# ANESTHESIA & ANALGESIA Infographic

### **Bubble Trouble:** Venous Air Embolism in Endoscopic Retrograde Cholangiopancreatography A VAE of 200 - 300mL can kill an adul 500,000+ ERCPs per year Air or CO<sub>2</sub> is insufficited<sup>2</sup> in the U for visualization 843 ERCPs VAE occurred with: were monitored with precordial •Stent placement Dilation doppler •Sphincterotomy • Biopsy •Gall stone removal Necrosectomy had no 10significant impact had 20 cardiac collapse had 10 hemodynamic effect had had VAE severe bradycardia The **HIGHEST** VAE rate was seen with cholangioscopy and stent removal + replacement **NO** VAE occurred with stent removal only or a diagnostic procedure The use of $CO_2$ , rather than air, had a protective effect

The advent of advanced endoscopy has brought about a new era of diagnostic and therapeutic procedures, which have the potential to address disease in less invasive manner. However, these procedures bring their own set of risks, such as pancreatitis, cholangitis, bleeding, perforation, and sedation risks. In addition, venous air embolism is a potentially catastrophic complication. In this infographic, we review the risk factors and incidence of venous air embolism in endoscopic retrograde cholangiopancreatography and highlight the associated procedures that have the highest degree of associated risk.

ERCP indicates endoscopic retrograde cholangiopancreatography; VAE, venous air embolism.

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The authors declare no conflicts of interest

#### REFERENCE

 Afreen LK, Nakayama T, Bryant AS, et al. Incidence of venous air embolism during endoscopic retrograde cholangiopancreatography. *Anesth Analg.* 2018;127:420–423.

### **EDITORIAL**

## Vascular Air Embolism and Endoscopy: Every Bubble Matters

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hile generally considered low-risk procedures, gastrointestinal (GI) endoscopy, and specifically endoscopic retrograde cholangiopancreatography (ERCP), can be associated with life-threatening complications such as vascular air embolism (VAE). As with many other procedures associated with uncommon, yet devastating complications, limited data exist to clarify the incidence, mechanisms, or mitigation strategies for the occurrence of VAE. To the initial question, Afreen et al<sup>1</sup> have provided intriguing evidence that VAE occurs in nearly 2.5% of ERCP patients. Moreover, half of these VAE events are associated with measurable hemodynamic perturbations, potentially including hypotension, decreased cardiac output, and even cardiovascular collapse.<sup>2</sup> Given that the number of reports of this complication associated with ERCP in both the anesthesiology and GI literature is limited,<sup>3-7</sup> one might erroneously conclude that VAE is a rare event. The current study by Afreen et al<sup>1</sup> indicates otherwise, and their observational analysis leaves other vital questions unanswered:

- 1. How does air embolism occur as a result of GI endoscopy (or any interventional procedures)?
- 2. What is the best strategy to mitigate the risks of VAE during ERCP procedures?
- 3. If VAE occurs, what should be the treatment algorithm?
- 4. Does just "a little air"—such as that commonly introduced by anesthesiologists into intravenous (IV) tubing during bolus medication injections—really matter?

The pathophysiology of VAE classically occurs when 2 conditions are met concurrently:

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- 1. Procedures for which the surgical site is above the plane of the heart (eg, sitting craniotomy), creating a gravitational gradient for air entry; and
- 2. A surgical incision or rent opens noncompressible venous channels (such as dural veins) creating an entry portal for air into the circulation.

More recently, medical and surgical procedures have created an additional, more insidious pathway for air and other gases to enter the circulation. Many diagnostic and therapeutic procedures require injection of pressurized air or gases (or fluids) into body cavities. While the pressure of injections is typically monitored, the volume of gas injected is seldom measured or known.

So how can VAE occur during GI procedures?<sup>6</sup> The endoscopist controls the intermittent flow of pressurized air (or other gas—see below) to optimize visualization and distention of the bowel, pancreatic, and biliary ducts. If the pancreas is necrotic, or even inflamed, this pressurized gas readily transits the pancreatic ducts into the extensive venous drainage of the head and body of the pancreas. From there, it is a short path to the superior mesenteric branches of the hepatic portal vein or even directly into the splenic vein. Moreover, in the prone or semiprone position typical for ERCP procedures, a small hydrostatic gradient is created between pancreatic ducts and the draining veins. Thus, VAE may potentially occur during any ERCP case.

