Abdominal Insufflation With CO_2 Causes Peritoneal Acidosis Independent of Systemic pH

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We have shown that the inflammation-attenuating effects of CO_2 pneumoperitoneum during laparoscopy are not due to changes in systemic pH. However, acidification of peritoneal macrophages in an in vitro CO_2 environment has been shown to reduce LPS-mediated cytokine release. We tested the hypothesis that the peritoneum is locally acidotic during abdominal insufflation with CO_2—even when systemic pH is corrected. Rats (n = 20) were anesthetized and randomized into two groups: continued spontaneous ventilation (SV) or intubation and mechanical ventilation (MV). All animals were then subjected to abdominal insufflation with CO_2. Mean arterial pH among SV rats decreased significantly from baseline after 15 and 30 minutes of CO_2 pneumoperitoneum (7.329 → 7.210 → 7.191, $P < 0.05$), while arterial pH among MV rats remained relatively constant (7.388 → 7.245 → 7.316, P = NS). In contrast, peritoneal pH dropped significantly from baseline and remained low for both groups during CO_2 abdominal insufflation (SV 6.74 → 6.41 → 6.40, $P < 0.05$; MV 6.94 → 6.45 → 6.45, $P < 0.05$). In a second experiment, rats (n = 10) were randomized to receive abdominal insufflation with either CO_2 or helium. Abdominal insufflation with helium did not significantly affect peritoneal pH (7.10 → 7.02 → 6.95, P = NS), and the decrease in pH among CO_2-insufflated animals was significant compared with helium-insufflated animals ($P < 0.05$). Peritoneal pH returned to baseline levels in all groups within 15 minutes of desufflation in both experiments. A significant local peritoneal acidosis occurs during laparoscopy which is specifically attributable to the use of CO_2 and which is independent of systemic pH. These data provide additional evidence that localized peritoneal acidosis is central to the mechanism of CO_2-mediated attenuation of the inflammatory response following laparoscopic surgery. (J GASTROINTEST SURG 2005;9:1245–1252)

KEY WORDS: Carbon dioxide, pH, acidosis, pneumoperitoneum, laparoscopy

The laparoscopic approach to surgery of the alimentary tract is now well accepted for appropriate procedures. Patients undergoing minimally invasive abdominal surgery benefit from less postoperative pain, shorter postoperative ileus, shorter hospital stays, a more rapid return to preoperative activity, and superior cosmesis compared with their laparotomized counterparts.[1–4] Because clinical data have shown that the release of inflammatory mediators is less following laparoscopy than following conventional open surgery,[5,6] the molecular mechanisms underlying the improved results observed following laparoscopic surgery have become an area of active investigation.

Work from our laboratory has shown that peritoneal insufflation with CO_2 blunts the hepatic expression of acute phase genes in laparoscopic models of perioperative sepsis.[7,8] Furthermore, we have recently shown that abdominal insufflation with CO_2, but not helium or air, significantly increases survival among animals with LPS-induced sepsis and that the protective effect of CO_2 pneumoperitoneum is even capable of "rescuing" animals from abdominal sepsis that have already undergone a laparotomy.[9]

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We have also provided evidence suggesting that the mechanism of CO_2 insufflation–specific reduction of the inflammatory response involves interleukin (IL)-10–mediated downregulation of tumor necrosis factor (TNF)-α.[9,10]

Finally, we have shown that the attenuation of inflammation when CO_2 pneumoperitoneum is used during laparoscopy are not due to changes in systemic pH.[11] However, macrophages harvested from CO_2-insufflated peritoneal cavities, as well as peritoneal macrophages acidified in an in vitro CO_2 environment, exhibit blunted proinflammatory cytokine release profiles in response to endotoxin stimulation. Therefore, we hypothesized that the peritoneum becomes locally acidotic during pneumoperitoneum—even when systemic pH is corrected. Additionally, we hypothesized that this effect occurs because of the unique biological properties of CO_2, and thus does not occur when pneumoperitoneum is achieved with a biologically inert gas such as helium.

