

Effect of laparoscopic antireflux surgery upon renal blood flow

Chandrakanth Are, M.D., Michael Kutka, M.D., Mark Talamini, M.D.*,
Jeffrey Hardacre, M.D., Mario Mendoza-Sagaon, M.D., Eric Hanley, M.D.,
Thomas Toung, M.D.

Department of Surgery, John Hopkins University School of Medicine, 600 N. Wolfe Street, Blalock 665, Baltimore, MD 21287, USA

Manuscript received December 17, 2001; revised manuscript January 10, 2002

Abstract

Background: Hypercapnia and local pressure effects unique to CO₂ base minimally invasive surgery alter renal blood flow. We have demonstrated laparoscopic antireflux surgery to have an additional impact upon hemodynamics (decreased cardiac output), potentially extending known effects upon renal blood flow.

Methods: We measured renal blood flow with radioactive microspheres during laparoscopic antireflux surgery in a porcine model. Six pigs were anesthetized, monitoring lines were placed, and microspheres injected five time points associated with a laparoscopic antireflux operation. After euthanasia kidneys were retrieved and fixed, and representative samples counted for radioactivity specific for each of the five time points.

Results: The greatest reduction in renal blood flow was 36% below baseline ($p < 0.05$). Concurrently, cardiac output had a maximum reduction of 39%.

Conclusions: Laparoscopic Nissen fundoplication in this pig model is associated with a significant reduction in renal blood flow, probably related to reduction in cardiac output. Caution is warranted when considering laparoscopic antireflux surgery in patients with a compromised renal blood flow. © 2002 Excerpta Medica, Inc. All rights reserved.

Keywords:

Laparoscopy is associated with alterations in blood flow to organ systems in the body [1–4]. Hypercapnia associated with respiratory acidosis, seen in conditions such as chronic obstructive airway disease, has been shown to cause reduced renal blood flow and urine output [5,6]. Carbon dioxide pneumoperitoneum used during laparoscopic surgery can therefore be expected to alter renal blood flow and renal function. Such an effect has been reported by several authors [7–9]. Ben-David et al. reported a case of acute renal failure following laparoscopic cholecystectomy [10]. Studies have been performed in both animal models with only abdominal insufflation [7–9] and in humans [10,11] undergoing laparoscopic cholecystectomy. Laparoscopic antireflux surgery is unique, in that it exposes both the peritoneum and the mediastinum to CO₂ under pressure, potentially creating additional influence on the cardiovascular system both by direct effect, and a more widespread

dispersion of CO₂. Since other hemodynamic parameters appear to be more drastically effected by this invasion of two cavities [12], renal blood flow may be adversely affected during laparoscopic Nissen fundoplication.

Renal ischemia caused by hypercapnia can increase plasma renin activity by a variety of mechanisms [13–15]. The main effects of increased plasma renin activity are on the systemic hemodynamics or cardiac function and are mediated via angiotensin-regulated vasoconstriction. Increased plasma renin activity can cause pulmonary vasoconstriction, leading to pulmonary hypertension, possibly compromising cardiac function.

A variety of means exist to study blood flow. Doppler flow probes directly measure the velocity of blood flow within a target blood vessel in real time. However, the placement of flow probes requires an invasive intervention itself. The use of radioactive microspheres is cumbersome, but provides a precise, reproducible means of directly measuring blood flow to an organ. The technique depends upon the intravascular injection of a small volume of microspheres, which circulate throughout the arterial tree, but are

* Corresponding author. Tel.: +01-410-955-0377; fax: +1-410-614-9493.

just too large to pass through capillary beds, where they become lodged. They are distributed throughout the body in a manner proportionate to the blood flow at the time of the injection. Each particular radioisotope can only be used for one time point measurement, providing a snapshot of the distribution of blood flow at that time. As a limited number of radioisotopes exist, a limited number of time points can be examined.

The aim of this study was to determine if changes in renal blood flow occur during laparoscopic Nissen fundoplication in a porcine model by using radioactive microspheres as a direct blood flow measurement.

