Improving Technologies in Anesthesia

Patrick Kolbay, Joseph Orr, Kai Kück*
University of Utah

***Abstract* - General anesthesia is well known to offer physicians access to a broad variety of invasive procedures otherwise deemed too risky. Anesthesia machines provides the means for anesthetizing patients safely in the hospital operating room. However, these devices are increasingly unable to meet the demands and needs outside of the hospital. Developing countries struggle to purchase and maintain these costly devices, leading to a 40-fold increase in anesthesia-related deaths compared to developed countries. Small-office practices in the United States experience significantly poorer anesthesia outcomes and increased legal claims versus their larger hospital counterparts, resulting in 60% more anesthesia-related deaths. Environmental impacts and global health concerns from the emitted anesthetic gases have brought into serious question the prevailing notion that unchecked emissions were sustainable. These factors can all be attributed to anesthesia machine design and technology having the primary intended use in the traditional operating room. The long-term goal of this work is to develop technologies in anesthesia that expand its safe use, decrease underlying costs, and reduce the total emissions. The immediate objective of this work is to create a feedback-controlled anesthetic gas vaporizer-scavenger system and evaluate its performance. The central hypothesis is that the combined use of mesoporous materials and feedback control provide the opportunity for repeatable capture and release of expired anesthetic gases during anesthesia delivery. Our rationale is that such a device will help reduce the amount of anesthetic needed while simultaneously offering improved control over the delivery of anesthetic gases.**

I. INTRODUCTION

Anesthesia machines and systems are at the center of surgical care and provide support for anesthesiologists to administer anesthesia. These devices provide a multitude of functions, including confirming intubation, monitoring cardio-pulmonary function, delivering both intravenous and inhalational anesthetic gases, and determining the depth of unconsciousness for a given patient. Historically anesthesiology represented one of the risker aspects of medicine, however several technological advances have led to a drastic improvement in anesthesia safety in the hospital, transforming it from one of the most dangerous aspects of surgery to one of the safest. [1–5] While these improvements are welcome, many diverse problems still exist in anesthesia that need to be addressed in a new era of technologies.

II. ISSUES IN ANESTHESIA

Global Access to Anesthesia

There are 5 billion people globally that still have inadequate access to anesthetic care, primarily in South Asia and Sub-Saharan Africa.[6] Hospitals in austere conditions that have been able to provide anesthetic care have been unable to match the reduction in anesthesia-related morbidity and mortality seen in the developed world.[7,8] This discrepancy stems from a combined lack of clinical staff, equipment, space, and systems of surgical care delivery.[9,10] Significant efforts have been made to increase access to clinical staff, primarily through increases in local education programs as well as humanitarian efforts through programs like Médecins Sans Frontières (MSF, also known as Doctors Without Borders).[11–14] Deficits in technical resources and equipment remain an unsolved problem none the less. Lack

of healthcare resources and infrastructure has led many developing countries to import equipment despite it being ill-suited for the environment. Much of this healthcare equipment is being funded by both international donors and foreign governments, with donations comprising nearly 80% of the incoming anesthesia equipment for some developing countries.[15] Despite these donations, the expertise and parts required to maintain them leads to as little as 10% of these donated machines ever becoming operational.[9,16] Rudimentary anesthesia machines have been developed in an effort to overcome this issue by incorporating uninterruptible power supplies, oxygen concentrators, and simple draw over vaporizers.[17,18] While certainly beneficial, these anesthesia machines still fail to provide any access to patient monitoring, the primary method by which clinicians prevent anesthesia-related morbidity and mortality in the developed world.[19] Additionally these devices do nothing to address the need of anesthetic scavenging systems in resource-limited settings.[11] Ultimately, this resource gap contributes to a scarcity of operating facilities in low resource areas, with the estimated number of operating rooms being more than 25 times less than high-income regions, culminating in a 40 fold increase in anesthesia-related death.[8,9]

