods

A literature search was conducted electronically using Medline, Embase and the Cochrane libraries on April 1, 2005. This search was then repeated on July 1, 2005 to ensure reliability. The search queried all entries in Medline from 1966, in Embase from 1980 and in the Cochrane Library from 1990. Language was restricted to English. The medical subject headings *renal blood flow*, *pneumoperitoneum*, *renal function* and *laparoscopy* were searched in various combinations in all three databases.

All articles identified by this search were reviewed by one author and then included if they were original scientific data of an experimental nature. Review articles evaluating RBF or function during pneumoperitoneum were also included. Studies comparing graft function in renal transplant recipient patients were not included since they do not evaluate acute changes in renal function and perfusion. Furthermore, the reference lists from included articles were verified to identify additional articles.

3. Results:

The results of our search are summarized in figure 1. The Medline search identified 22 studies evaluating RBF and 151 studies evaluating renal function. Embase identified 15 studies evaluating RBF and 65 studies evaluating renal function while no studies were retrieved in the Cochrane Library. Cross referencing of Embase and Medline revealed much duplication, so that combining these two databases resulted in 24 studies evaluating RBF and 163 studies evaluating renal function.
After reviewing these articles, 9 articles concerning RBF and 18 articles concerning renal function were included. Articles were included if the subject matter was deemed relevant based on the title and abstract. Furthermore, by reviewing the reference lists of these articles, another 11 articles about RBF and 6 articles about renal function were identified. This resulted in a total of 20 articles about RBF and 24 articles about renal function.

Tables 1 + 2 summarize the studies evaluating RBF, including review articles (Table 1) and animal studies (Table 2). There were no studies evaluating renal perfusion in humans. Tables 3 – 5 summarize studies evaluating renal function, with Table 3 listing review articles, Table 4 human studies and Table 5 animal studies. Studies are sorted alphabetically by year published.

4. Discussion:

a) Pneumoperitoneum and Renal Perfusion

The question of whether RBF is affected by PP has been debated particularly since the advent of LLDN. This question has important clinical implications to the quality of grafts that are harvested laparoscopically. This section is divided into review articles and animal studies.

i) Review articles concerning renal perfusion

Table 1 summarizes the three review articles evaluating RBF during PP that were identified. Neudecker et al. (10), in association with the European Association for Endoscopic Surgery, established clinical practice guidelines for laparoscopy in 2001. They noted that there was good evidence to conclude that RBF decreases with the initial phase of PP. Closer examination however, reveals this conclusion to
be based on only two studies. Furthermore, there is an error in the referencing of this article since neither of the two studies pertain to RBF during PP. Thus, while they conclude that RBF is decreased during PP, it is not clear which studies were used to support this data.

Schafer et al. (13) reviewed the effect of laparoscopy on intraabdominal blood flow. They identified five animal studies (8, 14-17), all of which showed a decrease in RBF during PP. The decrease in RBF ranged from 12 to 40% and depended on the level of intraabdominal pressure (IAP) used. They concluded that while there is good data to show that RBF decreases during PP, it is unlikely that this will affect most healthy patients unless there is underlying altered renal function.

Lastly, Ben-Haim et al. (18) reviewed arterial hypertension and splanchnic ischemia during raised IAP. They noted that an IAP greater than 20 – 25mmHg caused splanchnic vasoconstriction and renal ischemia. This pressure is quite high however and generally not used in clinical situations. Moreover, most of the studies quoted were either fairly old, (19-21) or were models of abdominal compartment syndrome and not PP. (22, 23)

ii) Animal studies evaluating renal perfusion

17 animal studies examining the relationship between RBF and PP were identified (Table 2). It is important to note that the tremendous variation in study designs and models used make it difficult to directly compare these studies. For example, there are different methods of measuring RBF: this can be done by placing a flow probe around the renal artery, by placing a laser Doppler probe on
the renal parenchyma, by using colour or radiolabeled microspheres injected into the bloodstream, or by using a hydrogen washout technique. Second, different animal models (including canine, rodent, and porcine) are used and these models all have their own inherent biases. Third, the magnitude of the decrease in RBF depends on the magnitude of the IAP used. Taking these factors into account however, it is still possible to examine the studies for overall trends in results.

Of the 17 studies identified, 14 (82%) reported a decrease in RBF with PP. Eleven studies used a pig model (8, 14-17, 24-29), and reported decreases in RBF ranging from 12 to 60%. There were also two dog models (20, 30) that reported decreases in RBF of 26 and 75%, and one rat model (31) that reported a decrease of 38-40%.

While the cause of this decrease in RBF is not clear, these studies demonstrate certain characteristics of PP. For example, Junghans et al. (16) studied 18 pigs and demonstrated that the decrease in RBF is dependent on the positioning of the animal. They showed that this decrease occurs with the head up position. Second, London et al. (8) demonstrated that this decrease can be prevented with aggressive fluid hydration. They undertook a randomized study of 18 pigs using a renal artery flow probe to measure RBF. Pigs were randomized into 3 fluid groups: maintenance, bolus and hypertonic saline. They noted that the maintenance group had a decrease in RBF of 30%, whereas the bolus and hypertonic saline groups maintained their RBF. Third, this decrease does not seem to depend on the gas used. Rosin et al. (29) evaluated 5 pigs using a nitrogen PP and showed that pressures of 15 mmHg nitrogen or more caused significant decreases in RBF. Shuto et al. (17) studied 16 pigs using helium or CO₂ with stepwise increases in IAP from
8 to 20mmHg. With an IAP of 20, RBF decreased to 26% of baseline with similar decreases between helium and CO₂. Fourth, the decrease in RBF during PP is clearly pressure dependent. Chiu et al.(27) studied 6 pigs comparing a laser Doppler probe placed in the renal parenchyma with a flow probe around the renal artery. They documented an almost exponential decrease in RBF with increasing IAP. With an IAP of 15mmHg, the RBF decreased to 25% of baseline. Hashikura et al. (15) measured RBF using a hydrogen washout method on 7 pigs and noted decreases in RBF as IAP was increased. This only reached significance however with an IAP of 24mmHg. Brundell et al. (26) studied 25 pigs using a radiolabelled microsphere technique comparing different gases and pressures. Interestingly, while RBF was decreased during PP at all pressures, this only reached significance with a pressure of 8mmHg, not with a pressure of 4 or 12 mmHg. Fifth, other non-PP models that mimic an elevated IAP cause similar decreases in RBF as with PP. Razvi et al.(30) placed a pressure cuff around the renal parenchyma (being careful not to compress the hilum) of 6 dogs. This cuff was inflated to a pressure of 15mmHg. Effective RBF was measured using para-amniohippuric acid and they documented a decrease in RBF by 26% during cuff insufflation. Harman et al.(20) studied seven dogs and simulated PP by placing a bag intraperitoneally that was then inflated to a pressure of 20 or 40mmHg. RBF was noted to decrease to less than 25% of baseline. Finally, this decrease in RBF occurs during different types of laparoscopic procedures. Are et al.(24) performed antireflux surgery on 6 pigs and measured RBF using a radioactive microsphere technique. They showed an initial nonsignificant increase, then a decrease in RBF to 31% below baseline. Cisek et al.(14) undertook partial nephrectomies in 12 pigs to evaluate the effect of PP in a
model of chronic renal failure. They documented a decrease by 12% in RBF using a Doppler flow probe with an IAP of 20mmHg.

Three studies reported no change in RBF during PP. Lindberg et al. (32) measured RBF with a laser Doppler probe in 13 pigs and demonstrated no change with an IAP of 12mmHg compared to control. However, within the PP group, a significant decrease in RBF was noted at 5 min of insufflation as compared to baseline. What is more, a PP of 12mmHg may not produce large changes in RBF in pigs. Furthermore, pigs received 60cc/kg/hr of crystalloid, which is probably enough fluid to maintain RBF during PP. Ali et al. (33) compared pigs at baseline to a PP of 15mmHg with or without ethyl nitrate. Neither group showed a decrease in RBF as compared to baseline. This data was based on only 5 pigs however, and the amount of fluid given was not described. Finally, Yavuz et al. (34) used colour microspheres to measure perfusion in 18 pigs comparing high (15, 24mmHg) versus low (5, 10mmHg) IAPs. While decreases in splenic, pancreatic, esophageal and gastric mucosal blood flow were noted, RBF was preserved in both groups. However, this study was not performed specifically to evaluate RBF and it is possible that the study was underpowered to detect changes in RBF. In fact, RBF with a PP of 24mmHg was decreased by 11% as compared to baseline (although this was not significant).

b) Pneumoperitoneum and Renal function

The difficulty with this topic is that there is no ideal marker of renal function in the acute setting. The best method is to measure the glomerular filtration rate (GFR). Creatinine clearance is usually used as an estimate of GFR, but it is not
intended for rapid measurements of renal function, and should not be used for a period of study less than eight hours. (35) Furthermore, it has limitations in reproducibility and accuracy, and overestimates GFR significantly. (36) Inulin has also been used to measure GFR, but this method is difficult and costly and likely not useful in the acute setting. (37) Urine output has also been used, but it is more a reflection of overall salt-water balance (controlled by hormonal factors and the distal collecting duct of the kidney) rather than simply renal perfusion. Thus while many studies report data on renal function acutely during PP, it is important to recall that most of these data have certain limitations. The search results are divided into review articles, human and animal studies.

i) Review articles

Four review articles evaluating changes in renal function during PP were identified (Table III). Neudecker et al. (10) concluded that GFR and urine output decreased during the initial phase of PP. (38, 39) This is based on two incorrectly referenced articles however. The group also identified one study, in German, that did not reveal a significant decrease in renal function during PP. (40) They concluded that in healthy subjects (ASA I, II), an IAP of 12 -14 mmHg had no clinically relevant effects on renal function.

Dunn et al. (41) conducted a nonsystematic review and concluded that oliguria occurred as a physiologic result of increased IAP. The cause appeared to be multifactorial, occurring because of vascular and parenchymal but not ureteral compression, as well as systemic hormonal effects. (20, 42, 43) These changes did not depend on the choice of insufflant and appeared to be pressure dependent. (9)
After release of PP, renal function and urine output returned to normal and there was no evidence of any microscopic renal tubular damage. (9, 44)

Nguyen et al. (45) reviewed the effects of PP on the morbidly obese. They concluded that PP causes a pressure-dependent oliguria. Possible mechanisms include direct pressure on the renal cortex and renal vasculature, release of ADH, renin and aldosterone. While the urine output decreased, there was no change in perioperative serum creatinine or creatinine clearance and they concluded that a PP of 15mmHg was clinically safe.

