

Gas Flow During Bronchoscopic Ablation Therapy Causes Gas Emboli to the Heart*

A Comparative Animal Study

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Background: Thermal ablation is one of the most commonly used modalities to treat central airway obstruction. Both laser and argon plasma coagulation (APC) have been reported to cause gas emboli and cardiac arrest. We sought to determine whether bronchoscopic ablation therapy can result in systemic gas emboli, correlate their presence with the rate of gas flow, and establish whether a zero-flow (ZF) modality would result in the significant reduction or elimination of emboli.

Methods: CO₂ laser delivered through a photonic bandgap fiber (PBF) and APC were applied in the trachea and mainstem bronchi of six anesthetized sheep at varying dosages and gas flow rates. Direct epicardial echocardiography was used to obtain a four-chamber view and detect gas emboli.

Results: The presence of gas flow accompanying APC and the CO₂ laser with forward flow correlated significantly with the appearance of gas bubbles in the atria. A definite dose response was observed between the gas flow rate and the number of bubbles seen. When the CO₂ laser was delivered through a PBF with ZF to the trachea or bronchi, no bubbles were observed.

Conclusion: Bronchoscopic thermal ablation therapy using gas flow is associated with gas emboli in a dose-dependent fashion. The use of the flexible PBF with ZF is not associated with the development of gas emboli. Further study is required to determine whether a clinically safe threshold of gas emboli exists, and the relationships among the pathologic depth of tissue destruction, gas flow, pulse duration, and the development of gas emboli. (CHEST 2008; 133:892–896)

Key words: bronchoscopy; central airway obstruction; gas emboli; laser; thermal ablation

Abbreviations: APC = argon plasma coagulation; CAO = central airway obstruction; LF = low flow; ZF = zero flow

Central airway obstruction (CAO) can result from both malignant and nonmalignant disease.¹ Though the incidence and prevalence of CAO in the US population are unknown, it is estimated that complications associated with airway obstruction develop in 20 to 30% of patients with lung cancer,² and that up to 40% of lung cancer deaths may be attributable to loco-regional disease.³ The approach to and management of patients with CAO has been extensively reviewed.¹ The thermal techniques used to treat patients with CAO include electrocautery, laser, argon plasma coagulation (APC), cryotherapy, and radiofrequency

ablation. Though generally considered safe, especially in experienced hands, all of these therapies have associated complications. Specifically, there have been several case reports of gas emboli attributed to the use of both the Nd-YAG laser and APC in the airway.^{4–9}

The CO₂ laser is extensively used in head and neck surgery. A benefit of using the CO₂ laser is that it is extremely precise with a depth of penetration of approximately 10 μm, resulting in a reduced risk of damaging underlying structures. The major drawback of this modality lies in the fact that the wavelength of the CO₂ laser (10,600 nm) requires a rigid,

articulated, mirror delivery system, making it difficult, if not impossible, to use in the distal airways.¹⁰ A photonic bandgap fiber (OmniGuide, Inc; Cambridge, MA) has been developed that is able to transmit the CO₂ laser through a flexible fiber, thus allowing the application of the CO₂ laser to the distal airways. We performed initial animal experiments investigating the safety and efficacy of the flexible fiber using a flow rate of 2 L/min in delivering the laser for thermal ablation to the airways (unpublished data); however, 2 of 20 sheep died immediately after the conclusion of ablational therapy. Though postmortem analysis suggested that viral myocarditis may have been the cause of death, we considered the possibility that gas emboli associated with laser delivery contributed to the animals' demise. After these preliminary results, a zero-flow (ZF) fiber (OmniGuide, Inc) was developed that does not require any gas flow distal to the fiber tip.

Gas is used in certain devices delivering ablational therapy because cooling of the fiber tip is required to prevent thermal damage to the delivery device. Cooling can be achieved with gas (*eg*, air, carbon dioxide, nitrogen, or helium) or fluid. Gas is more commonly used as it provides improved visibility and in some cases directs the distribution of the laser. Inadequate gas flow may result in thermal damage to the probe, and settings of 0.5 to 1.5 L/min are commonly used during laser therapy in the airways.⁵ Even with gas flow rates of 0.4 L/min, the pressure of air exiting the distal coaxial sheath has been measured to be as high as 500 mm Hg.⁷

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The purpose of this study was as follows: (1) to determine whether bronchoscopic ablation therapy with the CO₂ laser fibers and other currently used devices can result in intravascular gas emboli; (2) to correlate the presence of gas emboli with the rate of gas flow used in conjunction with thermal ablation; and (3) to establish whether a ZF ablative modality using a fiber developed specifically by OmniGuide, Inc, because of our findings could result in the significant reduction or elimination of emboli observations.