Increases in U.S. Anesthesia Complications

The economics and demands of healthcare in the United States are pushing anesthesia from in-hospital to outpatient and small-office settings, raising concerns over quality of care and patient safety.[20] Initial lack in mandatory accreditation of small office anesthesia practices may have contributed to a marked increase in adverse events in anesthesia. An ASA Closed Claims analysis showed that for small office claims, more than 40% of monitored anesthesia care (MAC) claims involved permanent brain damage and 21% of MAC claims had unaddressed respiratory depression, half of which were deemed preventable by better patient monitoring.[21] While new mandatory accreditation and stricter state regulation have improved these outcomes in small-office practice, there still remains a discrepancy in the standard of care compared to hospitals.[22,23] The capital cost, space requirements, and necessity for scavenging systems in anesthesia machines cause many clinicians to turn to total intravenous anesthetics (TIVA) without the safety net of ventilation equipment or monitoring, a primary contributing factor of these negative outcomes.[24] Due to their higher fat solubility, intravenous anesthetics often result in drug accumulation and then subsequent delays in recovery once infusion has stopped.[25] More importantly, the inability measure drug concentration, and therefore anesthetic depth, is the most pronounced reason for avoiding intravenous anesthetics. As a result, titrating a dose correctly requires an experienced clinician to account for patient variability, nonlinear relationships between dose and effect, and the synergistic effects between drugs. In a study of 90 patients receiving either propofol (an intravenous anesthetic), isoflurane, or desflurane (both inhalational anesthetics) for anesthesia maintenance, the percentage of patients with purposeful movement was 63% for those who received propofol, and only 23% and 6.7% for those receiving isoflurane and desflurane respectively.[26] Attempts have been made to monitor the effects of intravenous anesthetics on the brain using the Bispectral Index (BIS), however there exists widespread controversy on its consistency in determining patient awareness.38 In contrast, inhalational anesthesia is set by alveolar concentration, which has a far more robust and established relationship to effect.[27] Inhalational anesthesia has also shown to be preferable for induction and maintenance in pediatric cases, as children often have a fear of needles, and inhalational induction is painless and entirely noninvasive.[28] Finally, because inhalational anesthesia is delivered by concentration and not dose, the maximum concentration in the body is capped, decreasing the likelihood of overdose.

Environmental Impacts of Anesthesia

Alongside the need for patient monitoring, the ability to safely scavenge expired anesthetic gases from the anesthesia machine and away from clinicians remains another hurdle outside of the hospital.[11,29–31] This hurdle encourages the use of TIVA over inhalational anesthetics at both increased financial cost and risk of undetected

respiratory depression.[24] Even with appropriate anesthetic scavenging or respiratory monitoring, a secondary impact of inhalational anesthetics is the negative environmental impact.[32] Anesthetic gases have a global warming potential more than 3700 times that of carbon dioxide and contribute to over 1% of the global ozone depletion despite the relatively small size of anesthesia emisisons.[33,34] The introduction of semi-closed anesthesia rebreathing circuits and low fresh gas flow techniques have reduced anesthetic waste, but these still require scavenging systems and additionally necessitate carbon dioxide scrubbing.[35,36] This environmental impact could be dismissed in the face of immediate patient health. However, it is estimated the damages generated by health-care industry pollutants well exceed the 44,000-98,000 who die annual due to preventable medical errors.[37,38] In anesthesia, volatile agent release marks the primary environmental burden (Figure 3.1-1).[39,40]

A system that "reflects" anesthetics back to the patient would remove the need for a scavenging and carbon dioxide removal while also significantly reducing the environmental impact of anesthesia by reintroducing open non-rebreathing circuits. Removing carbon dioxide scrubbing has additional benefits beyond costs and complex logistics. The absorbents used can cause inhaled anesthetics to degrade into carbon monoxide, particularly during low fresh gas flow and when the absorbent is desiccated, with concentrations being lethal in porcine experiments and posing significant risks to pediatric patients.[41,42] Open breathing circuits additionally reduce the technological barriers to using volatile anesthetics in tandem with sophisticated ICU ventilators, potentially allowing for the use of volatile agents