Finally, Schilling et al. (46) reviewed the physiologic changes occurring to the kidney during PP. They concluded that there was a decrease in urine output during PP, albeit based on only three studies. (42, 47, 48)

ii) Human studies evaluating renal function

Six human studies evaluating renal function during PP were identified (Table IV). Five of the six studies (83%) reported decreases in renal function during PP. Nguyen et al. (49) compared laparoscopic versus open gastric bypass in a randomized control trial and noted that urine output was decreased in the laparoscopic group, but there were no significant differences in postoperative creatinine levels. They concluded that PP significantly reduced intraoperative urine output but did not adversely affect postoperative renal function. Perez et al. (50) studied patients during laparoscopic colectomy and found a decrease in urine output and creatinine clearance with a PP of 15mmHg. Low dose dopamine administration during surgery seemed to prevent these changes. Miki et al. (43) reported a decrease in urine output, GFR and effective renal plasma flow in patients undergoing laparoscopic cholecystectomy but not when an abdominal wall lift device was used.
Similarly, Koivusalo et al. (51) evaluated laparoscopic cholecystectomy comparing 12-13mmHg CO2 PP with an abdominal wall lift device in 30 randomized patients. The PP group had significantly lower urine outputs as well as higher urine-N-acetyl-B-D-glucosaminidase (U-NAG) levels (a sensitive marker of proximal tubular cell damage). They concluded that the abdominal wall lift device provided protection against renal ischemia that occurs during CO2 PP. Nishio et al.(52) compared adrenalectomy in patients undergoing CO2 PP (n=6) versus a gasless procedure (n=3). They noted a decreased urine output in patients who received CO2 PP.

In contrast to these studies, Micali et al. (53) compared 31 patients who underwent laparoscopic procedures with 28 similar open patients. They found no difference in U-NAG levels in the urine and concluded that no significant renal tubular injury occurs during PP.

iii) Animal studies evaluating renal function during PP

Table V summarizes the 14 studies retrieved by the literature search. Of the 14 studies, 10 (71%) showed decreases in renal function during PP while 4 showed no changes.

Four of the 10 studies used a porcine model (8, 14, 54-56) and demonstrated significant decreases in urine output and creatinine clearance with a PP of 15mmHg. One of these studies (8) showed that these changes could be overcome with aggressive fluid hydration or the use of hypertonic saline. Schachtrupp et al.(56) demonstrated low-grade proximal tubule necrosis on histopathologic examination after PP. Cisek et al. (14) noted that the decreases in GFR (by 63%) and urine output (by 80%) were reversible. Three of four rodent model studies (42,
57, 58) demonstrated significant decreases in creatinine clearance, sodium excretion and urine output with a PP of 8-10mmHg, while Akbulut et al. (59) evaluated rodents using an oxidative stress model. They demonstrated that during LLDN in rats, PP was an independent risk factor causing oxidative stress to the kidney. Two studies, discussed previously, used non-PP models in dogs. (20, 30) Razvi et al. (30) demonstrated that urine output decreased by 63% and GFR by 21% in a kidney that was compressed with a cuff around the parenchyma. Harman et al. (20) inflated an intraperitoneal bag to 20mmHg and demonstrated that GFR decreased to less than 25% of baseline.

Four studies (27%) revealed no significant decreases in renal function during PP. Lindberg et al. (32) compared 13 pigs undergoing a 12 mmHg CO\textsubscript{2} PP vs control. While there was a trend towards a decrease in urine output in the PP group, this was not significant. Hazebroek et al. (60) studied 36 rats and compared CO\textsubscript{2} and helium PP versus control. They demonstrated no significant differences in kidney histology or immunohistochemistry after performing a nephrectomy. Subsequently, in a long-term follow-up study, Hazebroek et al. (61) showed no differences in GFR acutely or by immunohistochemical staining one year after transplantation for kidneys procured laparoscopically when compared to open. Finally, Lee et al. (44) studied 24 rats undergoing variable lengths of PP. Kidneys were then harvested and studied histologically with no differences in histologic scores between PP and a control group.
5. Conclusion

a) Renal Blood Flow:

The data from this review demonstrate compelling evidence that RBF decreases during PP. 17 of the 20 studies, including three review articles and 3 different animal models, demonstrate that RBF decreases during PP. Only three studies (all using a pig model) found that there was no decrease in RBF during PP. This decrease is pressure dependent (with 12 – 15mmHg the most common values cited), worsened with positioning (head up), improved with fluid hydration, and is not dependent on the gas used. The magnitude of the decrease likely also varies with each specific animal model, the method of measurement of RBF and the experimental design chosen.

While this decrease in RBF is well documented, it is unclear whether this is of any clinical significance. It is likely that these changes in RBF are not significant in healthy patients under most normal conditions but may be important in cases where RBF is already compromised.

b) Renal function:

Notwithstanding the difficulties in measuring renal function acutely, 19 of the 24 studies reveal a decrease in renal function during PP. This includes various animal models, human studies and review articles. Five studies (one human and four animal) demonstrated no decrease in renal function during PP. The magnitude of the decrease in renal function likely varies with the numerous factors described previously for RBF. This decrease in renal function appears to be temporary however with function returning to normal a variable time after PP is released. In
conclusion, while these data demonstrate that renal function is decreased during PP, the clinical significance of this phenomenon is not certain since renal function appears to return to normal after PP is released.
Diagram 1: Literature Search

Electronic Search of databases:
24 RBF, 163 renal function

Studies excluded 15 RBF, 145 renal function

Included 9 RBF, 18 renal function

References reviewed, 11 RBF + 6 renal function added

20 RBF and 24 renal function studies included
Table I: Review articles of renal blood flow and peritoneum

<table>
<thead>
<tr>
<th>Author + Year</th>
<th>Comment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neudecker et al.</td>
<td>Error in references, unable to verify which studies are quoted</td>
<td>Significant decrease in RBF, although not clinically relevant in healthy individuals (ASA I+II) Recommend use of lowest pressure allowing adequate exposure</td>
</tr>
<tr>
<td>(10) 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schafer et al.</td>
<td>Based on five animal studies</td>
<td>Decrease in RBF but varies greatly with pressure used</td>
</tr>
<tr>
<td>(13) 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben-Haim et al.</td>
<td>Older studies, non-PP models</td>
<td>Raised pressure increases peripheral vascular resistance which causes visceral vasoconstriction and decreased RBF</td>
</tr>
<tr>
<td>(18) 1999</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
RBF = renal blood flow, PP = pneumoperitoneum
Table II: Animal studies of renal blood flow and pneumoperitoneum

<table>
<thead>
<tr>
<th>Author + Year</th>
<th>Model</th>
<th>Design</th>
<th>Pressure (mmHg)</th>
<th>RBF measurement</th>
<th>Change in RBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al. (33) 2005</td>
<td>11 pigs</td>
<td>Control vs a) CO₂ PP and b) CO₂ PP + Ethyl nitrate</td>
<td>15</td>
<td>Laser doppler flow probe</td>
<td>No significant change in either group vs control</td>
</tr>
<tr>
<td>Lindberg et al. (32) 2003</td>
<td>13 pigs</td>
<td>Control vs CO₂ PP</td>
<td>12</td>
<td>Transonic flow probe on artery</td>
<td>No difference between groups. In PP group, ↓ in RBF at 5 min of insufflation</td>
</tr>
<tr>
<td>Are et al. (24) 2002</td>
<td>6 pigs</td>
<td>Laparoscopic antireflux surgery</td>
<td>15</td>
<td>Radiolabelled microsphere technique</td>
<td>Initial ↑, then ↓ to 31% below baseline</td>
</tr>
<tr>
<td>Brundell et al. (26) 2002</td>
<td>25 pigs</td>
<td>Helium vs CO₂ PP and Variable IAPs</td>
<td>4, 8, 12</td>
<td>Radiotracer microsphere technique</td>
<td>↓ for all but only significant with pressure of 8mmHg CO₂</td>
</tr>
<tr>
<td>Rosin et al. (29) 2002</td>
<td>5 pigs</td>
<td>Nitrogen PP, effect on RBF and on intracranial pressure</td>
<td>0, 5, 15, 25</td>
<td>Transonic doppler probe on artery</td>
<td>↓ with PP of 15 or 25</td>
</tr>
<tr>
<td>Schafer et al. (31) 2001</td>
<td>12 rats</td>
<td>Variable pressures</td>
<td>4 or 10</td>
<td>Radiolabelled microsphere technique</td>
<td>RBF ↓ 40% with pressure of 10</td>
</tr>
<tr>
<td>Yavuz et al. (34) 2001</td>
<td>18 pigs</td>
<td>Variable pressures</td>
<td>0, 5, 10 vs 0, 15, 24</td>
<td>Colour-labelled microsphere technique</td>
<td>No significant changes</td>
</tr>
<tr>
<td>London et al. (8) 2000</td>
<td>18 pigs</td>
<td>Maintenance, bolus and hypertonic saline fluid groups.</td>
<td>15</td>
<td>Renal artery ultrasonic flowprobe</td>
<td>Maintenance: ↓RBF by 30% Bolus + HTS: RBF maintained</td>
</tr>
<tr>
<td>Cisek et al. (14) 1998</td>
<td>12 Pigs</td>
<td>Partial nephrectomy, see if PP worsens renal failure</td>
<td>20</td>
<td>Transonic Doppler flow probe</td>
<td>↓12%</td>
</tr>
<tr>
<td>Junghans et al. (16) 1997</td>
<td>18 pigs</td>
<td>Various gases, positions and pressures</td>
<td>8, 12, 16</td>
<td>Transonic flowmeter on renal artery</td>
<td>RBF ↓ with PP &gt; 12 and head-up position. No effect of different gases.</td>
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<tr>
<td>McDougall</td>
<td>6 pigs</td>
<td>MRI to measure</td>
<td>15</td>
<td>Measured by</td>
<td>↓28 – 30%</td>
</tr>
<tr>
<td>Study</td>
<td>Animals</td>
<td>Methodology</td>
<td>Pressure Ranges</td>
<td>Result/Findings</td>
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<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>et al. (25) 1997</td>
<td></td>
<td>RBF in PP vs control</td>
<td></td>
<td>MRI, verified with radio-labelled microspheres</td>
<td></td>
</tr>
<tr>
<td>Chiu et al. (28) 1996</td>
<td>15 pigs</td>
<td>Effect of pressure, IVC compression + norepinephrine</td>
<td>15</td>
<td>Laser needle probe in parenchyma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ by 60% with pressure of 15</td>
<td></td>
</tr>
<tr>
<td>Razvi et al. (30) 1996</td>
<td>6 dogs</td>
<td>Pressure cuff placed around renal parenchyma</td>
<td>15 via pressure cuff</td>
<td>Effective renal blood flow using para-amniophippuric acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ 26%</td>
<td></td>
</tr>
<tr>
<td>Shuto et al. (17) 1995</td>
<td>16 pigs</td>
<td>Different gases and pressures</td>
<td>8, 10, 12, 16, 20</td>
<td>Hydrogen washout with electrode placed on renal cortex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RBF ↓ by 74% with pressure of 20. No difference in gas used</td>
<td></td>
</tr>
<tr>
<td>Chiu et al. (27) 1994</td>
<td>6 pigs</td>
<td>Increasing pressure</td>
<td>0 – 40</td>
<td>Ultrasonic flow probe around renal artery + laser Doppler probe in parenchyma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ by 75% with pressure of 15</td>
<td></td>
</tr>
<tr>
<td>Hashikura et al. (15) 1994</td>
<td>7 Pigs</td>
<td>Variable pressures</td>
<td>6, 12, 18, 24</td>
<td>Hydrogen washout technique with electrode in renal cortex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ in RBF as pressure ↑s, only significant with pressure of 24</td>
<td></td>
</tr>
<tr>
<td>Harman et al. (20) 1982</td>
<td>7 Dogs</td>
<td>Intraperitoneal bag used to simulate PP</td>
<td>0, 20, 40</td>
<td>Radionuclide count using spectrometer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75% ↓ with pressure of 20</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
PP = pneumoperitoneum, RBF = renal blood flow, MRI = magnetic resonance imaging, IAP = intraabdominal pressure, HTS = hypertonic saline, IVC = inferior vena cava
Table III: Review articles of renal function and pneumoperitoneum