But VAE is certainly not unique to GI procedures. Indeed, VAE is a well-known complication during a host of surgical operations, including neurosurgical procedures (especially those in the sitting position), cesarean delivery, scoliosis surgery, and even pars plana vitrectomy operations (Table).<sup>8,9</sup> In addition, VAE can also be associated with medical procedures such as central venous catheterization, hemodialysis, vacuum gynecologic procedures, and radiocontrast injection for computerized tomography and other imaging modalities.

### CAN WE **REDUCE** THE **RISK** OF VAE DURING ERCP?

Because of the current<sup>1</sup> and previous publications<sup>6</sup> that noted the risks of air embolization during ERCP, nearly all GI centers converted their insufflation gas from air to carbon dioxide (CO<sub>2</sub>). CO<sub>2</sub> is better suited as a distending gas because it is chemically inert, colorless, inexpensive, readily available, and essentially not combustible. Moreover, CO<sub>2</sub> (with a solubility of 0.54 mL gas/mL blood) is nearly <u>50 times</u> more soluble than air (nitrogen = 0.012 mL gas/mL blood),<sup>10</sup>

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## Table. Surgical and Other Related Procedures With Known Risk of Vascular Air Embolism

Gastrointestinal surgery
Laparoscopic surgeries
Gastrointestinal endoscopy (endoscopic retrograde
cholangiopancreatography)
Liver transplantation
Neurosurgical (especially sitting position craniotomies)
Sitting craniotomy
Posterior fossa procedures
Craniosynostosis repair
Cervical laminectomy
Spinal fusion
Torticollis corrective surgery
Deep brain stimulator placement
Ophthalmologic procedures
Pars plana vitrectomy <sup>9</sup>
Otolaryngology procedures (especially in a reverse Trendelenburg
position)
Radical neck dissection
Thyroidectomy
Orthopedic
Total hip arthroplasty
Arthroscopy
Thoracic
Thoracentesis
Open chest wounds
Obstetric- <mark>gynecologic</mark>
Cesarean delivery
Laparoscopic procedures
Vacuum abortion
Urology
Prostatectomy

Adapted from Brull and Prielipp.8,9

markedly increasing the safety margin of unintended gas migration into the circulation. In addition, exclusive use of  $CO_2$  to visualize the gut, biliary tree, and pancreatic ducts during ERCP significantly reduces postoperative abdominal distention, lowers abdominal pain scores, and reduces the overall rate of complications.<sup>11</sup> However, anesthesiologists must remember that  $CO_2$  may also be associated with hypercapnia, metabolic and respiratory acidosis, activation of the sympathetic nervous system, altered mental status, and even alterations of immune function.

### WHAT ABOUT VAE RESCUE?

In the event that prevention strategies fail, early diagnosis may provide the best opportunity for rescue before cardiac arrest. Rescue steps<sup>12</sup> include:

- 1. Immediately terminate the insufflation flow of any gas.
- 2. Administer high-flow, 100% oxygen to the patient. Discontinue nitrous oxide administration if it is being used.
- 3. Consider patient position. To reduce the air lock within the right atrium and right ventricle, it was traditional to place the patient in left lateral decubitus position and/or steep Trendelenburg position. However, experimental animal studies have found no reliable improvement in cardiac output or right ventricular blood flow subsequent to such maneuvers, and human data are lacking.

- 4. Aspirate air from an indwelling central venous catheter. This maneuver, although theoretically appealing and potentially effective, presumes the presence of a catheter at the time of air entrainment, a routine recommendation that exists only for sitting craniotomy patients.
- 5. Full cardiac resuscitation with epinephrine, vasopressin, and chest compressions. In selected cases, extracorporeal hemodynamic support should be considered, including modalities such as percutaneous extracorporeal membrane oxygenation, cardiopulmonary bypass, or hyperbaric oxygen therapy.
- 6. Because of the complexity of therapy in advanced VAE and the rarity of such events, simulation-based team training should be considered for endoscopy teams.