MATERIAL AND METHODS

General Procedures

All procedures were part of an animal protocol reviewed and approved by the Johns Hopkins Medical Institutions Animal Care and Use Committee. Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA), 10–12 weeks old and weighing 250–300 g, were housed in cages where standard chow and water were available ad libitum. The animal housing environment was maintained at a temperature of 22 °C with a 12-hour light/dark cycle. The rats were acclimatized to their environment for 3–5 days upon arrival and then fasted overnight prior to intervention. All procedures were performed under aseptic conditions. Anesthesia was induced in an isoflurane chamber for all animals. Maintenance vaporized isoflurane was delivered through a nosecone and, eventually, through an endotracheal tube in the mechanically ventilated animals. Rats randomized to receive mechanical ventilation were intubated with a 14-gauge angiocatheter under endoscopic vision using a 3-mm laparoscope as a laryngoscope as previously described.[12] Ventilator settings for this group were a tidal volume of 2.5 mL and a respiratory rate of 100 breaths/min (minute ventilation = 250 mL/min or approximately 900 ml/kg/min). Catheters for arterial and venous blood sampling made from polyethylene tubing with an outer diameter of 0.965 mm and an internal diameter of 0.58 mm flushed with heparinized saline were placed in the right femoral arteries and left femoral veins under direct vision through 1-cm groin incisions. Arterial and venous blood was analyzed using a portable handheld blood gas analyzer (iStat; Abbott, East Windsor, NJ). Pneumoperitoneum was achieved by delivering either carbon dioxide (CO_2) or helium through an 18-gauge angiocatheter placed percutaneously through the abdominal wall. Insufflation pressure was maintained at 4 mm Hg using a laparoscopic insufflator (Olympus America Inc., Melville, NY). Peritoneal pH was measured using an Accumet AB15 Basic benchtop pH meter (Fisher Scientific International Inc., Hampton, NH). An MI-508 esophageal pH microelectrode (Microelectrodes Inc., Bedford, NH) was placed in a dependant portion of the peritoneal cavity posterior to the liver such that the tip of the catheter was constantly bathed in the small amount of peritoneal fluid present there. The electrode was positioned through the abdominal wall via a percutaneously placed 14-gauge angiocatheter. An MI-402 reference electrode (Microelectrodes Inc.) was inserted into the rectum through the anus. The system was calibrated before each animal by immersing the tips of the pH and reference electrodes in sterile commercially prepared buffer solutions (Fisher Scientific, Fair Lawn, NJ) of pH 7.0 and pH 4.0. All animals were euthanized via anesthetic overdose at the end of the experiments. Figure 1 shows the setup for these procedures.

Effect of Mechanical Ventilation on Vascular-Peritoneal pH Gradient

Rats (n = 20) were anesthetized and randomized into two groups: continued spontaneous ventilation or intubation and mechanical ventilation. Femoral artery and vein catheters were inserted and a peritoneal pH probe was placed behind the liver as described above. Rats randomized to the mechanical ventilation group were intubated and mechanically ventilated. Baseline pH measurements were obtained (t = 0 minutes), and all animals were then subjected to abdominal insufflation with CO_2 at 4 mm Hg for 30 minutes. Additional pH measurements were obtained after 15 minutes of insufflation (t = 15 minutes), at the end of 30 minutes of insufflation (t = 30), 15 minutes following desufflation (t = 45 minutes), and 30 minutes following desufflation (t = 60 minutes).

Effect of CO_2 or Helium Gas on Vascular-Peritoneal pH Gradient

Rats (n = 10) were anesthetized and then randomized to receive abdominal insufflation with either