<table>
<thead>
<tr>
<th>Author + Year</th>
<th>Comment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen et al. (45) 2005</td>
<td>Only reviews PP in morbidly obese</td>
<td>Despite intraoperative oligura, PP at 15mmHg is safe. No change in perioperative creatinine or BUN.</td>
</tr>
<tr>
<td>Neudecker et al.(10) 2002</td>
<td>Error in referencing. Conclusions based on few references</td>
<td>Significant decrease in GFR + u/o although not clinically relevant in healthy (ASA I+II) individuals Patients with impaired renal function should volume loaded before + during PP</td>
</tr>
<tr>
<td>Dunn et al.(41) 2000</td>
<td>Nonsystematic, few references</td>
<td>PP causes oliguria but no histologic evidence of renal tubular damage. Changes are pressure dependent and are usually not apparent at pressure &lt; 15mmHg.</td>
</tr>
<tr>
<td>Schilling et al. (46) 1996</td>
<td>Nonsystematic, few references</td>
<td>Decrease in u/o during PP, little data on clinical significance of this.</td>
</tr>
</tbody>
</table>

Legend:
BUN = blood urea nitrogen, PP = pneumoperitoneum, GFR = glomerular filtration rate, , u/o = urine output, PP = pneumoperitoneum
<table>
<thead>
<tr>
<th>Author + Year</th>
<th>Type of study</th>
<th>Outcome</th>
<th>Pressure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen et al. (49) 2002</td>
<td>RCT of 45 lap vs 50 open gastric bypass patients</td>
<td>Urine output</td>
<td>15</td>
<td>↓ by 64% in lap group No differences in creatinine</td>
</tr>
<tr>
<td>Perez et al. (50) 2002</td>
<td>40 lap colon surgery pts Dopamine vs control</td>
<td>Creatinine clearance, urine output</td>
<td>15</td>
<td>↓ in creatinine clearance and u/o in control, prevented by low dose dopamine</td>
</tr>
<tr>
<td>Micali et al. (53) 1999</td>
<td>31 laparoscopic vs 28 open procedures</td>
<td>Urinary NAG level</td>
<td>Not mentioned</td>
<td>No difference in urinary NAG levels</td>
</tr>
<tr>
<td>Nishio et al. (52) 1999</td>
<td>9 laparoscopic adrenalectomies, 6 with PP, 3 gasless.</td>
<td>Urine output</td>
<td>10</td>
<td>&gt;50% ↓ in u/o in gas laparoscopy. No change in gasless group</td>
</tr>
<tr>
<td>Koivusalo et al. (51) 1997</td>
<td>CO2 PP vs abdominal wall lift device in 30 lap chole pts</td>
<td>U/o and U-NAG</td>
<td>13mmHg vs 0</td>
<td>U-NAG ↑ 153% and u/o ↓ &gt;90% in PP group</td>
</tr>
<tr>
<td>Miki et al. (43) 1996</td>
<td>PP vs abdo wall lift device 7 lap choles</td>
<td>GFR, urine output</td>
<td>12</td>
<td>GFR ↓ 24% urine output ↓ 60%</td>
</tr>
</tbody>
</table>

**Legend:**
- RCT = randomized control trial, GFR = glomerular filtration rate, u/o = urine output, PP = pneumoperitoneum, U-NAG (urine N-acetyl-B-D-glucosaminidase)
### Table V: Animal studies of renal function and pneumoperitoneum

<table>
<thead>
<tr>
<th>Author + Year</th>
<th>Type of study</th>
<th>Outcome</th>
<th>Pressure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazebroek et al. (61) 2003</td>
<td>72 rats, Lap vs open procurement, kidney transplantation</td>
<td>GFR, histology and immunohistochemistry</td>
<td>12</td>
<td>no differences in GFR, histology or immunohistochemistry one year after transplantation</td>
</tr>
<tr>
<td>Lindberg et al. (32) 2003</td>
<td>13 pigs, Control vs CO₂ PP</td>
<td>Urine output</td>
<td>12</td>
<td>Trend towards ↓ during PP but not significant</td>
</tr>
<tr>
<td>Lindstrom et al. (58) 2003</td>
<td>18 rats, Control vs CO₂ PP</td>
<td>GFR, u/o</td>
<td>0 vs 5 vs 10</td>
<td>↓ in GFR by 70% with IAP 10. ↓ in u/o by 75% with IAP of 10</td>
</tr>
<tr>
<td>Akbulut et al. (59) 2002</td>
<td>30 rats, Control vs laparoscopic donor nephrectomy, oxidative stress independent factors</td>
<td>Tissue-oxidative stress markers</td>
<td>12</td>
<td>PP and warm ischemia independent factors causing oxidative stress</td>
</tr>
<tr>
<td>Hazebroek et al. (60) 2002</td>
<td>36 rats, 2 hours of CO₂ vs helium vs no insufflation, then nephrectomy</td>
<td>Histology and immunohistochemistry</td>
<td>8</td>
<td>No changes</td>
</tr>
<tr>
<td>Schachtrupp et al. (56) 2002</td>
<td>12 pigs, effect of 24 hours of PP</td>
<td>U/o, histology</td>
<td>15</td>
<td>u/o ↓ by 59% Evidence of low-grade proximal tubular necrosis on histopathology.</td>
</tr>
<tr>
<td>London et al. (8) 2000</td>
<td>18 pigs, randomized into 3 fluid groups (euvolemia vs bolus vs HTS)</td>
<td>U/o, Creatinine clearance</td>
<td>15</td>
<td>Euvolemic Group: u/o ↓ by 73%, creatinine clearance ↓ by &gt; 50% Bolus + HTS: urine output maintained but creat clearance ↓</td>
</tr>
<tr>
<td>Lee et al. (44)</td>
<td>24 Rats, Control vs. varying length of PP</td>
<td>kidney histology</td>
<td>15</td>
<td>No difference in histologic score at 1 week and 3 months</td>
</tr>
<tr>
<td>Cisek et al. (14) 1998</td>
<td>12 Pigs with surgically created CRF</td>
<td>U/o, GFR</td>
<td>20</td>
<td>u/o ↓ by 80% GFR ↓ by 63%</td>
</tr>
<tr>
<td>Horvath et al. (54) 1998</td>
<td>24 pigs, open vs CO₂ vs Helium PP vs abdominal wall lifter for lap colectomy</td>
<td>Hemodynamics, u/o</td>
<td>15</td>
<td>↓ u/o by 50% as compared to open</td>
</tr>
<tr>
<td>Dolgor et al. (57) 1998</td>
<td>72 rats, role of vasopressin antagonist during PP</td>
<td>ADH, u/o</td>
<td>8</td>
<td>ADH ↑ with PP Sig ↓ in u/o during PP, ↓ prevented with ADH antagonist</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>u/o, GFR</td>
<td>15 via pressure cuff, NO PP</td>
<td>u/o ↓63% GFR ↓21% in compressed kidney</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Razvi et al. (30) 1996</td>
<td>6 dogs, pressure cuff placed around renal parenchyma, compared to other kidney</td>
<td>u/o, GFR</td>
<td>0, 5, 10</td>
<td>u/o ↓with IAP of 10, not sig with IAP of 5</td>
</tr>
<tr>
<td>Kirsh et al. (42) 1994</td>
<td>67 rats, effect of IAP on u/o</td>
<td>u/o, serum creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harman et al. (20) 1982</td>
<td>7 Dogs, effect of IAP on renal function</td>
<td>u/o, GFR</td>
<td>0, 20, 40</td>
<td>GFR ↓ by 75% with IAP of 20 Anuric and GFR ↓ by 93% with IAP of 40</td>
</tr>
</tbody>
</table>

**Legend:**

ADH = antidiuretic hormone, GFR = glomerular filtration rate, IAP = intraabdominal pressure, u/o = urine output, PP = pneumoperitoneum, CRF = chronic renal failure
C. Transition:

It is evident from this review that PP results in a decrease in RBF and renal function. The next issue then becomes, what can be done about this phenomenon? Are there strategies that can be used to prevent this decrease in RBF during PP? A few strategies have been examined experimentally that are worth discussing.

One such method was the addition of a vasodilator to the gas insufflated into the abdomen. Ali et al. (33) attempted to attenuate reductions seen in splanchnic blood flow during PP by adding ethyl nitrate to the insufflation admixture. While this addition prevented a decrease in hepatic blood flow during PP, it did not affect renal blood flow. Other pharmacologic attempts at maintaining RBF during PP have also been attempted. Perez et al. (50) evaluated the use of intravenous dopamine administration to prevent decreases in urine output observed during PP. They found that low dose dopamine administration during surgery prevented a decrease in urine output and creatinine clearance seen in those patients who did not receive dopamine.