### WHAT ABOUT THOSE INEVITABLE SMALL AIR BUBBLES DURING MEDICATION INJECTIONS?

It was generally believed that a small amount of injected air, such as typically occurs with bolus dosing of IV medications, was a benign, even "routine," event during most anesthetics. However, this may not be true. In some instances, even when the IV tubing sets, extension tubing, 3-way connectors, and syringes are deaired, paradoxical air embolism can occur, leading to significant morbidity and hemodynamic instability.<sup>13,14</sup> The presence of small amounts of air in prefilled syringes also has been reported, and expulsion of the air before IV drug administration, particularly in emergencies, may not always occur, placing patients at risk of VAE.<sup>15</sup>

In other settings, air is purposely injected IV for diagnostic evaluation of intracardiac shunts, such as echocardiographic studies that use agitated saline that contains microbubbles. These microemboli vary in size between 0 and 110  $\mu$ M. In a rat model of cerebral air microembolization, air bubbles with a diameter >45  $\mu$ M (45 vs 160  $\mu$ M) induced strokes of similar frequency or severity, suggesting that even injections of microbubbles are not benign.<sup>16</sup> As expected, the number and size of the microbubbles in the agitated saline increase as a larger volume of agitated saline is used.

The ultimate clinical impact of VAE depends on a number of factors, including the size of the air embolus, the vascular tree in which it occurs (arterial versus venous), the end-organ in which it lodges (carotid or coronary arteries versus lungs), the type of gas (air versus CO<sub>2</sub>), and the intense inflammatory response initiated by microemboli trapped in the capillaries of the lungs or other end organs. The pathogenesis of these emboli is partially dependent on, and can even by modulated by, the inflammatory cascade initiated by leukocytes that are activated by the microair emboli. The consequences can therefore be modulated—at least in the experimental laboratory setting—by establishing leukopenia before the embolic insult.<sup>17</sup> Obviously in most clinical scenarios, this preprocedural establishment of leukopenia is not feasible.

Given the multitude of potential (and real) complications associated with gas embolism during endoscopy, it appears that the recommendation to use  $CO_2$  instead of room air (as most of the current endoscopy device makers

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currently manufacture and sell) is a prudent one: the transition to  $CO_2$  insufflation improves patient safety.<sup>18,19</sup> Additionally, the use of  $CO_2$  for insufflation during endoscopic procedures including ERCP is associated with less postprocedural pain, flatus, bowel distension, and patient discomfort<sup>18,19</sup> without adverse pulmonary events or  $CO_2$ retention in patients with no underlying pulmonary disease. We congratulate the authors<sup>1</sup> for reintroducing the discussion about the occurrence of gas embolism during ERCP; this discussion should ultimately lead to the recognition that  $CO_2$  is preferable to air as the insufflating gas, and should "clarify the barriers to moving to  $CO_2$  insufflation on the part of endoscope manufacturers, as well as endoscopy units and endoscopists."<sup>18</sup>

### **SUMMARY**

Endoscopists and anesthesiologists must remain vigilant during ERCP for uncommon but potentially devastating complications such as VAE. Insufflation with CO<sub>2</sub> clearly mitigates this risk, and concurrently reduces postoperative abdominal pain, distension, and overall complications. Moreover, it is increasingly recognized that even "small air bubbles" do matter, and anesthesia providers should institute practices to minimize the embolic gas load to all patients.

### DISCLOSURES

Name: Richard C. Prielipp, MD, MBA, FCCM.

**Contribution:** This author helped with the design, formulation, preparation, and construction of the editorial.

**Conflicts of Interest:** R. C. Prielipp is a member of the Speakers Bureau for Merck & Co, Kenilworth, NJ.

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#### REFERENCES

 Afreen LK, Bryant AS, Nakayama T, et al. Incidence of venous air embolism during endoscopic retrograde cholangiopancreatography. *Anesth Analg.* 2018;127:420–423.