Materials and methods

Six female pigs (25–30 kg) were used according to a protocol approved by the Johns Hopkins University Animal Care Committee. Our methodology and surgical technique has been reported previously [12]. Pigs were anesthetized with ketamine (15 mg/kg) and maintained with bolus intravenous injections of pentobarbital (30 mg/kg) and continuous infusion of fentanyl (2 μ g/kg/h). Animals were paralyzed with a continuous infusion of pancuronium (0.2 mg/kg/h) and ventilated mechanically via an oral cuffed endotracheal tube. Body temperature was maintained between 38 and 39 °C with a heating pad and lamp. Hydration was maintained by infusion of Lactated Ringer's solution at 10 mL/kg/h. Oxygenation was maintained near 100% by a 10 L/min flow. The following monitoring lines were placed: (1) central arterial catheter through the right femoral artery with the tip in the thoracic aorta; (2) central venous catheter through the right femoral vein with the tip in the right atrium (5F balloon-tipped pulmonary artery catheter); (3) abdominal venous caval pressure (subdiaphragmatic) through the left femoral vein; (4) wedge pressure, and thermolulution catheter for cardiac output through the left external jugular vein (5F balloon-tipped pulmonary artery catheter); and (5) left pleural catheter through a fourth or fifth intercostal space minithoracotomy. In addition, a 7 Fr pulmonary artery catheter was placed with its tip in the left ventricle for injection of microspheres. Another catheter was introduced with the tip in the abdominal aorta for extracting a reference sample for each animal. Pressure data were collected continuously. Arterial blood gas samples were measured for pH, $p\text{CO}_2$, HCO_3^- , and $p\text{O}_2$. Following preparation, a Veress needle was inserted, and the abdomen insufflated with CO_2 to a pressure of 15 mm of mercury. Five 10–12 mm trocars were placed in a standard pattern to accomplish a Nissen fundoplication. The gastroesophageal junction was dissected by separating the right and left crus and the diaphragmatic attachments from the distal esophagus and the gastroesophageal junction. A fundoplication was performed with three sutures, each 1 cm apart. Further details of the operative procedure are as described previously [12].

Bloodflow measurements

Regional blood flow was measured with radioactive microspheres according to the reference-sample method of Heymann et al. [6] 15 μ m plastic spheres (NEN Research Products, Boston, MA) labeled with one of five isotopes; $^{95}\text{niobium}$ (Nb), $^{46}\text{scandium}$ (Sc), $^{104}\text{ruthenium}$ (Ru), cobalt (Co), or ^{113}tin (Sn) were used to measure organ flow at five different time points in each animal. A dose of 5×10^6 microspheres was injected into the left ventricle over 30 s, followed by a 20 cc flush of saline. The isotopes were administered in the following sequence: 20 min after the initiation of anesthesia (baseline), 20 min after establishment of the pneumoperitoneum with CO_2 (pneum 20), 20 min after initiation of dissection of the esophageal hiatus (diss 20), 40 min after initiation of dissection (diss 40), and 20 min (desuff 20) after the release of pneumoperitoneum. The reference sample was recovered at a rate of 3.8 cc/min for a period of 2 min after each isotope was injected. After administration of the last radioactive isotope, the animals were euthanized while still under anesthesia with an intravenous overdose of KCl. The kidneys were retrieved and fixed in 10% formalin for 3–5 days. Each specimen was then weighed. Following that, assays were performed, tabulated, and analyzed on each kidney, as well as reference blood samples, in a Minox 5000 Series gamma scintillation spectrometer (Packard Instrument Company, Downer's Grove, IL).

Data analysis

Blood flow was calculated according to a standardized computer algorithm derived from the radiation counts obtained from the scintillation counter as previously reported [6] (Microflo version 2.01, The Johns Hopkins University School of Medicine, Baltimore, MD). The data were analyzed using statistical software (Microsoft Excel). The student's t test was used, and statistical significance was defined as $p \leq 0.05$.

Results

The changes in renal blood flow, cardiac output and PaCO_2 are summarized in Table 1. There was an initial mild increase in renal blood flow in the early stages of the procedure by 13% (not statistically significant). At diss 40, once the pneumomediastinum was well established, renal perfusion was 31% below baseline ($p \leq 0.04$). This reduction in renal blood flow persisted even after desufflation (desuff 20) decreasing to a nadir of 36% ($p \leq 0.04$). Cardiac output showed a downward trend from baseline at all stages of the procedure with a nadir of 41% at the "desuff 20" time-point. PaCO_2 increased upon initiation of the pneumoperitoneum and remained between 33% and 46% above baseline until 40 min after desufflation, when it returned to baseline.