Another method to avoid decreases in renal perfusion is to avoid the use of CO₂ PP altogether. Koivusalo et al. (51) studied patients undergoing laparoscopic cholecystectomy comparing PP with an abdominal wall lift device. They demonstrated that the abdominal wall lift device provided protection against renal ischemia that occurs during CO₂ PP. Unfortunately, the limited practicality of the abdominal wall lift device has diminished its utility and it has not gained widespread acceptance.

Finally, it has been demonstrated that fluid administration improves RBF during PP. Animal hemorrhage models (62, 63) have demonstrated that
resuscitation with fluid administration after an iatrogenic vascular injury restored renal perfusion and function. Since then, two subsequent studies have evaluated fluid administration as a means of restoring renal perfusion or function during PP. Lindstrom et al. (58) demonstrated that giving rats volume expansion, as well as an angiotensin II receptor antagonist, improved renal function during PP. London et al. (8) compared three different fluid groups in pigs. They demonstrated that volume resuscitation via bolus administration or hypertonic saline maintained renal perfusion during PP, while an euvoletic group did not.

Thus fluid administration and dopamine have been shown to be beneficial in preventing decreases in renal perfusion and function during PP. We sought to further investigate the non-pharmacologic alternative to maintaining RBF during PP. While fluid administration is used clinically to maintain RBF, there is a paucity of experimental data to confirm this practise. Thus a porcine model was designed to investigate the effects of bolus fluid administration on renal perfusion and function during PP. This next paper describes this study.
D. Does Aggressive Hydration Reverse the effects of Pneumoperitoneum on Renal Perfusion?

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Abstract

Introduction: Although pneumoperitoneum (PP) decreases renal blood flow, it remains unclear whether this impacts renal function. Our aim was to characterize the effects of PP on renal perfusion and function using two fluid strategies for intravenous fluid administration. Methods: Twelve 30 kg pigs were randomized into two groups: Maintenance (3cc/kg/hr of Normal Saline (NS)) and Bolus (15cc/kg/hr + 20cc/kg NaCl bolus prior to induction of PP). Pigs were studied in a blinded fashion for 30 minutes prior, 60 minutes during and 30 minutes after release of 15 mmHg CO₂ PP. Cardiac output (CO) and Stroke Volume (SV) were measured using an esophageal doppler probe, renal cortical perfusion (RCP) with a laser doppler probe on the right kidney, and renal function using the fractional excretion of sodium (FeNa) and urine output. Statistical analysis was performed with area under the curve (AUC) analysis and ANOVA. Results: AUC analysis revealed moderate effect size for CO (0.416), and small effect size for SV (0.366) and RCP (0.363), with decreases seen in the control group but not the bolus group. During PP, urine output increased in the bolus group (p=0.04) but not in the control group; there was no difference in FeNa in either group. Conclusion: Aggressive fluid hydration during CO₂ PP of 15mmHg preserves CO, SV and RCP, while increasing urine output. No effect on renal function as measured by FeNa was observed in either group.

Keywords

Pneumoperitoneum – Renal perfusion – Renal function - laparoscopic nephrectomy
Introduction

The systemic physiologic consequences of pneumoperitoneum are not yet fully understood despite much research in this field. In particular, the precise consequences of pneumoperitoneum on renal perfusion and function require further studies. This has particular importance for laparoscopic live donor nephrectomy (LLDN), where donor morbidity must be minimized and graft quality maintained. If subtle ischemic damage is occurring to the grafts due to pneumoperitoneum, these effects may not be manifest until many years post transplantation.

There is compelling experimental evidence that CO₂ pneumoperitoneum decreases renal blood flow (RBF) and renal cortical perfusion (RCP) (8, 9, 16, 27, 28, 61, 64). The magnitude of this decrease is affected by the level of pneumoperitoneum (16), baseline volume status (8), degree of hypercarbia (42), positioning (16), and individual hemodynamic and renal reserve. The cause of this drop in RCP is multifactorial, and may include direct compression of the kidney and renal vein (27, 65), increased resistance in the renal vasculature (66), neurohormonal responses due to increases in vasopressin, the renin-angiotensin system and catecholamines (67) and to a lesser extent, the negative effects of absorbed CO₂ on cardiac contractility (65). One of the principal theories to explain the decline in renal perfusion during pneumoperitoneum is that the increased intraabdominal pressure results in a decrease in venous return to the heart (preload) due to compression of the inferior vena cava and femoral vessels. This decreases cardiac output, which results in a decrease in effective circulating blood volume and RCP (8, 24). However, we were previously unable to demonstrate a decrease in an index of preload in patients during LLDN at 12-15mmHg pneumoperitoneum (68).
or in a pig model (69, 70), and others have even demonstrated an increase in preload during pneumoperitoneum (71, 72).

Whatever the exact mechanism, it has been previously shown that aggressive fluid hydration can prevent the decrease in renal perfusion and urine output seen during pneumoperitoneum (8). In a pig model with a pneumoperitoneum of 15mmHg, aggressively hydrated pigs (with 0.45% NS or hypertonic saline) maintained their baseline renal perfusion, while euvoletic pigs did not. Interestingly, decreases in creatinine clearance were still seen in the well-hydrated pigs. The importance of maintaining perfusion if in fact function is not preserved remains unclear. Nonetheless, recommendations that patients undergoing LLDN be given “vigorous hydration” to “optimize preload” have been made (73). Although frank pulmonary edema is rare after LLDN, it may be more common than reported (74), and more subtle deleterious effects of overhydration in general are increasingly recognized. (5) The optimal level of hydration for LLDN thus remains to be determined.

The objective of the present study was to assess whether a simple hydration strategy preserved renal perfusion and function during a CO₂ pneumoperitoneum of 15mmHg.

Methods

Animals and Anesthesia

All experiments were performed in accordance with the guidelines for the care and use of laboratory animals as outlined by the Animal Care Committee of the McGill University Health Centre. Twelve female domestic pigs weighing 31.4 (range 26-
37) kgs were fasted overnight with free access to water. Animals were premedicated with atropine 0.04mg/kg IM, acepromazine 1mg/kg IM, ketamine 15mg/kg IM, and butorphanol 0.2mg/kg IM twenty minutes prior to the induction of the anesthesia. Anesthesia was induced with sodium pentobarbitol 20-30mg/kg IV via an auricular vein. Animals were then intubated oro-tracheally and ventilated with a Nuffield ventilator (Penlon, Abingdon, UK). The ventilator was set at an FiO\textsubscript{2} of 40%, with a flow of 0.3 to 0.4 L/s, at an I:E ratio of 1:2. An end-tidal carbon dioxide (ETCO\textsubscript{2}) sensor was used (Nellcor, Tyco Healthcare, Mansfield, MA), and the ventilator settings adjusted to maintain ETCO\textsubscript{2} between 35-45 mmHg. Anesthesia was maintained with intavenous propofol (bolus 400ug/kg, infusion 100ug/kg/min) and fentanyl (50ug every 30 mins).

**Surgical Preparation**

The animals were placed in the supine position. A pulse oxymeter (Nellcor, Tyco Healthcare) was fixed to the animal’s gum to measure oxygen saturation. A cutdown was performed of the right neck and a 20 gauge angiocatheter connected to a transducer was inserted in the carotid artery to continuously measure arterial blood pressure. A 6 Fr catheter (Edwards Lifesciences, Irvine, CA) was inserted into the internal or external jugular vein and attached to a transducer for measurement of CVP and blood sampling. An esophageal doppler probe (Deltex, Chichester, UK) was used to measure cardiac output (CO) and stroke volume (SV). The probe was inserted into the esophagus via the mouth under direct vision using a laryngeal blade. It was advanced into the lower third of the esophagus, at a distance of 18 to 22 cm from the snout, until an optimal doppler signal was observed. A
rectal thermometer was used to monitor temperature, with temperature maintained between 37.5 °C and 38.5 °C using a heating lamp and a warming pad.

Access to the peritoneal cavity was established through the lower midline using a veress needle. C0₂ pneumoperitoneum was established and maintained at an intra-abdominal pressure of 15mmHg. A 10mm trocar was inserted via the umbilicus and two 5mm trocars were inserted in the right anterior axillary line. The pig was placed in the left lateral decubitus position and Gerota’s fascia over the right kidney was incised under videoscopic guidance. An small incision was made in the lateral abdominal wall over the kidney to allow placement of the laser doppler probe (LDP) on the renal parenchyma, under Gerota’s fascia. The LDP (Transonic Systems Inc, NY, USA) measures perfusion in a 1mm³ area of tissue. The urinary bladder was catheterized laparoscopically. A grasper forcep was used to hold the bladder against the abdominal wall and a Seldinger technique was used to insert a catheter. During experimental setup, all pigs received maintenance fluid of 3cc/kg/hr NS.

Experimental Protocol

Once all the monitoring equipment was in place, pneumoperitoneum was released, the animals were repositioned in the supine position, and 20 minutes was allowed for the animals to accommodate. The 12 animals were then randomized between two groups of fluid management (Control vs. Bolus, n=6 animals each). The investigator recording the data was unaware of group allocation. The experiment consisted of three study periods: baseline, pneumoperitoneum, and postpneumoperitoneum. During the 30-minute baseline period, the control group
received IV NS at a rate of 3 cc/kg/hr, representing a maintenance rate. The bolus
group received IV NS at 15 cc/kg/hr. Prior to induction of a 60 minute period of
pneumoperitoneum, the bolus group received a 20 cc/kg bolus of IV NS. These
values were based on those used by London et al. (8) The animals were then
observed during a 30 minute period after the release of pneumoperitoneum. The
animals were then euthanized with a KCl injection.

BP, CVP, renal cortical perfusion (RCP), ETCO₂ and esophageal Doppler measures
were monitored continuously and recorded every ten minutes. Blood samples to
determine serum sodium and creatinine concentration were drawn at 15 minutes
(baseline), while urine samples were obtained at 30 minutes (baseline), 75 minutes
(pneumoperitoneum) and 120 minutes (release) for calculation of the fractional
excretion of sodium (FeNa). FeNa was calculated as (serum creatinine x urine
sodium)/(serum sodium x urine creatinine) x 100. Urine output was determined at
30 minute intervals. Due to technical difficulties with urine collection, 4 pigs were
excluded (n=1 maintenance, n=3 bolus) from the urine output and FeNa analyses.