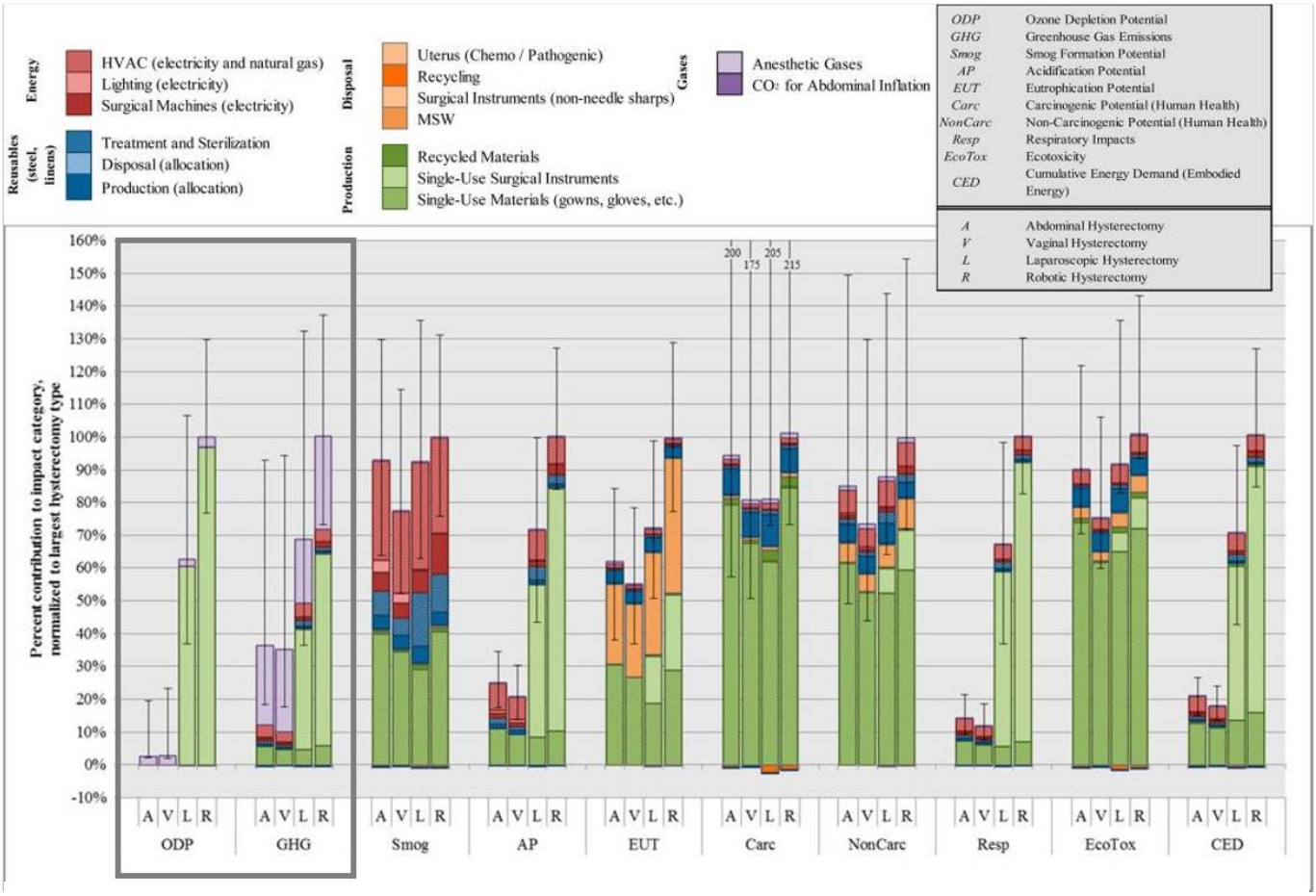

Figure 3.1-1 *Total life cycle environmental impacts of an average hysterectomy by surgery type (normalized to highest hysterectomy type in impact category). Negative values reflect positive environmental impacts due to recycling; Error bars represent 90% confidence interval from Monte Carlo Analysis.*[11]

in long-term sedation in the ICU. Porous materials, such as activated charcoal, have been shown effective in capturing anesthetics.[43] Once saturated, however, the adsorption and release of anesthetic gas could occur rapidly, allowing for capture during exhalation and reflection at inhalation, while simultaneously allowing carbon dioxide, oxygen, and nitrogen to pass freely. This research focuses of a variety of technological advances in anesthesia delivery to address these issues.