- 2. Albin MS. Venous air embolism: a warning not to be complacent–we should listen to the drumbeat of history. *Anesthesiology*. 2011;115:626–629.
- 3. Chavalitdhamrong D, Donepudi S, Pu L, Draganov PV. Uncommon and rarely reported adverse events of endoscopic retrograde cholangiopancreatography. *Dig Endosc*. 2014;26:15–22.
- 4. Silviera ML, Seamon MJ, Porshinsky B, et al. Complications related to endoscopic retrograde cholangiopancreatography: a comprehensive clinical review. *J Gastrointestin Liver Dis.* 2009;18:73–82.
- Donepudi S, Chavalitdhamrong D, Pu L, Draganov PV. Air embolism complicating gastrointestinal endoscopy: a systematic review. World J Gastrointest Endosc. 2013;5:359–365.
- Katzgraber F, Glenewinkel F, Fischler S, Rittner C. Mechanism of fatal air embolism after gastrointestinal endoscopy. *Int J Legal Med.* 1998;111:154–156.
- Nayagam J, Ho KM, Liang J. Fatal systemic air embolism during endoscopic retrograde cholangio-pancreatography. *Anaesth Intensive Care*. 2004;32:260–264.
- Brull SJ, Prielipp RC. Vascular air embolism: a silent hazard to patient safety. *J Crit Care*. 2017;42:255–263.
   Prielipp RC, Lanigan ML, Birnbach DJ. Venous air embo-
- Prielipp RC, Lanigan ML, Birnbach DJ. Venous air embolism and pars plana vitrectomy: silent co-conspirators. *Am J Ophthalmol*. 2016;171:xii–xiv.
- 10. O'Brien HR, Parker WL. Solubility of carbon monoxide in serum and plasma. *J Biol Chem.* 1922; 50:289–300.
- Zhang WY, Jiang XP, Miao L, Chen FC, Huang ZM, Huang XL. Efficacy and safety of carbon dioxide insufflation versus air insufflation for endoscopic retrograde cholangiopancreatography: a metaanalysis update. *Clin Res Hepatol Gastroenterol*. 2017;41:217–229.
- Mirski MA, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. *Anesthesiology*. 2007;106:164–177.
- Stegmayr BG. Sources of mortality on dialysis with an emphasis on microemboli. *Semin Dial*. 2016;29:442–446.
- 14. Kumar D, Gadhinglajkar SV, Moorthy K, Bhandari D. Paradoxical air embolism to left anterior descending artery during induction of anesthesia in a patient with an atrial septal defect. *A A Case Rep.* 2014;2:66–69.
- 15. Marsh M. Risk of air embolism from prefilled syringes. *Anaesthesia*. 2007;62:973.
- Bassett GC, Lin JW, Tran MM, Sistino JJ. Evaluating the potential risks of bubble studies during echocardiography. *Perfusion*. 2015;30:219–223.
- Helps SC, Gorman DF. Air embolism of the brain in rabbits pretreated with mechlorethamine. *Stroke*. 1991;22:351–354.
- Lo SK, Fujii-Lau LL, Enestvedt BK, et al; ASGE Technology Committee. The use of carbon dioxide in gastrointestinal endoscopy. *Gastrointest Endosc*. 2016;83:857–865.
- Dellon ES, Hawk JS, Grimm IS, Shaheen NJ. The use of carbon dioxide for insufflation during GI endoscopy: a systematic review. *Gastrointest Endosc.* 2009;69:843–849.

# Incidence of Venous Air Embolism During Endoscopic Retrograde Cholangiopancreatography

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**BACKGROUND:** Known complications of endoscopic retrograde cholangiopancreatography (ERCP) include pancreatitis, bleeding, duodenal perforation, and venous air embolism (VAE). The aim of this study was to determine the incidence of VAE during ERCP and be able to differentiate high-risk versus low-risk ERCP procedures.

**METHODS:** This is a prospective cohort study consisting of patients who underwent ERCP and were monitored with a precordial Doppler ultrasound (PDU) for VAE. PDU monitoring was digitally recorded and analyzed to confirm the suspected VAE. Demographic and clinical data related to the anesthetic care, endoscopic procedure, and intraoperative hemodynamics were analyzed.

**RESULTS:** A total of 843 ERCP procedures were performed over a 15-month period. The incidence of VAE was 2.4% (20 patients). All VAE's occurred during procedures in which stent placement, sphincterotomy, biopsy, duct dilation, gallstone retrieval, cholangioscopy, or necrosectomy occurred. Ten of 20 (50%) of VAEs were associated with hemodynamic alterations. None occurred if the procedure was only diagnostic or for stent removal. Subanalysis for the type of procedure showed that VAE was statistically more frequent when stents were removed and then replaced or if a cholangioscopy was performed.