MATERIALS AND METHODS

The study was approved by the Internal Review Board as well as by the Animal Research Committee at Brigham and Women's Hospital. Six sheep of mixed breed weighing 40 to 45 kg and 1 to 2 years of age were sedated with a combination of tiletine and zolazepam (Telazol; Wyeth; Madison, NJ), 6 mg/kg, and were placed under general anesthesia with a 1.5% solution of isoflurane and balanced oxygen after being intubated with a 9-mm endotracheal tube and were started on therapy with mechanical ventilation, with a fraction of inspired oxygen of 0.4, a tidal volume of 400 mL, a respiratory rate of 20 breaths/min, and zero positive end-expiratory pressure. Continuous monitoring of heart rate, ECG tracing, and oxygen saturation were performed as per the standard of care. A midline sternotomy was performed, and the pericardium was opened and secured to the sternum in order to provide direct access to the epicardium. Echocardiography was performed by a certified echocardiographer with a 3.5-MHz transducer, and a four-chamber view was obtained before, during, and after laser or APC activation. All echocardiograms were independently reviewed by a blinded echocardiographer.

As a control for the CO₂ laser, we used the APC ablation device. APC is one of the most commonly used modalities for the treatment of CAO, having the benefits of being a noncontact modality that is capable of destroying tumor tissue lateral to the tip of the probe, while having a penetration depth of only 2 to 3 mm. APC provides excellent hemostasis, and because of its shallow depth of penetration it carries only a minimal risk of airway perforation. The Nd-YAG laser was not used as the depth of penetration is significantly greater (up to 10 mm) than the CO₂ laser or APC; as such, it has fallen out of favor at our institutions as the "gold standard" for thermal ablation in the central airways.

Applications of the CO₂ laser with a low-flow (LF) and ZF fiber as well as APC were then performed sequentially, targeting the trachea, the right mainstem bronchus, and the left mainstem bronchus via flexible fibers (Omni-Guide, Inc; and ERBE-USA; Atlanta, GA) passed through an bronchoscope (XT-160; Olympus America Inc; Center Valley, PA). The CO₂ laser was applied with power settings of 20 W for 1, 2, 5, and 15 s using helium as the transport gas at a rate of 2 L/min for the LF fiber and 0.0 L/min forward flow for the ZF fiber. APC was applied with the settings typically used in therapeutic bronchoscopy, including a power of 40 W, and a flow rate of 0.5 L/min for durations of 1 and 5 s.

During the application of the CO₂ laser and APC, the bronchoscopists ensured similar visual thermal effects to those observed in actual patient cases, and the echocardiographer measured the presence or absence as well as the location of gas bubbles. During and for a few seconds after the ablation application, the animals were disconnected from positive-pressure ventilation. Recordings included the energy, gas flow, pulse duration, endobronchial area treated, the presence or absence of bubbles seen on echocardiography, as well as whether positive-pressure venti-

lation was being continued or whether thermal applications were performed under apneic conditions.

RESULTS

APC was used with the following typical clinical settings: a power of 40 W; forward gas flow rate of 0.5 L/min; and pulse durations of 1 and 5 s. With a pulse duration of 5 s applied to the trachea, intracardiac bubbles were visualized in 100% of applications (7 events in 7 applications) compared to 84% of applications (11 events in 13 applications) when performed in the bronchi. When used at a lower power of 20 W, and with an argon gas flow of 0.5 L/min keeping the pulse duration at 5 s, intracardiac gas was visualized in 100% of intratracheal applications (five events in 5 applications) and in 50% of bronchial applications (five events in 10 applications). One of the sheep treated with these settings in the bronchi went into cardiac arrest and died due to the accumulation of gas in the left ventricle and left anterior descending coronary artery. When used at a shorter pulse duration of 1 s, with an output of 40 W and an argon gas flow of 0.5 L/min, intracardiac gas was visualized in 80% of applications in the trachea (4 events in 5 applications) and in 84% of applications in the bronchi (11 events in 13 applications).

As an additional reference, the LF CO₂ fiber (OmniGuide, Inc), which requires forward gas flow, was used at a power of 20 W, a forward helium gas flow rate of 2.0 L/min, and various pulse durations. At 15-s pulses, the probability of visualizing intracar-

diac bubbles was 100% (three events in three treatments). With 5-s pulses, the probability of bubble visualization was 30% (three events in 10 treatments). With 2-s and 1-s pulse durations, the probabilities of bubble visualization were 20% (two events in 10 treatments) and 20.8% (five events in 24 treatments), respectively. As the presence of emboli and its correlation with gas flow were established with APC, additional studies on the laser fiber with LF were not deemed necessary.