Statistical Analysis

Data are expressed as mean (SD) and were analyzed using SPSS 11 for Mac OS X
(SPSS Inc, Chicago, IL). As there were 15 discrete time points of 10 minutes each
(4 prior to pneumoperitoneum, 7 during pneumoperitoneum, and 4 for recovery) a
statistical method for repeated measures was required. We chose to calculate the
area-under-the-curve (AUC), for each pig using the trapezoid method (75). This
was done for CO, SV and RCP. For each group we estimated the mean difference
in area under the curve and standard deviation, for all 15 time points. The difference
between groups divided by the standard deviation provides an estimate of the magnitude of effect, termed effect size. Cohen (76) classifies effect sizes as large (>0.8), medium (0.4 to 0.8) and small (<0.4). In order to compare the two groups of pigs over the 15 time points using t-tests, over 250 pigs would be needed for statistical significance to be achieved in this kind of a study design. For this reason the effect size from the area under the curve analysis was used to compare the systemic and renal hemodynamics in the two groups of pigs over the entire study period. The groups were compared at baseline using unpaired t-tests. Because urine was collected at 3 time points only, analysis of variance was used to compare the urine outputs and the FeNa results. P<0.05 was considered significant.

Results

There were no significant differences at Time = 0 (Table I). Area under the curve analysis (Table II) was calculated for CO, SV and RCP. This analysis revealed moderate (CO) and small (SV and RCP) effect sizes between the bolus and maintenance groups. When we examine these curves (figures 1a, b, c) we see that the two groups were similar at baseline, diverged during pneumoperitoneum, and then converged again during the recovery period. This indicates that the differences seen from the area under the curve analysis have occurred during pneumoperitoneum, as is expected. Again, looking at figures 1a, b, and c we see that CO, SV and RCP decreased at the onset of pneumoperitoneum in the control group, and remained decreased throughout pneumoperitoneum. In contrast, RCP, SV and CO were maintained in the bolus group throughout the study period.
During pneumoperitoneum, urine output remained unchanged in the control group and was significantly higher in the bolus group (Fig 2B). FeNa was low in both groups at baseline. Although no differences were seen as compared to baseline, FeNa was increased in the bolus as compared to the maintenance group during pneumoperitoneum (Fig 2A).

During the recovery part of the study, two pigs became tachycardic necessitating discontinuation of the experiment. This occurred for one pig in the bolus group (t=100) and for one pig in the maintenance group (t=130). Data missing from these two pigs for the remaining time points were recorded as zero and included in the analysis as suggested by our statistician.

Discussion

This study demonstrates that in this porcine model, decreases in CO, SV, and RCP are seen with a pneumoperitoneum of 15mmHg. These differences could be prevented by using a simple hydration strategy of 15cc/kg/hr NS with a 20cc/kg bolus at the onset of pneumoperitoneum (total fluid approximately 28cc/kg/hr), in accordance with the findings of London et al (8). Using this hydration strategy, urine output was increased during pneumoperitoneum in the bolus group, while it was maintained in the control group. In addition, there was no decrease seen in the FeNa from baseline, used as a marker of acute renal dysfunction.

The area under the curve analysis reveals that there was a moderate effect size between the groups for CO and a small effect size for SV and RBF. This analysis was used to assess the differences between the two groups over the complete study period. We were unable to further stratify the analysis into the three
study periods used because of a small sample size. Preliminary analysis revealed a low power to detect differences of this magnitude with a total sample size of 12. In fact, a sample size of about 200 pigs would be required to show statistical significance for this study design. For this reason the p-values (table II) are not significant. Instead, we illustrated the effect of a fluid bolus strategy by estimating the effect size. As mentioned previously, Cohen (76) classifies effect sizes as large (>0.8), medium (0.4 to 0.8) and small (<0.4). Our data demonstrate a moderate-to-low effect of the aggressive hydration strategy, supporting the notion that there are significant changes in CO, SV and RCP during pneumoperitoneum in the maintenance group that are not occurring in the bolus group. This implies that the bolus fluid strategy is preventing these changes from occurring during pneumoperitoneum.

Renal function has been measured in different studies using either urine output, glomerular filtration rate (GFR) or creatinine clearance (8, 61, 66, 77). There is no perfect marker of renal function however. Urine output is not very sensitive to acute changes while estimation of GFR by calculation of the creatinine clearance has limitations in reproducibility and accuracy, and overestimates GFR significantly (36). In addition, measurement of creatinine clearance usually requires a sampling period of twenty fours hours, but at the very least eight hours, to be reliable. (35) Other methods of obtaining GFR, such as with inulin clearance, are cumbersome to obtain.

The fractional excretion of sodium (FeNa) is a good marker of acute renal tubular function (78). Normally the FeNa is about 2 – 3%, but is dependent on the amount of sodium that is ingested and filtered. A low FeNa (<1%) indicates that the
kidney is exposed to a decreased effective circulating volume and is holding onto more sodium (a sign of prerenal dysfunction). The FeNa can also increase abnormally if the kidney is not able to hold onto sodium properly (usually a sign of acute tubular necrosis). FeNa can be obtained from a spot sample of urine and does not require a sampling period. Furthermore, it does not require prior infusion, unlike iothalmate. The FeNa has been used experimentally as an early marker of renal dysfunction in septic pigs, (79) and in critically ill preterm newborns (80).

While normal values for FeNa in pigs have not been well described in the literature, the percent change from baseline values under experimental conditions can be measured.

Contrary to our initial hypothesis that the bolus group would show no change in tubular function while the maintenance group would show a decrease, we did not find any acute decrease in renal tubular function in either group. This implies that even though the kidney is being less well perfused in the maintenance group (as measured by a decrease in RCP), it is not trying to hold onto more sodium. This is difficult to explain since the FeNa should respond to perceived hypovolemia through baroreceptors in the carotid body, aortic arch and macula densa. There also seemed to be an effect of pneumoperitoneum alone since FeNa went up in both groups (although not significant in the maintenance group), and then back down again after release of PP. Some authors have interpreted an increase in the FeNa as a sign of acute tubular necrosis. The fact that the FeNa decreases again rapidly after release of pneumoperitoneum in this case goes against this possibility.
Our data therefore imply that even though the RCP is decreased in euvolemic pigs during pneumoperitoneum, there are no significant changes in the ability of the kidney to conserve sodium during pneumoperitoneum. However, there are some important caveats to mention. First of all, this data is based on only eight of the 12 pigs because of difficulties with urine collection. Secondly, there was a large amount of variability in the urine data that was collected. Thirdly, it is possible that the introduction of anesthesia and surgical manipulation required for setup may have decreased the effective circulating volume which could lower the FeNa prior to commencement of the experiment. Thus our initial baseline FeNa would already be very low and therefore it might be difficult to detect any further decline during pneumoperitoneum. In fact, the mild increase in FeNa might indicate that the fluid received was enough to overcome some of the sodium retention occurring in the tubules during the anesthesia and setup periods, even though RCP decreased.

While we used FeNa as a marker of tubular function and did not demonstrate any decrease during pneumoperitoneum in the maintenance group, London et al. demonstrated a decrease in creatinine clearance in a similar experiment. However, the use of creatinine clearance as an estimate of GFR is problematic. As mentioned previously, it is not intended for rapid measurements of renal function, and should not be used for a period of study of less than eight hours. (35) In addition, their finding of a decrease in creatinine clearance in the bolus group in which RCP was maintained is difficult to explain physiologically, since GFR is mostly determined by the capillary pressure across the glomerulus (81).
There are limitations to the applicability of these results to patients undergoing laparoscopic donor nephrectomy. The pigs demonstrated great baseline variability, unlike kidney donor patients who are a fairly homogenous, healthy population (68). Although we perform donor nephrectomy clinically at a pneumoperitoneum of 12mmHg, we chose to use 15 mmHg in this study because we were unable to demonstrate significant changes in systemic and renal hemodynamics at 12mmHg in a previous porcine study (69). Nonetheless, Perez et al. (50) found a decrease in urine output and creatinine clearance in patients undergoing laparoscopic colon surgery with a pneumoperitoneum of 15mmHg, despite using crystalloids to maintain the CVP between 10-12. This may be because CVP is artificially elevated due to the transmitted intraabdominal pressure during pneumoperitoneum (68) and perhaps these patients were not adequately hydrated. Miki et al. (43) found a decrease in urine output, GFR and effective renal plasma flow in patients undergoing laparoscopic cholecystectomy at a pressure of 12mmHg, but not when an abdominal wall lift device was used. These effects were transient however, and the implications for the long-term function of kidneys procured laparoscopically remains theoretical. In a long-term rat study, Hazebroek et al. (61) showed no differences in GFR acutely or by immunohistochemical staining one year after transplantation for kidneys procured laparoscopically compared to open. To date, there are similar recipient outcomes overall following laparoscopic or open donor nephrectomy (2), although slower early graft function has been shown in some studies (82).

While we confirmed that aggressive hydration was able to overcome the negative effects of pneumoperitoneum on RCP, fluid overload may have clinically
deleterious effects, including negative effects on wound healing and gastrointestinal motility (6). There is therefore a need to ensure adequate hydration status during pneumoperitoneum without being overaggressive.

In conclusion, pneumoperitoneum of 15mmHg CO₂ causes changes in systemic and renal hemodynamics in pigs receiving 3cc/kg/hr of NS, which can be prevented by an aggressive hydration strategy. While we documented small to moderate effect sizes for bolus fluid in RCP, CO and SV, we found no acute effect on renal function as measured by the FeNa or urine output. The “correct” amount of fluid required to prevent the decrease in RCP seen during pneumoperitoneum likely varies with baseline hemodynamic and renal reserve, volume status, and other factors. Further studies are needed to evaluate strategies for fluid optimization during pneumoperitoneum.
**Table I: Measurements at Baseline (time=0). Data expressed as mean(SD).**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Bolus</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>96 (10)</td>
<td>94 (11)</td>
<td>0.70</td>
</tr>
<tr>
<td>MAP</td>
<td>73 (10)</td>
<td>83 (13)</td>
<td>0.19</td>
</tr>
<tr>
<td>CVP</td>
<td>3 (1)</td>
<td>4 (2)</td>
<td>0.28</td>
</tr>
<tr>
<td>CO</td>
<td>5.9 (1.8)</td>
<td>5.6 (2.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>SV</td>
<td>61 (14)</td>
<td>58 (19)</td>
<td>0.76</td>
</tr>
<tr>
<td>FTc</td>
<td>435 (53)</td>
<td>439 (31)</td>
<td>0.87</td>
</tr>
<tr>
<td>SVR</td>
<td>1025 (329)</td>
<td>1344 (695)</td>
<td>0.34</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>32 (4)</td>
<td>28 (3)</td>
<td>0.07</td>
</tr>
<tr>
<td>RCP</td>
<td>49 (17)</td>
<td>46 (13)</td>
<td>0.75</td>
</tr>
<tr>
<td>Weight</td>
<td>30 (2)</td>
<td>33 (4)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**Legend: Table I**

HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (L/min); SV = stroke volume (ml); FTc = flow time corrected for heart rate (msec); CVP = central venous pressure (mmHg); ETCO₂ = end-tidal CO₂ (mmHg); SVR = systemic vascular resistance (dynes*sec/cm²). RCP = renal cortical perfusion (cc/100gm/min); FeNa = fractional excretion of sodium (%); UO = urine output (cc/kg/hr)

p value calculated by unpaired t-test, p < 0.05 considered significant.
Table II: Area under the curve (AUC) analysis for CO, SV, and RCP.