Table 1

Comparison of renal blood flow (RBF) as measured by radioisotope microspheres (cc/min), cardiac output (cc/min), and PaCO₂ at baseline (BL), 20 min after establishment of pneumoperitoneum (Pneum20), 20 and 40 min after initiation of hiatal dissection (Diss20, Diss40), and 20 min after desufflation of the abdomen; percent change from baseline is in parentheses

	BL	Pneum20	Diss20	Diss40	Desuff20
RBF	299.2	337.5 (+12.7%)	339.2 (+13.3%)	206.9 (−31.1%)	190 (−36.4%)
CO	3900	2770 (−29%)	2570 (−34%)	2490 (−36%)	2390 (−38.7%)
PaCO ₂	30.15	43.4 (+43%)	40.3 (+33%)	44.4 (+46%)	44.4 (+46%)

Key hemodynamic measures are shown in Table 2. Mean arterial pressure increased by 12% over baseline during mediastinal dissection. Wedge pressure and central venous pressure increased dramatically by 76% and 275%, respectively, most likely reflecting the direct effect of pneumoperitoneum upon the intrathoracic pressure and the vena cava. PaCO₂ levels increased to a peak of 46% above baseline during the experiment. No attempt was made to maintain the CO₂ at a fixed level (range 30–45). The respiratory rate was kept between 12 and 16. The other measured parameters, such as hemoglobin, oxygen saturation, and pulse, remained more or less the same throughout the entire procedure.

Discussion

Renal blood flow accounts for slightly less than 25% of the cardiac output. The blood flow through the renal cortex (4–5 mL/kg/min) and medulla (0.2–0.03 mL/kg/min) is relatively large in comparison to other tissues (e.g. 0.5 mL/kg/min in the brain). This flow is necessary for essential functions such as glomerular filtration and tubular reabsorption and secretion. Alterations in renal perfusion can therefore have significant effects. Factors that can affect renal blood flow include general hemodynamics, the autonomic nervous system, the renin-angiotensin pathway, including antidiuretic hormone (ADH) or arginine vasopressin (AVP), and metabolic factors such as pCO₂ and pO₂. Autoregulation (metabolic and myogenic) of renal blood flow also plays a major role by varying the renal vascular resistance.

Changes in carbon dioxide and oxygen levels are especially important in regulating renal blood flow. This has been well documented in patients with chronic obstructive pulmonary disease [5,6,16–18]. Hypercapnia causes a rapid and significant increase in pulsatility index and renal vascular resistance leading to a fall in renal blood flow, as demonstrated in several animal studies [19–21] and as seen in human patients with respiratory failure [5,6,19–21]. Hypercapnic subjects with chronic obstructive pulmonary disease also fail to improve their renal blood flow with added oxygen, in comparison to normocapnic subjects. Hypercapnia causes the release of noradrenaline both systemically via chemoreceptors and locally in the kidneys via the sympathetic efferents. This causes renal vasoconstriction and reduced renal blood flow. Hypoxia also modifies renal blood flow. Although supplemental oxygen can reverse the effects of hypoxia on renal blood flow, addition of CO₂ negates these beneficial effects. These facts emphasize the importance and dominance of CO₂ in regulating renal blood flow in the presence of physiologic levels of pO₂, or even hyperoxemia [22].

Renin-angiotensin activation during hypercapnia leads to increased plasma renin activity that can further compromise renal blood flow. Release of renin is regulated via (1) intrarenal baroreceptors, (2) macula densa, (3) renal sympathetic nerves, and (4) blood borne substances such as adrenaline and noradrenaline [14]. Hypercapnia increases plasma renin activity either via stimulation of the sympathetic nervous system at a local or systemic level or by direct intrarenal effects on the juxta-glomerular apparatus. Fujii and Zehr [13] have shown that plasma renin activity

Table 2

Hemodynamic, pulmonary, respiratory data, and hemoglobin levels; values are average ± SEM. Numbers in parentheses denote percent increase or decrease from baseline (an asterisk denotes a change less than 10% from baseline)

	O2 Sat	Pulse (per min)	RR (per min)	CVP (mm Hg)	MAP (mm Hg)	Wedge (mm Hg)	PaCO ₂ (mm Hg)	HGB (g/dL)
Baseline	96.5 ± 1.44	142.8 ± 22.2	15.5 ± 1.20	2.42 ± 2.57	131.5 ± 12.8	4.3 ± 0.49	30.15 ± 2.04	9.64 ± 1.0
Pneumoperitoneum 20	98 ± 0.58*	174 ± 15.6 (+22)	14.5 ± 1.20*	8.17 ± 5.04 (+237)	135.0 ± 11.2*	5.8 ± 1.16 (+34)	43.4 ± 2.9 (+43)	9.7 ± 0.60*
Dissection 20	95.5 ± 2.18*	173.5 ± 18.8 (+22)	15.5 ± 1.2*	8.67 ± 4.54 (+258)	148.3 ± 8.51 (+12)	6.8 ± 0.92 (+58)	40.3 ± 4.21 (+33)	10.05 ± 0.99*
Dissection 40	93 ± 4.97*	180 ± 24.39 (+26)	16.5 ± 1.025*	9.08 ± 4.55 (+275)	148.8 ± 7.7 (+12)	7.6 ± 1.69 (+76)	44.4 ± 3.5 (+46)	9.22 ± 1.24*
Desufflation 20	95.5 ± 2.18*	177.5 ± 21.8 (+24)	14.5 ± 1.20*	4.33 ± 4.79 (+78)	132.8 ± 9.4*	4.6 ± 0.51*	44.4 ± 3.5 (+46)	9.7 ± 0.91*