**CONCLUSIONS:** The high incidence of VAE highlights the need for practitioners to be aware of this potentially serious event. Use of PDU can aid in the detection of VAE during ERCP and should be considered especially during high-risk therapeutic procedures. Detection may allow appropriate interventions before serious adverse events such as cardiovascular collapse occur. (Anesth Analg 2018;127:420–3)

### **KEY POINTS**

- **Question:** What is the incidence and risk factor(s) of venous air embolism during endoscopic retrograde cholangiopancreatography (ERCP)?
- **Findings:** Venous air embolism occurred in 20 patients (2.4%) of the 843 that underwent ERCP; half of these resulted in hemodynamic alterations such as cardiac collapse.
- Meaning: There is a high incidence of venous air embolism in patients that undergo ERCP, some of which result in a serious adverse event. Clinicians are encouraged to use modalities such as a precordial Doppler ultrasound for detection and intervention.

**E** (ERCP) is an advanced endoscopic diagnostic and therapeutic procedure used to treat a variety of conditions such as obstructive jaundice, traumatic or iatrogenic damage to the bile ducts, and obstruction related to bile duct and pancreatic tumors. ERCP was initially utilized for diagnostic purposes; however, it is now widely available and has become a very valuable tool for the management of biliary and pancreatic diseases.<sup>1</sup> ERCP is used for

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therapeutic interventions such as sphincterotomy, removal of biliary stones, dilation of strictures, and placement of plastic or metal stents. Today, over 500,000 ERCP's are performed annually in the United States.<sup>2</sup> Endoscopists are aware of common adverse events associated with ERCP such as pancreatitis, cholangitis, bleeding, postspincterotomy perforation, and sedation-related cardiopulmonary issues. However, less common, but potentially fatal complications include systemic venous air embolism (VAE).<sup>3</sup> A compilation of different case studies in which VAE occurred is shown in Supplemental Digital Content, Table 1, http:// links.lww.com/AA/C445. Air embolism is a rare adverse event that can cause fatal cardiopulmonary compromise. Patients who survive VAE can have long-term neurological effects.<sup>4</sup> Immediate recognition and intervention is needed to prevent possible catastrophic consequences. ERCP involves the use of insufflation of air or carbon dioxide to dilate the lumen of the gastrointestinal tract, thereby improving visualization during the procedure. It is presumed that insufflation of gas coupled with disruption of a mucosal vascular barrier predisposes patients to a VAE.

Precordial Doppler ultrasound (PDU) has been shown to be an efficacious, inexpensive, and noninvasive monitoring device for the detection of VAE. Changes in the heart tones,

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usually referred to as "mill-wheel murmur," are characteristic of VAE. The anesthesiologist has an important role in the detection of these characteristic sounds and subsequent intervention.<sup>5</sup> As shown in Supplemental Digital Content, Table 1, http://links.lww.com/AA/C445, there have been numerous case reports, but no quantitative data have been published regarding the incidence and risk factors of VAE during ERCP. The primary objective of the present study was to assess the incidence of VAE in patients undergoing ERCP. A secondary objective was to assess which procedural factors were associated with VAE in patients undergoing diagnostic and therapeutic ERCP at a busy academic institution.

### **METHODS**

### General

This was a prospective cohort study evaluating the incidence of VAE in patients >19 years scheduled for ERCP in the GI Endoscopy Suites of the University of Alabama at Birmingham Hospital. This study was approved by the University of Alabama at Birmingham's Institutional Review Board and requirement for written informed consent was waived by the institutional review board. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Patients, ≥19 years of age, undergoing an ERCP during the study interval were included. Patients who had a failed ERCP were excluded from the analysis. A failed ERCP was defined as an incomplete procedure due to various causes; the primary cause being the inability to cannulate the ampulla or due to surgical changes making access to the ampulla impossible. Demographic and other clinical data such as type of anesthetic, positioning, gas used for insufflation, and therapeutic procedures performed were recorded for each patient. Type of stent was also recorded because metal stents have been proposed as a risk factor for VAE. Anesthetic management was left to the discretion of the attending anesthesiologist.

### **Detection of VAE**

Monitoring and the detection of VAE were performed using a PDU (Medasonics Versatone, Model D8; Cooper Surgical, Trumball, IL). The face of the PDU probe was coated with acoustic gel and placed in the third intercostal space 1 cm to the right of the left sternal border adjusting position until clear heart tones were heard. The probe was then secured using an adhesive dressing. The majority of patients were then placed in the prone position for the procedure. A digital audio recorder was plugged into the output port of the PDU and activated at the beginning of the procedure. If a VAE was suspected based on distinct changes in the sounds detected by the PDU, the attending anesthesiologist and gastroenterologist were notified, and the event was noted in the anesthetic record. Interventions were performed at the discretion of the attending anesthesiologist in collaboration with the gastroenterologist. To assure that intraoperatively observed events were supportive of a VAE event, digital recordings were reviewed by investigators with experience in PDU monitoring, and anesthetic records were assessed for additional evidence of VAE such as hemodynamic changes or alterations in end-tidal gas monitoring. Hemodynamic changes were

defined as a significant increase or decrease in heart rate and decrease in blood pressure resulting in an intervention (eg, cardiovascular collapse and severe bradycardia).