<table>
<thead>
<tr>
<th></th>
<th>Total AUC</th>
<th>t-test (p value)</th>
<th>Effect Size (Δ/SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CO:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus: 67</td>
<td>67</td>
<td>0.72 (0.49)</td>
<td>0.415 (moderate)</td>
</tr>
<tr>
<td>Maintenance 55</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SV:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus: 649</td>
<td>649</td>
<td>0.63 (0.54)</td>
<td>0.366 (small)</td>
</tr>
<tr>
<td>Maintenance 546</td>
<td>546</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RCP:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus: 506</td>
<td>506</td>
<td>0.63 (0.54)</td>
<td>0.363 (small)</td>
</tr>
<tr>
<td>Maintenance 466</td>
<td>466</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: Table II
CO = cardiac output (L/min); SV = stroke volume (ml); RCP = renal cortical perfusion (cc/100gm/min).
Figure 1a: Comparison of cardiac outputs in bolus and maintenance groups

Cardiac Output in Bolus vs Maintenance Groups

Figure 1b: Comparison of Stroke Volume in bolus versus maintenance groups

Stroke Volume in Bolus vs Maintenance Groups
Figure 1c: Comparison of renal cortical perfusion in bolus versus maintenance groups

Legend: Figures 1a,b,c
Error bars are standard error of the mean
Figure 2a: Comparison of Fractional excretion of sodium (FeNa) in bolus versus maintenance groups

**Legend: Figure 2a**
* = significant difference between Bolus and Maintenance Group

Figure 2b: Comparison of urine outputs in bolus versus maintenance groups

**Legend Figure 2b**
* = significant difference in bolus group as compared to baseline
E. Transition:

This study validated the concept that aggressive fluid hydration maintains RBF during PP. Thus one method to maintain renal perfusion during PP is to administer large volumes of fluid to all patients during PP. This notion has in fact been adopted by many renal transplant surgeons. It is now common practice for donors to receive sufficient crystalloid intraoperatively to maintain a urine output of up to 500 ml/h (83) in an effort to preserve renal perfusion during PP.

However, aggressive fluid hydration can have negative clinical consequences (5, 74) and not all patients require such large volumes of fluid to maintain RBF during PP. A rational approach to fluid therapy during PP would be to individualize fluid administration so that only those who need it (those who demonstrate a decrease in RBF), receive extra fluid. The objective of this next study was therefore to evaluate whether an esophageal Doppler (ED) could be used to optimize fluid administration in a porcine model during PP.

First, a pilot study was performed to evaluate the feasibility of using esophageal Doppler stroke volume measurements to guide fluid administration. Next, a randomized study was undertaken to compare bolus, maintenance and esophageal Doppler guided measurements. This next paper describes this study.
F. Targeting Individual Hemodynamics to maintain Renal Perfusion during Pneumoperitoneum

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Abstract

Introduction: While aggressive fluid hydration prevents a decrease in renal cortical perfusion (RCP) during laparoscopic donor nephrectomy, fluid overload can be deleterious. We assessed the feasibility of lower volume fluid management to maintain RCP during pneumoperitoneum (PP) using goal-directed fluid administration. Methods: In a pilot study of 7 pigs, goal-directed fluid administration was guided by Esophageal Doppler. During 15mmHg CO₂ PP, a bolus of 5cc/kg NS was given when stroke volume (SV) fell below 90% of baseline. Next, 18 pigs were randomized into 3 groups: Group 1: Control (5cc/kg/h), Group 2: Bolus (25cc/kg/h) and Group 3: Goal-directed. Urine output, HR, MAP, CO, SV, and RCP were recorded every 15 minutes. Data were analyzed with paired t-tests. * p<0.05 significant. Results: Comparing baseline with PP in the pilot study, mean RCP (cc/min/100g) was maintained (40 vs 39) using goal-directed therapy. In the randomized study, mean RCP was decreased in Group 1 (43 vs 29)*, but maintained in Group 2 (46 vs 40) and in Group 3 (42 vs 39). Mean SV (mL) was maintained in Group 1 (57 vs 61) and Group 2 (50 vs 61) while it was increased in Group 3 (50 vs 57)*. In Group 3, mean fluid administered during PP was 10 cc/kg with 3/6 of pigs receiving boluses. Urine output was decreased in all 3 groups. Conclusion: A goal-directed strategy during PP allows for tailored fluid administration and maintains RCP with lower volumes of intravenous fluid (10 cc/kg vs 25cc/kg).

Keywords
Pneumoperitoneum – renal perfusion – renal function - laparoscopic nephrectomy – fluid hydration
Introduction

A well recognized phenomenon that occurs during pneumoperitoneum (PP) is a decrease in urine output. This has been documented in various laparoscopic procedures such as gastric bypass,(45) colectomy,(50) cholecystectomy, (43) adrenalectomy,(52) and live donor nephrectomy.(73) This decrease in urine output is thought to be the clinical manifestation of a decrease in renal blood flow (RBF) that occurs during PP. (8, 9, 16, 27, 28, 61, 64) One explanation for this decrease in RBF is that the pressure exerted by PP compresses the iliac veins and the inferior vena cava, which decreases preload and thereby decreases cardiac output (CO) and RBF. (8, 84) Other proposed mechanisms include direct compression of the renal parenchyma(30) or vasculature(16), and neurohormonal responses from increases in ADH (85), vasopressin, the renin-angiotensin system(32) and catecholamines.(67)

The clinical consequences of this decrease in renal perfusion during pneumoperitoneum have particular relevance to laparoscopic donor nephrectomy. Although the incidence of delayed graft function is similar in recipients of kidneys procured laparoscopically or open(82) some studies show higher early serum creatinine in recipients of laparoscopically harvested kidneys(82, 86), and in laparoscopic donors(86, 87). Although these differences do not persist at one year post transplant(82, 86), longer-term outcomes are not yet available. If there is subtle, subclinical damage occurring to the donor kidney during LLDN, this may only be apparent many years after transplantation.

Animal studies, in both non-pneumoperitoneum and pneumoperitoneum models, have shown that volume replacement improves RBF.(8, 62, 63) London et al demonstrated that the decline in RBF associated with pneumoperitoneum could
be prevented with fluid hydration\(^8\), and we reported similar findings \((88)\).

Accordingly, current recommendations are that laparoscopic donors receive aggressive intraoperative hydration up to 2 L/h \((4)\) to “optimize preload.” \((73)\)

However, aggressive fluid hydration may have negative clinical consequences\((5, 74)\), and the optimal approach to fluid management in laparoscopic donor nephrectomy is not known.

Using a porcine model, we previously found that only pigs with low echocardiographic preload at baseline demonstrated a decline in RBF with pneumoperitoneum \((69)\). Thus the level of hydration required for an individual to maintain RBF under pneumoperitoneum presumably varies with individual baseline volume status, hemodynamics, the degree of pneumoperitoneum, and renal function. A rational approach to fluid therapy would be to individualize fluid administration so that only those who need it (those that demonstrate a decrease in RBF) would receive extra fluid. However, direct measurement of RBF clinically requires the placement of a probe on the kidney or other cumbersome techniques.

The objective of this study was therefore to evaluate whether the esophageal Doppler (ED), a minimally invasive continuous hemodynamic measurement device placed in the esophagus to measure blood flow in the descending aorta, could be used to optimize fluid administration in a porcine model during PP.

**Methods**

All experiments were performed in accordance with the guidelines for the care and use of laboratory animals as outlined by the Animal Care Committee of the McGill University Health Centre. The study consisted of two parts: 1) a pilot study
of 7 pigs to assess the feasibility of using the ED to guide fluid administration, and
2) a randomized study of 18 pigs comparing ED guided fluid therapy with
maintenance and bolus regimens.

Animal Model

The model and setup for these experiments has been previously described
(88). Briefly, animals were anesthetized, intubated and ventilated. Carotid artery
and jugular vein catheters were placed for hemodynamic measurements and blood
sampling. An esophageal Doppler probe (Deltex, Chichester, UK) was used to
measure cardiac output (CO) and stroke volume (SV). The probe was inserted into
the esophagus via the mouth under direct vision and advanced into the lower third
of the esophagus, until an optimal Doppler signal was observed. The Doppler
measures changes in frequency in the descending aorta and converts this to a
velocity against time curve. Calculation of the area under the curve results in the
stroke distance, which, when multiplied by the cross sectional area of the aorta,
results in SV. Aortic blood flow is then obtained by multiplying SV by HR, and this
is about 70% of the CO.

PP was established slowly, with a Veress needle using a flow of 1 – 1.5
L/min. A pressure of 8 – 10mmHg CO₂ was used for setup. A 10mm trocar was
inserted via the umbilicus and two 5mm trocars were inserted in the right anterior
axillary line. The pig was placed in the left lateral decubitus position and Gerota’s
fascia over the right kidney was incised laparoscopically. A small incision was
made in the lateral abdominal wall over the kidney to allow placement of the laser
Doppler probe (LDP) on the renal parenchyma, under Gerota’s fascia. The LDP
(Transonic Systems Inc, NY, USA) measures perfusion in a 1mm³ area of tissue.
The urinary bladder was catheterized laparoscopically and urine output was recorded throughout the experiment. During experimental setup, pigs received maintenance fluid of 3cc/kg/h of normal saline (NS). Once all the monitoring equipment were in place, PP was released, and the animals were allowed to accommodate for 20 minutes. Blood and urine samples were taken to calculate the fractional excretion of sodium (FeNa) at the end of baseline and at the end of PP (FeNa = (serum creatinine x urine sodium)/(serum sodium x urine creatinine) x 100). At the end of each experiment, animals were euthanized with a KCl injection.