The ZF CO₂ fiber (OmniGuide, Inc) was used with a 20-W power output, a 0.0 L/min forward gas flow rate, and 5-s pulse durations. With these settings, intracardiac gas bubbles were not visualized when applied to either the trachea (no events in 17 applications) or the bronchi (no events in 38 applications) [Fig 1]. Even when used at a longer pulse duration of 10 s, a power output of 20 W, and a forward gas flow rate of 0.0 L/min, intracardiac gas was not visualized with either tracheal use (zero events in one application) or bronchial use (zero events in four applications) use. Whenever the ablation was directed in the trachea proximal to the carina, the gas emboli were noted in the right atrium, while emboli detected due to ablation in either bronchi were seen in the left atrium.

DISCUSSION

Thermal ablation of airway lesions is one of the most commonly performed procedures for endobronchial therapy. Many but not all of the devices used for

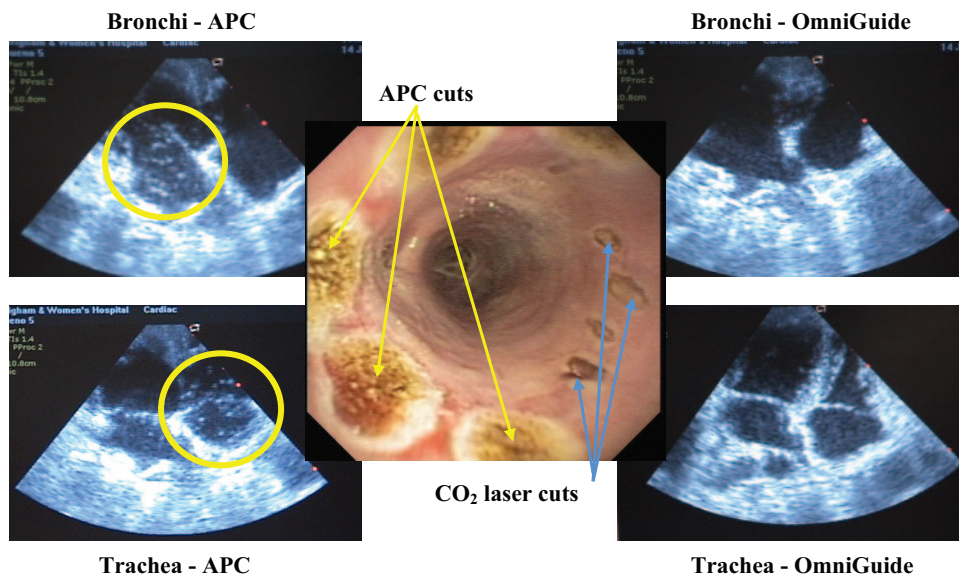


FIGURE 1. Gas bubbles can be seen in the left and right heart when APC is applied to the bronchi and trachea, respectively. Bubbles were not seen during the application of the CO₂ laser with the ZF fiber (OmniGuide, Inc).

endobronchial ablational therapy require gas flow for cooling, field clearing, or plasma-generation purposes. Though APC and the Nd-YAG laser are generally considered to be safe, there have been case reports⁴⁻⁹ of gas embolization with both devices. These emboli can lead to stroke, seizure, cardiac ischemia, other end-organ ischemia, and death. For example, Tellides et al⁵ performed transesophageal echocardiography in a patient undergoing Nd-YAG laser therapy for a right upper lobe tumor after two prior patients experienced cardiac arrest and seizure that were suggestive of gas embolization. During this third case, transesophageal echocardiography confirmed air bubbles in the left atrium, left ventricle, and ascending aorta. After reducing the air coolant flow from 1.5 to 0.8 L/min, they immediately noted the abrupt cessation of echocardiographic air, the resolution of previously noted ECG changes, and the improvement in hemodynamics and oxygenation. For these reasons, many operators tend to set gas flow rates as low as possible.

We found a direct correlation between the rate of gas flow and the presence of gas emboli following ablational therapy in the airways. Emboli were not seen in the absence of ablational therapy, suggesting that both gas flow and injury to the airway are required for this phenomenon. The gas was generally seen in the period immediately after APC or laser activation, suggesting that small bronchovascular defects are created and positive-pressure ventilation forces air into the vasculature. As we did not sample the gas in the left or right ventricles, it is unclear whether it was composed of argon, helium, or atmospheric/ventilating gas. Cases of gas embolism have also been reported^{11,12} after transbronchial lung biopsy, presumably due to small bronchovenous fistulas that were created during the biopsy and air entering the pulmonary venous circulation after the initiation of positive-pressure ventilation.