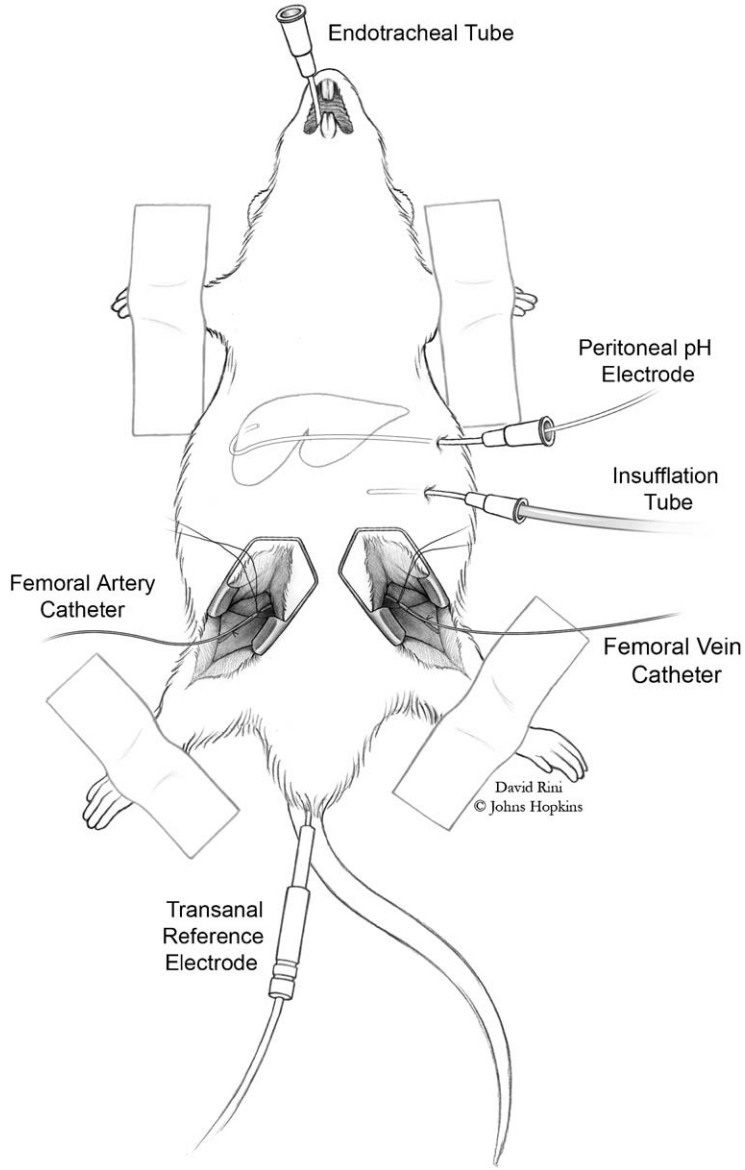

Fig. 1. Setup for rodent pneumoperitoneum, mechanical ventilation, arterial and venous blood sampling, and peritoneal pH monitoring.

CO_2 or helium gas. Femoral artery catheters and peritoneal pH probes were inserted as described above. All animals maintained spontaneous ventilation, receiving vaporized isoflurane through a nosecone. pH measurements were again obtained at baseline (t = 0 minutes), after 15 minutes of insufflation (t = 15 minutes), at the end of 30 minutes of insufflation (t = 30), 15 minutes following desufflation (t = 45 minutes), and 30 minutes following desufflation (t = 60 minutes).

Data Analysis

Mean arterial blood, venous blood, and peritoneal pH measurements after insufflation were compared with average baseline parameters using the Student's *t* test. Mean change in arterial blood and peritoneal pH following insufflation with CO_2 was compared with the mean change following insufflation with helium using the Student's *t* test. Differences between groups were considered significant when $P \leqslant 0.05$. Analysis was performed using Excel software (Microsoft Corporation, Seattle, WA).

RESULTS

In order to determine the effect of pneumoperitoneum with and without mechanical ventilation on both peritoneal and systemic acid-base status, pH

was measured in three compartments (arterial, venous, and peritoneal) before, during, and after 30 minutes of abdominal insufflation with CO_2 (Fig. 2). Mean arterial pH among spontaneously ventilated rats decreased significantly from baseline after 15 and 30 minutes of CO_2 pneumoperitoneum (7.329 ± 0.065 → 7.210 ± 0.022 → 7.191 ± 0.056, $P < 0.05$ for both time points, mean ± SD), while arterial pH among mechanically ventilated rats remained relatively constant (7.388 ± 0.022 → 7.245 ± 0.136 → 7.316 ± 0.087, P = NS for both time points, mean ± SD). In contrast, peritoneal pH dropped significantly from baseline and remained low for both groups during CO_2 abdominal insufflation (spontaneous ventilation 6.74 ± 0.32 → 6.41 ± 0.40 → 6.40 ± 0.42, $P < 0.05$ for both time points, mean ± SD; mechanical ventilation 6.94 ± 0.25 → 6.45 ± 0.26 → 6.45 ± 0.24, $p < 0.05$ for both time points, mean ± SD). Peritoneal pH returned to baseline levels in both groups within 15 minutes of desufflation. Venous pH also dropped significantly from baseline and remained low for both groups during insufflation with CO_2 (spontaneous ventilation 7.323 ± 0.023 → 7.094 ± 0.007 → 7.078 ± 0.004, $P < 0.05$ for both time points, mean ± SD; mechanical ventilation 7.386 ± 0.040 → 7.148 ± 0.044 → 7.166 ± 0.056, $P < 0.05$ for both time points, mean ± SD).