### **Statistical Analysis**

Statistical analyses were performed by using SAS version 9.4 (Cary, NC). Patient demographics and intraoperative data were summarized using means and ranges (for continuous variables) and frequencies and percentages (for categorical variables). The 2-sample *t* test and Fisher exact test were used to compare patients with and without VAE. Point estimates and exact binomial (Clopper-Pearson) CIs for the proportion of subjects having a VAE were calculated. Fisher exact test was used to evaluate the association between type of procedure and incidence of VAE. A *P* value <.05 was considered statistically significant.

### RESULTS

Between January 2013 and April 2014, 948 patients were scheduled to undergo ERCP and were monitored for VAE using PDU. Of these, 105 had an incomplete or a failed procedure and were excluded. The majority of failed procedures were attributed to the inability to cannulate the ampulla or due to surgical changes making access to the ampulla impossible. Notably, the incidence of VAE in those 105 patients was 0. The demographics of the remaining 843 patients that underwent ERCP are shown in Table 1. Twenty subjects had a VAE identified, making the overall incidence proportion of VAE in subjects undergoing ERCP 2.4% (95% CI, 11.5%–3.6%). There were no significant differences observed in the demographics between the patients who developed VAE and those that did not.

Table 2 indicates the incidence of VAE in subgroups of patients who received various additional interventions. For each type of intervention, Fisher exact test was used to assess whether the incidence proportion of VAE for patients receiving that intervention significantly differed from those not receiving the intervention. Forty-nine (5.8%) of the procedures were purely diagnostic and 794 (94.2%) were therapeutic ERCP procedures. All VAE occurred in subjects who underwent therapeutic interventions in which there was a potential for physical disruption of a mucosal/vascular barrier. If one combines ERCPs done for diagnostic purposes only (n = 49) with those done in which stent removal was the only therapy performed (n = 151; both groups had a 0% incidence of VAE observed),then there is a statistically significant relationship between ERCPs associated with minimally invasive additional procedures and those associated with more invasive procedures (P = .006). There was also a significant relationship between type of procedure and the incidence of VAE. Two procedure types had significantly higher incidences of VAE: stent removal with replacement (4.4% vs 1.8%; P = .049) and cholangioscopy (9.1%vs 2.1%; P = .040). That is, patients receiving these procedures had higher incidences compared to those requiring other procedures. A metal stent was used in 152 cases, only 1 of which resulted in the development of a VAE suggesting that use of a metal stent is not a risk factor for VAE.

Hemodynamic changes (eg, increase or decrease in heart rate and decrease in blood pressure) were noted in only 10 (50%) VAE patients. There was cardiovascular collapse in

Data Stratified by VAE Event <sup>a</sup>						
	Patients With VAE (N = 20)	Patients With No VAE (N = 823)	P Value <sup>i</sup>			
Age (y)	58.7 ± 17.8 (24–89)	57.8 ± 16.0 (19–94)	.807			
Gender	(_ · · · · )	()				
Male	13 (65%)	436 (53%)	.366			
Female	7 (35%)	387 (47%)				
Height (inches)	$69.2 \pm 5.1$	67.3 ± 4.2	.053			
	(61-77)	(56.3–85)				
Weight (lb)	$166.5 \pm 41.7$	171.9 ± 42.2	.575			
	(124–259)	(83–327)				
BMI	$24.4 \pm 4.8$	$26.6 \pm 6.1$	.100			
	(17.6–33.7)	(12.6–54.6)				
Race						
Caucasian	13 (65%)	543 (66%)	.242			
African American	3 (15%)	200 (24%)				
Other	4 (20%)	80 (10%)				
Anesthesia						
General	12 (60%)	561 (68%)	.470			
MAC	8 (40%)	262 (32%)				
Position <sup>c</sup>						
Lateral	1 (5%)	52 (6%)	.999			
Prone	17 (85%)	672 (82%)				
Supine	2 (10%)	85 (10%)				
Insufflation agent						
Air	17 (85%)	749 (91%)	.417			
CO <sub>2</sub>	3 (15%)	74 (9%)				

Table 1 Patient Demographics and Intraoperativ

Abbreviations: BMI, body mass index; CO<sub>2</sub>, carbon dioxide; MAC, monitored anesthesia care; VAE, venous air embolism.