Study Design

1) Pilot study

Seven pigs were studied for 30 mins during baseline and 80 mins during a 15mmHg CO2 PP. An average SV was obtained by calculating the mean SV obtained during baseline. Measurements of mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), renal cortical perfusion (RCP), stroke volume (SV), cardiac output (CO), temperature (T) and end tidal carbon dioxide (ETCO2) were monitored continuously and recorded every five minutes. During PP, measures were taken every 15 minutes. Pigs received 5cc/kg/h of NS during baseline, and then received no further maintenance fluid during PP. During PP, a fluid algorithm was used to guide fluid administration (Figure 1). Pigs received a 5cc/kg NS bolus each time the SV fell by more than 10% from baseline. With measures performed every 15 minutes, pigs could receive up to a maximum of 6 boluses during PP.

2) Randomized study
18 animals were studied for 30 mins at baseline and 60 mins during PP. During baseline, pigs received 5 cc/kg/h of NS. Measurements of BP, CVP, HR, RCP, SV, CO, temperature and ETCO$_2$ were monitored continuously and recorded every five minutes and a mean SV was calculated for baseline. Next, a 15mmHg CO$_2$ PP was induced and pigs were randomized into one of the three fluid groups (n=6 in each). Group 1 ("Control") received 5cc/kg/hr of NS, Group 2 ("Bolus") received 25cc/kg/hr NS and Group 3 ("Goal-directed") received 5cc/kg/hr NS and, in addition, received goal-directed therapy as per the pilot study. During the 60 minutes of PP, measures were repeated every 15 mins and pigs could receive up to a maximum of 5 boluses.

**Statistical Analysis**

Data are expressed as mean (SD) and were analyzed using SPSS 11 for Mac OS X (SPSS, 2003). Paired t-tests were used to compare data obtained at the end of the baseline (t=30) with that obtained at the end of PP (t= 110 in pilot, t=90 in randomized study). P<0.05 was considered significant. For the pilot study, we performed a sample size calculation to ensure that the study would be adequately powered to show a difference in RCP between baseline and PP. Based on our previously experiments in this model (88) showing a 30% decrease in RCP between baseline and PP in the control group, for a power of 80%, the sample size was found to be 7.

**Results**

1) **Pilot Study**

7 pigs, with mean weight 34.4 (0.8) kgs completed the study. Mean fluid administered was 12.1cc/kg. The mean number of boluses administered was 2.4 per
pig (range 0-5) with one pig not receiving any additional fluid (Table I). Using this strategy during PP, mean RCP (40 vs. 39 cc/min/100g, p=0.8), SV (50 vs. 52mL, p=0.3), CO (5.0 vs. 5.1 L/min, p=0.7), urine output (1.4 vs. 1.3 cc/kg/hr, p=0.7) and FeNa (0.3 vs. 0.16, p=0.2) were not significantly different from baseline (Table II).

2) Randomized study

Two pigs were excluded early in the study because of hemodynamic instability at the onset of pneumoperitoneum while 18 pigs, with mean weight 33 (1.4) kgs, were included. In the control group, RCP was significantly decreased at the end of PP compared to baseline (43 vs. 29 cc/min/100g, p=0.02, Table III). In contrast, CO (6.0 vs. 6.8L/min, p=0.2), SV (57 vs. 61mL, p=0.5), HR (103 vs. 110bpm, p=0.2) and MAP (73 vs. 70mmHg, p=0.5) were unchanged. Mean urine output was decreased (1.46 vs. 0.69cc/kg/h, p=0.02) to 42% of baseline while FeNa (0.36 vs. 0.32%, p=0.6) was maintained at 89% of baseline.

In the bolus group, comparing baseline with PP, RCP (46 vs. 40cc/min/100g, p=0.5) and SV (50 vs. 61mL, p=0.14) were maintained, while CO (4.4 vs. 6.6L/min, p=0.007) increased from baseline (Table IV). HR (90 vs. 105bpm, p=0.01) was also increased during PP while MAP (73 vs. 69mmHg, p=0.7) remained the same. Mean urine output decreased to 61% of baseline (1.13 vs. 0.69cc/kg/h, p=0.006) as did FeNa (0.22 vs. 0.091%, p=0.07) to 41% of baseline during PP.

As in the bolus group, RCP was maintained during PP in the goal-directed group (42 vs. 39cc/min/100g, p=0.5). SV (50 vs. 57mL, p=0.02) and CO (4.5 vs. 5.7L/min, p=0.01) increased during PP, while HR (91 vs. 95bpm, p=0.42) and MAP (72 vs. 73mmHg, p=0.8) remained unchanged. While the FeNa was maintained.
during PP (0.15 vs. 0.15%, p=0.95), mean urine output was decreased to only 54% of baseline (0.94 vs. 0.51cc/kg/h, p=0.01). In this goal-directed group, mean fluid administered was 10cc/kg (SD) with 3 pigs receiving boluses (1, 2 and 3) and 3 pigs not receiving any additional fluid (Table VI). Figure 2 depicts the RCP for the three groups during the two time periods. In all three groups, significant increases in CVP and EtC02 were noted during PP.

While no pigs died, one pig (Group 1) became very tachycardic (HR up to 140bpm) towards the end of the study. The etiology of this was unclear. ED measurements at the end of PP were not available in one pig (Group 1) because of an equipment malfunction. Urine output was not available in 1 pig (Group 3) due to technical difficulties.

Discussion

Pneumoperitoneum is associated with decreased renal perfusion and urine output. Based on porcine studies, aggressive fluid hydration has been recommended to maintain RBF and preserve graft function during LLDN.(4, 73) However, overhydration can be deleterious. Although frank fluid overload (ie. pulmonary edema) is not common after LLDN, it may be underreported.(74) Excess perioperative fluid administration can affect recovery of gastrointestinal motility, tissue oxygenation, wound healing, coagulation and cardiac and pulmonary function.(6) Furthermore, evidence that fluid hydration improves graft function in recipients of laparoscopically procured kidneys is lacking.(89)

During LLDN, an optimal fluid management strategy would take into account individual differences in the effect of pneumoperitoneum on renal perfusion, presumably influenced by baseline hydration status and hemodynamics,
renal function, and individual neurohormonal responses. However, continuous monitoring of renal blood flow requires invasive or cumbersome techniques. The esophageal Doppler (ED) has been used in humans to guide optimal fluid administration and has proven effective in clinical studies.(90-92) We previously validated the use of ED under PP in a porcine model, demonstrating good correlation between the esophageal Doppler and Swan Ganz measurements of SV and CO.(93) We then assessed the relationship between preload and RCP, finding that only pigs with low preload at baseline (assessed by left ventricular end diastolic diameter echocardiographically) dropped their RCP under PP. (69) We have also used the ED to follow trends in CO and SV during PP, comparing an aggressively hydrated group with a control group. Using area under the curve analysis, we found a decline in SV and CO in the control group, but not in the hydrated group.(88) In this study, the pigs with low baseline SVs significantly dropped their RCP during PP (to a mean of 74% of baseline, p=0.049), while those with higher baseline SV maintained their RCP (106% of baseline, p=1).

In the present study, we used ED measurements of SV to guide fluid therapy under pneumoperitoneum. We tested whether this approach would enable the preservation of RBF seen with aggressive fluid hydration, while using lower volumes of fluid. The pilot study demonstrated that RCP was indeed maintained during PP with a mean of 2.4 boluses per pig. The randomized study demonstrated that using the ED to guide fluid therapy preserved RCP during PP. Because not all pigs received extra fluid, the ED is targeting only those pigs whose baseline volume status, or individual hemodynamic parameters, require additional fluid to maintain RCP during PP. Directly targeting only those animals who need extra fluid allows
for less fluid to be given to the group as a whole. In this study only 10cc/kg was
given to the goal-directed group while 25cc/kg was given to the bolus group. Thus
the ED allows for noninvasive, SV guided fluid administration that maintains renal
perfusion during PP at much lower fluid volumes than previously used.

The average number of boluses given in the pilot and the randomized study
are quite different (2.4 vs. 1). Also, while 6/7 pigs in the pilot study received
boluses, only 3/6 pigs in the randomized study received boluses. The most likely
reason for this difference is that in the randomized study pigs received 5cc/kg/h of
maintenance fluid during PP (in addition to any boluses received) while in the pilot,
pigs only received bolus fluid. Comparison of the average amount of fluid (12.1 vs
10cc/kg/h) between the two groups reveals that they were in fact quite similar.

While RCP was maintained in the 2 groups receiving additional fluid, urine
output was not. In contrast, both RCP and urine output were maintained in the pilot
study. In addition, in our previous study, urine output increased in an aggressively
hydrated group.(88) However, urine output was only obtained in 3/6 pigs in this
group because of technical difficulties. London et al.(8) noted that aggressive
hydration reversed the changes in RBF and urine output, but that impaired
creatinine clearance persisted. They suggested that while fluid therapy improved
RBF, it did not completely prevent renal dysfunction. Since both bolus and goal-
directed groups did not maintain their urine output while maintaining RCP, it is
likely that RCP is not the sole determinant of urine output during PP. While urine
output is used clinically as a marker of renal perfusion in non-PP conditions, this
may not be true during PP. Other factors specific to PP such as release of ADH,
atrial natriuretic peptide and aldosterone may play a significant role.
The fractional excretion of sodium (FeNa) was used as a marker of acute tubular function in this study. In previous work (88) we found an increase in the FeNa during PP. Unfortunately, the FeNa data demonstrates great variability both between groups and within groups. What is more, changes in the FeNa did not follow the trends seen in either RCP or urine output. For example, in the control group (where both RCP and urine output were decreased), the FeNa was maintained. This finding is difficult to explain physiologically. One possible explanation for the limited usefulness of FeNa is that values were already low during baseline, possibly from hypovolemia occurring during anesthesia and equipment setup prior to baseline. Thus, with FeNa values already very low during baseline, it may not be sensitive enough to demonstrate further changes in tubular function during PP. The data suggest therefore that the FeNa is not adequately sensitive or specific to changes in tubular function during PP in this porcine model.

Examination of measurements of FeNa during initial setup could perhaps answer some of these questions.

One important limitation to this study is the applicability of this porcine model to patients undergoing LLDN. Unlike the healthy, relatively homogenous population who undergo LLDN, porcine hemodynamics are highly sensitive to fluid balance, anesthesia, and acid-base status and thus exhibit a large amount of variability. (94) Also, in this model, a pressure of 15mmHg was used, although this is a relatively high intraabdominal pressure for animals of this size. While we perform LLDN with an intraabdominal pressure of 12mmHg in humans, we were previously unable to demonstrate decreases in RCP using a pressure of 12mmHg in this porcine model. (69) Finally, the pigs were studied in the left lateral decubitus
position while LLDN is usually performed on the left kidney (in right lateral decubitus). These opposing positions may alter hemodynamic parameters during PP.