increases in direct proportion to PaCO₂ levels in mongrel dogs. Plasma renin activity levels can also increase in response to decreased renal blood flow. Hypercapnia associated with CO₂ pneumoperitoneum can therefore be expected to alter renal blood flow. In addition to the factors mentioned above, CO₂ pneumoperitoneum can affect renal blood flow by direct mechanical effects.

In the current study, there was a statistically insignificant increase in renal blood flow of 13.3% from baseline in the initial stages of the procedure (“pneum 20” and “diss 20”). This was accompanied by an increase in PaCO₂ of 43%. Renal vasodilation resulting from increased PaCO₂ can increase renal blood flow (metabolic theory of autoregulation) overriding other factors capable of reducing renal perfusion [13,14]. This occurred despite a reduction in cardiac output (nadir of –34% at diss 20, $p < 0.005$) was also noted, which was probably due to direct mechanical compression of the PP.

At the “diss 40” stage, the renal blood flow was by 31.1% ($p < 0.05$) below baseline, with the PaCO₂ levels still remaining 46% above baseline. Although the initial effects of hypercapnia increase renal blood flow temporarily, prolonged hypercapnia leads to a reduction of renal perfusion as noted in our study. The CO₂ mediated vasodilation is short lived, after which the vascular tone returns to normal or may even increase. In addition, hypercapnia related renin-angiotensin activation [5,6,13–15] and sympathetic activation with the release of noradrenaline can potentiate the vasoconstrictor effects of sustained hypercapnia, leading to renal ischemia. Cardiac output dropped a bit further (–36%, $p < 0.05$) despite a lack of change in PaCO₂ levels and pneumoperitoneum pressures. This could be due to the vasoconstrictor effects of the renin-angiotensin system on the pulmonary circulation, which would further compromise cardiac function.

Renal blood flow continued to fall to a nadir of 36% ($p < 0.05$) below baseline, at a timepoint 20 min after desufflation (desuff 20). The drop in renal blood flow even after desufflation underscores the importance of hypercapnia on renal circulation (PaCO₂ 40% above baseline) [22–24]. Similarly, we noted a maximal reduction in cardiac output (41%, $p < 0.005$) at the same time point. Peak renal ischemia may have stimulated maximal increases in renin levels that can explain the continued fall in cardiac output despite desufflation.

The similar changes in renal blood flow and cardiac output in the later stages suggest a possible correlation between renal ischemia and cardiac function. Reduced cardiac output can certainly cause renal ischemia, and could be the initiating event. Such ischemia activates the renin-angiotensin pathway and the sympathetic nervous system leading to further compromise in cardiac function. On the other hand, increases in renin levels due to hypercapnia could be the initiating event leading to reduction in cardiac output. Since we did not measure renin levels in our study,

the cause and effect relation between renal ischemia and cardiac function is difficult to ascertain.

In summary, we conclude that laparoscopic Nissen fundoplication is associated with significant effects on renal perfusion. These effects seem to be related to acidosis produced by the inherent metabolic properties of carbon dioxide. In addition, renal ischemia secondary to hypercapnia can have effects on the cardiac function. Caution therefore needs to be exercised when subjecting patients with underlying cardiac or renal disease to laparoscopic Nissen fundoplication. Similarly, patients with chronic obstructive airway disease or pulmonary hypertension need to be cautioned about possible worsening of renal function after laparoscopic surgery. Further studies into the correlation between renal perfusion and cardiac function in the setting of pneumoperitoneum-based surgery are warranted.

Acknowledgment

This work was supported by a generous grant from the United States Surgical Corporation/TYCO Healthcare, Norwalk, Connecticut.