An unexpected finding was that gas bubbles were visualized in both the left and right atria, depending on the site of ablation. Thermal ablation in the trachea was more often associated with gas in the right atria, which was presumably due to drainage by systemic veins into the superior vena cava, whereas ablation in the bronchi leads to gas embolization to the left atria through the pulmonary venous system. We did not perform dedicated "bubble studies" during echocardiography to exclude the possibility of right-to-left intracardiac or pulmonary shunts. Goldman et al⁹ have suggested the possibility of a fistula created between the right segmental bronchus and the right pulmonary vein as a cause of gas embolization in the systemic circulation during a case in which APC was used for destruction of a carcinoid tumor in the right middle lobe. They postulated that

Table 1—Probability of Bubble Event*

Variables	Trachea	Bronchi
APC		
20 W, 0.5 L/min argon flow rate, 5-s pulses	100† (5/5)	50‡ (5/10)
40 W, 0.5 L/min argon flow rate, 1-s pulses	80† (4/5)	84‡ (11/13)
40 W, 0.5 L/min argon flow rate, 5-s pulses	100† (7/7)	84‡ (11/13)
OmniGuide LF		
20 W, 2 L/min flow rate, 15-pulses	100 (3/3)	
20 W, 2 L/min flow rate, 5-s pulses	30 (3/10)	
20 W, 2 L/min flow rate, 2-s pulses	20 (2/10)	
20 W, 2 L/min flow rate, 1-s pulses	20.8 (2/24)	
20 W, ZF, 5-s pulses	0.00§ (0/17)	0.00 (0/38)
20 W, ZF, 10-s pulses	0.00 (0/1)	0.00 (0/4)

*Values are given as % (No. of bubbles present/No. of applications).

†Bubbles in the right atrium.

‡Bubbles in the left atrium.

§Unclear single bubble in review (if included, 6%).

||Fiber leakage generated two bubble events (if included, 5%).

the defect is sealed by the APC, but only after gas enters the pulmonary vein. A similar mechanism could certainly be present in the veins draining the trachea.

We noted a reduction in emboli as the pulse duration decreased (Table 1). This may be due either to the duration of the pulse itself or to the fact that longer pulse durations are associated with more tissue destruction. Further study is warranted to determine the relationships among the pathologic extent of tissue destruction, gas flow, and pulse duration on the development of emboli. It is certainly possible that short pulse durations, even in the presence of gas flow, may not produce clinically significant emboli.

Though series reporting on the safety of laser bronchoscopy may not list air emboli as a complication of the procedure, they do comment on cardiovascular complications, including arrhythmia and cardiac arrest.^{7,13-16} This may be due to the fact that the clinical diagnosis of gas embolization may be difficult to distinguish from other, more common causes of cardiovascular complications and that subclinical gas embolization can occur, especially in the pulmonary circulation. It is difficult to speculate why the event rate in our study was so much higher than those in the available clinical data. It is certainly possible that the incidence of subclinical emboli in humans undergoing thermal ablation is higher than previously thought. In order to accurately describe the incidence of clinically significant, and subclinical, gas emboli, a prospective human study utilizing real-time echocardiography is required.

Our study has several limitations, the first of which is that we were treating healthy airways in sheep. The threshold for developing clinically significant gas emboli in humans, especially when the airways are involved with tumor, is unknown. It is likely that a certain threshold of gas bubbles, both in terms of size and quantity, is required prior to any significant clinical manifestations. Agitated saline solution is routinely used as a contrast agent in echocardiography, and clinically significant emboli have not been reported. It is possible that the gas emboli associated with thermal ablation in the airway are larger than the bubbles created by an agitated saline solution. As we did not measure the size or total volume of the gas bubbles created, we are currently unable to comment on the impact this would have in the clinical setting.

Additionally, as mentioned above, we did not sample the gas to determine whether it was argon, helium, or atmospheric/ventilating gas. Given the echocardiographic appearance of the bubbles as well as the temporal relationship to thermal ablation, it is highly unlikely that the bubbles represent anything else. The physical properties of argon and helium in solution are different. Helium, which is used to cool the CO₂ and Nd-YAG lasers, is readily absorbable in blood, whereas argon is not. Though this may explain a difference in the incidence of clinically significant emboli, both gases have been associated with emboli in the clinical setting. As we studied anesthetized sheep treated during apnea, we are unable to comment on the risk of emboli in nonintubated animals or humans, or in subjects treated during positive-pressure ventilation. Nevertheless, it stands to reason that positive airway pressure during ablational therapy may increase the risk of emboli due to the presence of airway-vascular fistulas. We await further studies that will examine these relationships. Until this is more clearly understood, it may be prudent to reduce airway pressure as much as possible at the time of ablation and immediately thereafter without compromising patient safety.

CONCLUSION

Gas emboli in the pulmonary and systemic circulation are a known complication of thermal ablation techniques in the airway. Our study demonstrates that this phenomenon is caused by gas flow through the various thermal ablation devices and suggests that small airway-venous fistulas are created. Until further studies are performed, we recommend using as low a flow as possible, a noncontact mode,^{17,18} and the performance of thermal ablation during apnea or spontaneous breathing. We await future studies in-

vestigating the use of the ZF fiber (OmniGuide, Inc) in humans with airway pathology.

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