To confirm that the peritoneal pH effects observed with pneumoperitoneum were due specifically to the biologic activity of CO_2 rather than the mechanical effects of abdominal insufflation, the effect on pH of CO_2 pneumoperitoneum was compared with that of helium pneumoperitoneum (Fig. 3). Abdominal insufflation with helium did not significantly affect peritoneal pH (7.10 ± 0.06 → 7.02 ± 0.09 → 6.95 ± 0.13, P = NS for both time points, mean ± SD). A significant decrease in peritoneal pH over time among CO_2-insufflated animals was again observed (7.16 ± 0.04 → 6.63 ± 0.04 → 6.44 ± 0.26, $p < 0.05$ for both time points, mean ± SD), and this decrease was also found to be significant compared with the helium-insufflated animals ($P < 0.05$ for both time points). Peritoneal pH returned to baseline levels among animals insufflated with both CO_2 and helium within 15 minutes of desufflation.

DISCUSSION

A great deal of evidence now contests the once generally accepted notion that smaller incisions alone account for the observed differences between laparoscopic and conventional approaches to surgery of the abdominal viscera. Pneumoperitoneum has been shown to alter host physiology both through the mechanical effects of abdominal distention/pressure[10,13–17] and through the unique biological activity of carbon dioxide gas.[7–11,18–21] While CO_2 pneumoperitoneum clearly has specific effects on the body's response to inflammation and injury, the mechanism connecting CO_2 insufflation at one end with altered immune function at the other is still relatively disjointed.

One potential target of the mechanism underlying CO_2-pneumoperitoneum–mediated attenuation of

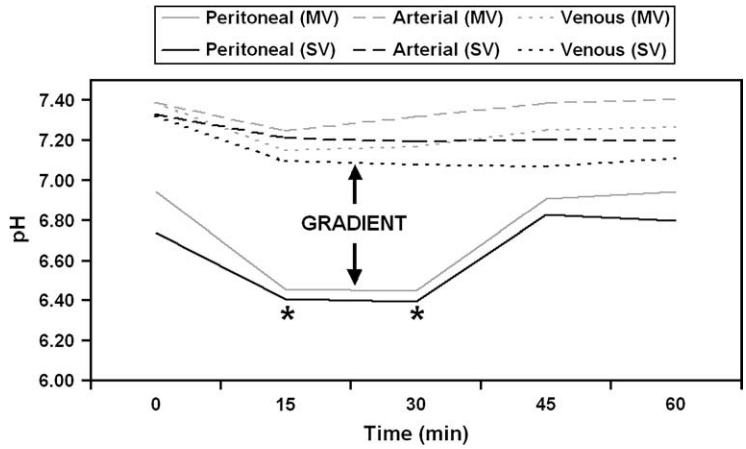

Fig. 2. Arterial (*dashed lines*), venous (*dotted lines*), and peritoneal (*solid lines*) pH before, during, and after 30 minutes of abdominal insufflation with CO_2 among spontaneously ventilated SV (*black lines*) and mechanically ventilated MV (*gray lines*) rats. A vascular-peritoneal pH gradient develops rapidly following induction of pneumoperitoneum and resolves equally quickly following desufflation. *$P < 0.05$ for peritoneal pH among both spontaneously ventilated and mechanically ventilated animals compared with preinsufflation baseline parameters.

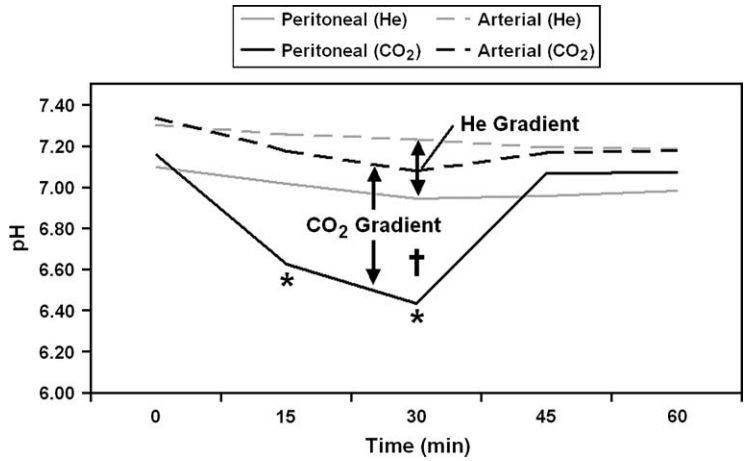

Fig. 3. Arterial (*dashed lines*) and peritoneal (*solid lines*) pH before, during, and after 30 minutes of abdominal insufflation with CO_2 (*black lines*) or helium (He, *gray lines*) among spontaneously ventilated rats. The significant vascular-peritoneal pH gradient that develops immediately following insufflation with CO_2 does not occur with helium. $^*P < 0.05$ for peritoneal pH among CO_2-insufflated animals compared with preinsufflation baseline. $^\dagger P < 0.05$ for change in both arterial and peritoneal pH following insufflation with CO_2 compared with the change in these parameters following insufflation with helium.