References

- [1] Fujii Y, Tanaka H, Tsuruoka S, Toyooka H, Amaha K. Middle cerebral artery blood flow velocity increases during laparoscopic cholecystectomy. *Anesth Analg* 1994;78:80–3.
- [2] Bloomfield GL, Ridings PC, Blocher CR, et al. Effects of increased intra-abdominal pressure upon intracranial and cerebral perfusion pressure before and after volume expansion. *J Trauma* 1996;40:936–41.
- [3] Diebel LN, Wilson RF, Dulchavsky SA, Saxe J. Effect of increased intra-abdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. *J Trauma* 1992;33:282–3.
- [4] Eleftheriadis E, Kotzampassi K, Botsios D, et al. Splanchnic ischemia during laparoscopic cholecystectomy. *Surg Endosc* 1996;10:324–6.
- [5] Akoi H, Hilgers H, Brown EB, Kittle CF. Hemodynamic effect of hypercapnia. *Surg Forum* 1963;14:232–4.
- [6] Brooker W, Ansell JS, Brown EB. Effect of respiratory acidosis on renal blood flow. *Surg Forum* 1959;10:867–72.
- [7] Guler C, Sade M, Kirkali Z. Renal effects of carbon dioxide insufflation in rabbit pneumoretroperitoneum model. *J Endourol* 1998;12:367–70.
- [8] Chiu AW, Chang LS, Birkett DH, Babayan RK. The impact of pneumoperitoneum, pneumoretroperitoneum, and gasless laparoscopy in the systemic and renal hemodynamics. *J Am Coll Surg* 1995;181:397–406.
- [9] McDougall EM, Bennett HF, Monk TG. Functional MR imaging of the porcine kidney: physiologic changes of prolonged pneumoperitoneum. *JSL* 1997;1:29–35.
- [10] Ben-David B, Croitoru M, Gaitini L. Acute renal failure following laparoscopic cholecystectomy: a case report. *J Clin Anesth* 1999;11:486–9.
- [11] Iwase K, Takenaka H, Ishizaka T, et al. Serial changes in renal function during laparoscopic cholecystectomy. *Eur Surg Res* 1993;25:203–12.
- [12] Talamini MA, Mendoza-Sagaon M, Gitzelmann CA, et al. Increased mediastinal pressure and decreased cardiac output during laparoscopic Nissen fundoplication. *Surgery* 1997;122:345–53.

- [13] Fujii H, Zehr JE. The effects of respiratory acidosis on plasma renin activity in the dog. *Jpn Circ J* 1975;39:1115–21.
- [14] Fujii H, Zehr JE, Mitsuyama T, et al. The influence of renal sympathetic nerves on renal hemodynamic and renin responses during hypercapnia in dogs. *Jpn Circ J* 1985;49:1185–9.
- [15] Rose CE, Walker BR, Erickson A, et al. Renal and cardiovascular responses to acute hypercapnic acidosis in conscious dogs: role of renin-angiotensin. *J Cardiovasc Pharmacol* 1982;4:676–87.
- [16] Kilburn KH, Dowell AR. Renal function in respiratory failure. Effects of hypoxia, hyperoxia and hypercapnia. *Arch Intern Med* 1982;127:754–62.
- [17] Howes TQ, Deane CR, Levin GE, et al. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. *Am J Respir Crit Care Med* 1995;151:378–83.
- [18] Farber MO, Roberts LR, Weinberger MH, et al. Abnormalities of sodium and H₂O handling in chronic obstructive lung disease. *Arch Intern Med* 1982;141:1326–30.
- [19] Daugherty RM Jr, Scott JB, Dabney JM, Haddy FJ. Local effects of O₂ and CO₂ on limb, renal, and coronary vascular resistances. *Am J Physiol* 1967;213:1102–10.
- [20] Zillig B, Schuler G, Truniger B. Renal function and intrarenal hemodynamics in acutely hypoxic and hypercapnic rats. *Kidney Int* 1978;14:58–67.
- [21] Stone JE, Wells J, Draper WB, Whitehead RW. Changes in renal blood flow in dogs during inhalation of 30% carbon dioxide. *Am J Physiol* 1958;194:115–9.
- [22] Sharkey RA, Mulloy EM, O'Neill SJ. The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with acute exacerbation of COPD. *Chest* 1999;115:1588–92.
- [23] Sharkey RA, Mulloy EM, O'Neill SJ. Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. *Eur Respir J* 1998;12:653–7.
- [24] Shirahata M, Nishino T, Honda Y, et al. Effects of hypercapnia on renal nerve activity. *Jpn J Physiol* 1985;35:391–9.