In summary, using the ED to guide fluid therapy and maintain SV within 10% of baseline preserved RCP during PP. By only targeting pigs who needed extra fluid to preserve SV, RCP was maintained with less fluid administration (10-12 cc/kg/h) than in the bolus group (25cc/kg/h). Further studies need to be undertaken to validate this work and to assess its potential use in LLDN patients.
Figure 1: Fluid Algorithm used for Goal Directed Group

Measure SV baseline

Bolus 5cc/kg NS

PP 15mm CO2, Measure SV

SV decrease > 10%

SV not decreased < 10%

Wait 15 min and repeat measures, no further fluid until SV decreases by 10%

Legend:

SV = Stroke Volume, NS – normal saline, CO2 = carbon dioxide
Table I: Pilot Study: Amount of fluid received by each pig

<table>
<thead>
<tr>
<th>Pig #</th>
<th>Number of boluses</th>
<th>Total Fluid received (cc/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>2.4 (1.7)</td>
<td>12.1 (8.6)</td>
</tr>
</tbody>
</table>
Table II: Pilot Study: Hemodynamics at t=30 (end of Baseline) and t=110 (end of PP)

<table>
<thead>
<tr>
<th></th>
<th>Baseline t=30 (SD)</th>
<th>PP t=110 (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>97 (7)</td>
<td>100 (16)</td>
<td>0.7</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (13)</td>
<td>92 (22)</td>
<td>0.7</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>1.4 (1.1)</td>
<td>5.7 (1.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>EtCO₂ (mmHg)</td>
<td>29 (2)</td>
<td>38 (6)</td>
<td>0.5</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5.0 (1.4)</td>
<td>5.1 (1.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>50 (14)</td>
<td>52 (13)</td>
<td>0.3</td>
</tr>
<tr>
<td>RCP (mL/min/100g)</td>
<td>40 (9)</td>
<td>39 (9)</td>
<td>0.8</td>
</tr>
<tr>
<td>u/o (mL/kg/h)</td>
<td>1.4 (0.2)</td>
<td>1.3 (0.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>0.3 (0.25)</td>
<td>0.16 (0.13)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Legend:
HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (L/min); SV = stroke volume (ml); CVP = central venous pressure (mmHg); EtCO₂ = end-tidal CO₂ (mmHg); RCP = renal cortical perfusion (cc/min/100g); FeNa = fractional excretion of sodium (%); u/o = urine output (cc/kg/hr)
P value calculated by paired t-test, p < 0.05 considered significant.
Table III: Control Group: Hemodynamics at t=30 (end baseline) and t = 90 (end PP)

<table>
<thead>
<tr>
<th></th>
<th>Baseline t=30 (SD)</th>
<th>PP t=90 (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>103 (11)</td>
<td>110 (18)</td>
<td>0.2</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>73 (12)</td>
<td>70 (11)</td>
<td>0.5</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5 (2)</td>
<td>8 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>EtC0₂ (mmHg)</td>
<td>32 (3)</td>
<td>42 (3)</td>
<td>0.004</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.0 (2.5)</td>
<td>6.8 (1.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>57 (17)</td>
<td>61 (7)</td>
<td>0.5</td>
</tr>
<tr>
<td>RCP (mL/min/100g)</td>
<td>43 (11)</td>
<td>29 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>U/o (mL/kg/h)</td>
<td>1.46 (0.39)</td>
<td>0.69 (0.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>0.36 (0.41)</td>
<td>0.32 (0.5)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Legend:
HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (L/min); SV = stroke volume (ml); CVP = central venous pressure (mmHg); EtCO₂ = end-tidal CO₂ (mmHg); RCP = renal cortical perfusion (cc/min/100g); FeNa = fractional excretion of sodium (%); UO = urine output (cc/kg/hr)
P value calculated by paired t-test, p < 0.05 considered significant.
### Table IV: Bolus Group: Hemodynamics at t=30 (end baseline) and t = 90 (end PP)

<table>
<thead>
<tr>
<th></th>
<th>Baseline t=30 (SD)</th>
<th>PP t=90 (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>90 (10)</td>
<td>105 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>73 (15)</td>
<td>69 (4)</td>
<td>0.7</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5 (1)</td>
<td>9 (3)</td>
<td>0.005</td>
</tr>
<tr>
<td>EtCO$_2$ (mmHg)</td>
<td>32 (2)</td>
<td>43 (5)</td>
<td>0.009</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.4 (0.9)</td>
<td>6.6 (1.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>50 (14)</td>
<td>61 (15)</td>
<td>0.1</td>
</tr>
<tr>
<td>RCP (mL/min/100g)</td>
<td>46 (12)</td>
<td>40 (11)</td>
<td>0.5</td>
</tr>
<tr>
<td>U/o (mL/kg/h)</td>
<td>1.13 (0.3)</td>
<td>0.69 (0.18)</td>
<td>0.006</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>0.22 (0.19)</td>
<td>0.091 (0.083)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Legend:**
- HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (L/min); SV = stroke volume (mL); CVP = central venous pressure (mmHg); ETCO$_2$ = end-tidal CO$_2$ (mmHg); RCP = renal cortical perfusion (cc/min/100g); FeNa = fractional excretion of sodium (%); UO = urine output (cc/kg/hr)
- P value calculated by paired t-test, p < 0.05 considered significant.
Table V: Goal-Directed Group: Hemodynamics at \( t=30 \) (end baseline) and \( t=90 \) (end PP)

<table>
<thead>
<tr>
<th></th>
<th>Baseline ( t=30 ) (SD)</th>
<th>PP ( t=90 ) (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>91 (10)</td>
<td>95 (18)</td>
<td>0.4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>72 (9)</td>
<td>73 (9)</td>
<td>0.8</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>6 (2)</td>
<td>10 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>EtCO(_2) (mmHg)</td>
<td>33 (4)</td>
<td>41 (3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.5 (0.9)</td>
<td>5.7 (0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>50 (13)</td>
<td>57 (12)</td>
<td>0.02</td>
</tr>
<tr>
<td>RCP (mL/min/100g)</td>
<td>42 (10)</td>
<td>39 (14)</td>
<td>0.5</td>
</tr>
<tr>
<td>U/o (mL/kg/h)</td>
<td>0.94 (0.2)</td>
<td>0.51 (0.16)</td>
<td>0.01</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>0.15 (0.14)</td>
<td>0.15 (0.16)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Legend:
HR = heart rate (bpm); MAP = mean arterial pressure (mmHg); CO = cardiac output (L/min); SV = stroke volume (ml); CVP = central venous pressure (mmHg); EtCO\(_2\) = end-tidal CO\(_2\) (mmHg); RCP = renal cortical perfusion (cc/min/100g); FeNa = fractional excretion of sodium (%); UO = urine output (cc/kg/hr)
P value calculated by paired t-test, \( p < 0.05 \) considered significant.
Table VI: Goal-directed group: Amount of fluid received per pig

<table>
<thead>
<tr>
<th>Pig #</th>
<th>Number of boluses</th>
<th>Total Fluid received (cc/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>1 (1.2)</td>
<td>10 (6.3)</td>
</tr>
</tbody>
</table>
Figure 2: Renal Cortical Perfusion (RCP) comparing baseline and pneumoperitoneum for the 3 fluid groups

* = p<0.05
G. Conclusion:

"Always remember, a cat looks down on man, a dog looks up to man, but a pig will look man right in the eye and see his equal."

Winston Churchill

The hemodynamic changes that occur during PP are complex and diverse. With the advent of LLDN, it has become necessary to understand precisely what changes occur to renal perfusion and function during PP. This thesis has examined this subject and has evaluated strategies to maintain RBF during PP.

This work allows for some important conclusions to be made. Firstly, the systematic review demonstrates that renal perfusion and function are decreased during PP. The magnitude of this decrease is affected by the level of PP (16), baseline volume status (8), positioning (16), individual hemodynamics and preexisting renal reserve. The cause of this decrease is multifactorial (and beyond the scope of this thesis). However, the significance of this decrease is less evident since most experimental evidence suggests that changes to renal perfusion are not significant in healthy patients under normal conditions. This decrease may play a more significant role in prolonged cases or in situations where renal function is already compromised. Interestingly, there is experimental evidence to suggest that ischemic preconditioning (the prevention of organ damage from an ischemic insult as a result of a prior exposure to an ischemic period) limits reperfusion injury in the kidney. (95, 96) Thus a period of decreased RBF during PP might actually be
beneficial to graft function after transplantation. This concept certainly warrants more study.

Secondly, aggressive fluid hydration preserves renal perfusion during PP. Our porcine model comparing maintenance with aggressive fluid hydration demonstrated that renal perfusion was decreased in the maintenance group but preserved in the aggressively hydrated group. This is similar to previous work in a porcine model. (8) However, aggressive fluid hydration is not a benign therapy and it does not seem reasonable to give all patients, regardless of their individual hemodynamics and volume status, aggressive fluid hydration. This concept was the impetus to investigate a way to individualize fluid therapy in an attempt to decrease the amount of fluid administered while still maintaining renal perfusion.

In the final study, we demonstrated that the esophageal Doppler could be used to guide fluid administration based on changes in stroke volume during PP. This resulted in a preservation of renal perfusion while using less fluid than in a similar bolus fluid group. The esophageal Doppler thus offers a noninvasive and selective option to guide fluid administration and maintain RBF during PP. Instead of bolusing all patients with large amounts of fluid, one can select only those patients who need extra fluid by targeting their individual hemodynamic parameters.

Another important point to underscore is that measurement of renal function during PP in the acute setting is problematic. We have demonstrated that measurement of urine output during PP does not provide a reliable indicator of renal perfusion during PP. Our experience with the fractional excretion of sodium also did not provide consistent results enabling approximation of renal perfusion.
during PP. Future research projects may wish to evaluate other ways to measure renal function acutely during PP.

Finally, it must be remembered that these studies were undertaken in a porcine model with all of its inherent difficulties and sources of error. Subsequent work should evaluate the use of the esophageal Doppler in guiding fluid administration during PP in humans. Further research will hopefully clarify the best way to optimize renal perfusion in humans during LLDN. This would ultimately benefit both renal donors and recipients, which is the ultimate objective.
References:


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95. Toosy N, McMorris EL, Grace PA, Mathie RT. Ischaemic preconditioning protects the rat kidney from reperfusion injury. BJU Int 1999;84(4):489-94.

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