the inflammatory response relates to the effects of CO_2 absorption on acid-base chemistry. While it is well established that systemic absorption of CO_2 leads to increased carbonic acid production in the blood ($CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow HCO_3^- + H^+$),[19,22–30] this effect was initially dismissed as having little clinical significance given that patients undergoing laparoscopy are virtually always mechanically ventilated and can therefore have this hypercarbic load eliminated through increased minute ventilation.[12,31–35] Indeed, for many surgeons, the inability to correct significant aberrations in systemic pH is reason alone to convert from laparoscopy to an open procedure (or at least to temporarily desufflate the abdomen). However, pH is believed to be buffered so tightly in biological systems precisely because even subtle changes in pH can have profound effects on molecular physiology through changes in protein structure and function. With regard to laparoscopy, data from West et al show that macrophages acidified with CO_2 both in vitro (in culture) and in vivo (during pneumoperitoneum) produce significantly less TNF in response to in vitro lipopolysaccharide (LPS) stimulation compared with exposure to air or helium[36] and that maintenance of normal intracellular pH is required for LPS-stimulated macrophage TNF release.[37] One unavoidable feature of the experimental models used in these experiments is that an effective means of systemic CO_2 elimination is not provided for. However, the data from these experiments still strongly suggest that local cellular acidosis may be important with regard to the function of peritoneal macrophages during and after laparoscopy.

Therefore, because clear evidence of local peritoneal acidosis in the presence of systemically normalized acid-base status is essential to a pH-based mechanism of pneumoperitoneum-mediated inflammation attenuation and because the vascular-peritoneal pH gradient during laparoscopy has not been clearly defined, in the current study we sought to characterize the effects of pneumoperitoneum and ventilation on concurrent peritoneal and systemic pH. Furthermore, to demonstrate what portion of these effects is due specifically to carbon dioxide, we compared CO_2 insufflation to helium insufflation in our model of laparoscopy. We found that while the arterial acidosis that ensues following commencement of CO_2 pneumoperitoneum is corrected with mechanical ventilation and increased minute ventilation, the significant peritoneal acidosis that occurs during CO_2 abdominal insufflation remains regardless of whether the additional CO_2 load is eliminated and the arterial pH corrected. Furthermore, we confirmed that the peritoneal pH effects observed with pneumoperitoneum are due specifically to the biologic activity of CO_2 rather than to the mechanical effects of abdominal insufflation that would occur with any gas (helium in our experiment). The sharp increase in pH to baseline peritoneal levels following termination of insufflation with CO_2 indicates that the peritoneal acidosis of laparoscopy is a transient phenomenon. The persistently low venous pH observed following CO_2 pneumoperitoneum in our

study was likely a consequence of caudal venous stasis both from femoral vessel occlusion and the pressure of abdominal insufflation.

The current study confirms that local peritoneal acidosis—present as a pH gradient relative to the arterial circulation even in ventilated, systemically pH-normalized animals—is a potential and likely candidate piece in the mechanism underlying CO_2-pneumoperitoneum–specific attenuation of the inflammatory response. Future work should aim to verify that the immunomodulatory effects of CO_2-specific peritoneal acidosis can be replicated by recreating the acidic peritoneal environment with a non-gaseous acid. Furthermore, the specific intracellular mechanism whereby acidosis inhibits macrophage release of proinflammatory cytokines requires in depth investigation. Finally, the role of peritoneal acidosis in mediating other benefits of laparoscopy such as decreased postoperative pain, decreased ileus, etc., should be studied.

CONCLUSIONS

We have shown that a significant local peritoneal acidosis occurs during laparoscopy with CO_2. This effect is transient—occurring only during active abdominal insufflation—and is specifically attributable to the use of carbon dioxide. Furthermore, the vascular-peritoneal pH gradient is independent of minute ventilation and systemic pH. These data provide additional evidence that localized peritoneal acidosis is central to the mechanism of CO_2-mediated attenuation of the inflammatory response following laparoscopic surgery.