<sup>a</sup>Continuous values are presented as mean  $\pm$  standard deviation with (range). Categorical variables are presented as frequency with (percentage).

<sup>b</sup>*P* values from 2-sample *t* test (for continuous variables) and Fisher exact test (for categorical variables).

°Position was not available for 14 patients with no VAE.

Table 2. VAE I	ncidence	Rates by	Procedure	
Procedure	VAE <sup>a</sup>	Procedures Performed	Incidence (%)	P Value <sup>₅</sup>
Stent removal and replacement	8	180	4.4	.052
Initial stent placeme	nt 5	354	1.4	.168
Sphincterotomy	7	322	2.2	.821
Gallstone removal	5	214	2.3	.999
Dilation	5	146	3.4	.368
Biopsy	3	60	5.0	.165
Cholangioscopy	3	33	9.1	.040
Necrosectomy	1	13	7.7	.270
Stent removal only	0	151	0	-
Diagnostic only	0	49	0	-

Boldface indicates the P value is statistically significant (P < .05).

Abbreviation: VAE, venous air embolism.

<sup>a</sup>Some patients had more than 1 procedure.

 $^{\mathrm{b}}\ensuremath{\mathsf{Fisher}}\xspace's$  exact test (2-tailed) for incidence of this procedure versus rest of total sample.

2 subjects (hypotension, hypoxia, end-tidal carbon dioxide measure reduced >50%, procedures terminated), severe bradycardia in 2 additional subjects, a  $\geq$ 15 beat per minute increase in heart rate in 2 subjects and new-onset ectopic heartbeats in 2 subjects (1 of whom also had an increase in heart rate). The 2 cases associated with cardiovascular collapse were both associated with stent removal and replacement; in 1 case, the exchange was followed by necrosectomy. None of the embolism cases in which carbon dioxide was used as an insufflation agent had hemodynamic changes.

### DISCUSSION

The present study is the largest prospective series performed to date assessing for the incidence of VAE in subjects undergoing ERCP. As evidenced by these results, VAE can be a serious complication of ERCP. In our series, the incidence of VAE was 20 (2.4%) in 843 patients. Interestingly, no VAE occurred during minimally invasive procedures (stent removal only and diagnostic ERCP) but occurred in all other interventional subgroups including stent replacement, biopsy, cholangioscopy, sphincterotomy, dilation, gallstone retrieval, and necrosectomy. Incidence rates of VAE by procedure are listed in Table 2.

During ERCP, air or  $CO_2$  is used for insufflation to distend the bowel lumen to allow sufficient visualization and manipulation of instruments within the duodenum. Air is introduced at relatively high pressures and can be introduced at a flow of 30 mL/s.<sup>6</sup> The <u>amount of air entrained</u> that can cause a <u>lethal</u> event in an adult is estimated at 200–300 mL or approximately 3–5 mL/kg. The rate of air entrainment is also <u>important</u> as the pulmonary circulation and alveolar interface provide for dissipation of the intravascular gas.<sup>7</sup> In those patients in which <u>CO<sub>2</sub></u> was used as the insufflating agent and embolism occurred, there were no adverse hemodynamic consequences.

### Limitations

While this is the largest series to examine the relationship between ERCP and VAE, there are several limitations to this study. The primary limitation is that only PDU was used for detection of VAE; there was not another confirmatory method such as transthoracic echocardiogram or transesophageal echocardiogram used. Of the 20 VAE cases, 10 remained subclinical but for the PDU monitoring—the caveat to that is the act of monitoring may have altered clinical practice in those 10 patients thus preventing hemodynamic deterioration.

Transthoracic echocardiogram would not be possible in a prone patient and transesophageal echocardiogram could not be accomplished in a patient with an endoscope in place. End-tidal nitrogen monitoring was not utilized during these procedures. Additionally, detection of VAE would not be accomplished if the PDU probe was placed incorrectly or if the probe moved during prone positioning. Once the correct position was confirmed, the probe was attached with an adhesive dressing. Correct position was once again confirmed after prone positioning.

The present study is restricted to experience at 1 institution and thus limits the ability to generalize findings to other centers. In this study, several gastrointestinal procedural physicians with advanced training in ERCP with a range of years of experience in performing ERCP conducted the procedures. This is both a limitation and strength, as physicians with varying degrees of experience may actually make the results generalizable; yet it also introduces confounding.

Our institution utilizes the anesthesia care team model of attending anesthesiologist supervising certified registered nurse anesthetists or residents. A variety of attending anesthesiologists and certified registered nurse anesthetists provided care during this study. They received training regarding correct probe placement and the sounds to listen for. They were instructed to alert the procedural physician and the attending anesthesiologist if there was suspicion of

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a VAE. It is possible that a subtle finding could have been missed over the course of the study. Finally, while volume status could potentially impact hemodynamic changes if an embolism occurred, fluid administration was appropriate for all cases in this study; it was not considered as an outcome variable or any part of this study.

Air was the most commonly used insufflating agent during the course of the study and as a result, our institution is now using  $CO_2$  as the insufflating agent for ERCP in almost all instances.  $CO_2$  is absorbed faster than nitrogen, the principal gas in room air. Therefore, some authors recommend its use as the insufflating agent during endoscopic procedures due to its rapid absorption should an embolic event occur.<sup>8</sup>

### **CONCLUSIONS**

There is a significant incidence of VAE during ERCP, and therefore VAE should continue to be on the radar of anesthesia professionals. In this study, the occurrence of VAE is 2.4%; use of monitoring devices such as PDU may prove beneficial in detecting VAE. Consideration could be given to monitoring with PDU in all ERCP procedures even if a lower risk procedure is planned, as, at times, a low-risk procedure can become a high-risk procedure depending on clinical findings. Utilizing PDU monitoring can allow the detection of VAE. This can allow efforts to terminate the insufflation and immediately treat the patient thereby hopefully mitigating significant hemodynamic compromise or passage of air into the arterial system. Such monitoring should lead to improved patient outcomes after the occurrence of a VAE.

#### DISCLOSURES

Name: Lubana K. Afreen, BS.

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**Contribution:** This author helped with the interpretation of the data analysis and writing and editing of the manuscript. **Name:** Tetsuzo Nakayama, MD.

**Contribution:** This author helped with the development of methodology, assisted with patient recruitment, data collection, and entry.

Name: Timothy J. Ness, MD, PhD.

**Contribution:** This author helped with the development of the study methodology, data interpretation, and writing of the manuscript.

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**Contribution:** This author helped initiate the study, develop the methodology, recruit the patient, interpret the data, and write the manuscript.

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#### REFERENCES

- Chavalitdhamrong D, Donepudi S, Pu L, Draganov PV. Uncommon and rarely reported adverse events of endoscopic retrograde cholangiopancreatography. *Dig Endosc.* 2014;26:15–22.
- 2. Silviera ML, Seamon MJ, Porshinsky B, et al. Complications related to endoscopic retrograde cholangiopancreatography: a comprehensive clinical review. *J Gastrointestin Liver Dis.* 2009;18:73–82.
- Donepudi S, Chavalitdhamrong D, Pu L, Draganov PV. Air embolism complicating gastrointestinal endoscopy: a systematic review. World J Gastrointest Endosc. 2013;5:359–365.
- Chavalitdhamrong D, Draganov PV. Acute stroke due to air embolism complicating ERCP. *Endoscopy*. 2013;45(Suppl 2 UCTN):E177–E178.
- Tedim A, Pedro A, Castro A. Development of a system for the automatic detection of air embolism using a precordial. *Conf Proc IEEE Eng Med Biol Soc.* 2014;2014:2306–2309.
- Katzgraber F, Glenewinkel F, Fischler S, Rittner C. Mechanism of fatal air embolism after gastrointestinal endoscopy. *Int J Legal Med.* 1998;111:154–156.
- Mirski MA, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. *Anesthesiology*. 2007;106:164–177.
- Lo Simon K, Fuji-Lau LL, Enestvedt BK, et al. The use of carbon dioxide in gastrointestinal endoscopy. *Gastrointest Endosc*. 2016;83:857–865.