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Discussion

Dr. Stanley Ashley (Boston, MA): This is a nice study, it is convincing data, and it has an interesting hypothesis that I guess seems so simple that it makes it a little hard for us to believe that the reduction in peritoneal pH with CO_2 is responsible for many of the beneficial effects of laparoscopy. I have a couple of questions about the implications of your findings.

First, I know there have been some studies using other gases, helium or argon, for example. Has anybody ever really demonstrated clinically that there are differences in how people do when you use such inert gases as opposed to CO_2 for a laparscopic operation? One would expect the benefits of laparoscopy to be less.

The second question relates to what your findings mean for where we use laparoscopy. You have demonstrated attenuation of the inflammatory response to something like LPS, but that doesn't mean that if you really had a bacterial challenge that it wouldn't also suppress the immune response to that. So should we stop using CO_2 for perforated appendices or other acute infections?

And then the third question is does this mean that if we were not doing laparoscopy, if we were about to do a laparotomy, should we insufflate the abdomen with CO_2 ahead of time and would that anti-inflammatory effect last through a laparotomy and reduce the negative effects of it?

Thank you for the opportunity to comment.

Dr. Hanly: Thank you, Dr. Ashley. Regarding your first question, there have been a number of studies that have actually looked at the clinical use of other gases. As we all know, CO_2 has become the predominant gas, and that is principally because of the increased risk of venous gas embolism associated with some of the other gases. The nice thing about CO_2, of course, is that because dissolved CO_2 is so easily buffered in the bloodstream, it is more quickly absorbed and is less likely to come out of solution in the circulation. Furthermore, there have also been studies that have looked at immunologic differences between gases, and, indeed, there are data showing that CO_2 has specific immunologic advantages in humans. Other gases that have been studied include air, helium, nitrous oxide, argon, and nitrogen, among others.

The question regarding how these data should influence our choice about when to use laparoscopy is a very good one. When we initially started looking at this phenomenon, we found a much more accentuated difference with the CO_2 groups when there was a more ignited inflammatory response. So obviously the models that we are using are fairly robust with regard to the amount of inflammation that is generated. This suggests that the CO_2 effect is probably much more important in patients who have a large systemic inflammatory response, whether that is from infection or from extensive retroperitoneal dissection, etc.

Regarding whether or not our data suggest that we should insufflate patients for 30 minutes before doing a laparotomy, this is obviously something we have thought a lot about, and the same question

could be asked about septic patients in the ICU, for instance. Obviously we don't think that the data are mature enough yet to begin insufflating patients as a treatment for sepsis and inflammation, but there are data that suggest that the effect of CO_2 on the peritoneal macrophage is relatively enduring, and can last for up to 5 or 6 hours. So it is conceivable that if you could "turn off" the peritoneal macrophages for the period of time during which they are most exposed to surgical stress, you might be able to prevent negative downstream effects of the inflammatory cascade.

Dr. Gerald Larson (Louisville, KY): A simple question about the chemistry. What is the pH of CO_2 in the bottles, and if that is not acidic at that point, is it the chemical reaction when it combines with water that generates the hydrogen?

Dr. Hanly: As my freshman chemistry professor always used to say, "ions don't fly," so, by definition, you cannot measure the pH of a gas. However, I am sure that you all remember learning about Le Chatelier's principle from your undergraduate chemistry courses. Essentially, you have the CO_2 in pressure over a liquid, and as that CO_2 is dissolved in the liquid, it pushes the reaction equation toward carbonic acid and the release of protons. So, yes, the acid generated results from the dissolved CO_2.

Dr. Natalie Joseph (Philadelphia, PA): Since this does modulate our immune response, how does this impact laparoscopy when it is used, for example, in malignancy?

Dr. Hanly: That is obviously a very important question, and some of the early data, of course, were concerningly suggestive that laparoscopy might actually be deleterious in the setting of malignancy. The theory was that the altered immune response gave cancer cells a better chance to grow postoperatively, and this idea was used to explain the relatively high rates of port site metastases observed in the early reports of laparosopic surgery for cancer. However, I think that some of the more recent data we have seen—at least clinically with regard to laparoscopic colon cancer surgery, for example—suggest that laparoscopic approaches to oncologic surgery are not a problem as long as care is taken to handle tissues delicately and use wound protectors, etc. And, of course, there are research groups who are specifically dedicated to looking at this very question.