III. INNOVATIONS IN ANESTHESIA

Improving Monitoring in Anesthesia

Current methods of measuring anesthetic gas concentrations rely on the unique infrared absorption profile of each anesthetic gas. Determining the concentration therefore requires a variety of infrared filters to identify specifics absorptions peaks, followed by measuring the concentration via the Lambert-Beer Law. While effective, infrared spectroscopy is cost-intensive due to the optics required to continuously measure the adsorption of various infrared wavelengths. However, using differences in gas density using orifice-plate flow sensors poses an alternative method for measuring gas concentrations in binary mixtures. Orifice-plate flow sensors traditionally determine fluid velocity utilizing Bernoulli's Law (Figure 3.2-1). Given a known fluid velocity, they can instead be used to determine fluid density. By combining an orifice-plate sensor with an additional fluid velocity sensor independent to changes in density, the total fluid velocity and composition can be determined. This concept has been proven feasible for measuring various mixtures of helium, carbon dioxide, argon, and room air.[44–46] However, no one has yet developed an anesthetic gas sensor using this technique. The difference in density between anesthetic gas and room air nearly matches the difference between room air and helium (5 times and 6.8 times greater respectively). The accuracy of these devices is also much higher than infrared spectroscopy, with the percent error for such a device being between ±7.5% by volume compared to ±16.7% by volume for infrared spectroscopy.[44,47]

Furthermore, most flowmeters are sensitive to the presence of anesthetic gases. As a result, combining sensors with varying sensitivities to anesthetic gas concentrations can yield both a more accurate flow measurement as well as an anesthetic agent concentration. Statistical tools like Principal Component Analysis excel and determining what factors contribute to the measured signal. As a result, current testing is expanding beyond simply orifice-plate sensors and including hot-wire anemometers, spinning vane anemometers, ultrasound-doppler, ultrasound time-of-flight, and other hybrid sensors.

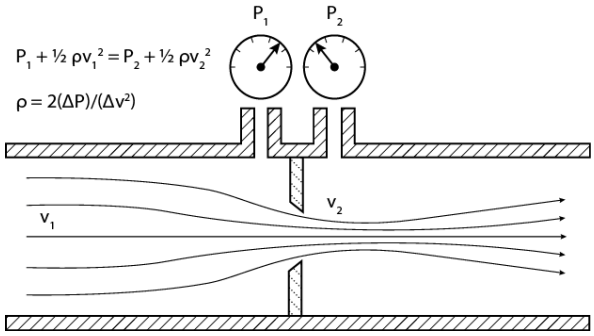

Figure 3.2-1 *Cutaway of an orifice plate flow meter. As gas flows through the orifice, it generates a pressure difference described by Bernoulli's Law. Alternatively, the phenomenon can instead by used to determine fluid density.*

Characterizing Mass Transfer of Anesthetics in Porous Materials

Our key innovation is developing a new method for reusing expired anesthetic gases through continuous, reversible sorption via mesoporous materials. Mesoporous materials have long been used for capturing volatile organic compounds, in some cases reversibly.[48] Utilizing mesoporous materials to reflect anesthetic gases is not an entirely novel idea, however it is poorly explored and understood.[49] The broad spectrum of pore sizes in activated charcoal has made it the material of choice for feasibility testing. However, other materials have remained untested in their ability to specifically capture and release anesthetic gases. We have previously measured the rate of release of release of isoflurane from activated charcoal.[50] In a similar way, we are investigating the effects of pore size, material affinity, flow rate, and gas/adsorbed phase concentration on the sorption isotherm with isoflurane, sevoflurane, and desflurane.

Feedback Control of Capture and Release of Anesthetic Gases

Reflecting anesthetic gas back to the patient through the means of a porous medium would represent a unique method for volatile anesthetic agent recovery and delivery. If this method of anesthetic delivery is successful, it would allow for anesthesia breathing circuits that remove scavenging systems, carbon dioxide scrubbers, and significantly reduce the amount of anesthetic used and wasted during anesthetic maintenance. Previously explored was incorporating such a device into the rebreathing circuit of an anesthesia machine. Such a device was able to show that over the course of a 2 hour mock surgery, activated charcoal is capable of reducing the anesthetic gas needed by over 90% and anesthetic concentrations were maintained to a given set point.[50,51] Future iterations depend largely on the material capabilities found in ongoing research, with this system being feasibly incorporated at various stages in the anesthesia breathing circuit, each with distinct advantages and disadvantages such as range of flow rates and synchrony with patient ventilation. In addition, incorporating feedback control into this device will enable a higher level of efficiency in anesthetic gas delivery and recovery. The basic principle of feedback control consists of measuring the difference between the feedback signal (anesthetic gas concentration) and the desired set point. A controller utilizes algorithms to then produce a related output that reduces this difference. The related output is converted to changes in an actuator (variable flow bypass, temperature, pressure, etc.) to illicit a physical change in concentration that better matches the set point. Feedback control systems, when implemented corrected, allow for more stable, accurate, and fast systems. Ultimately, a device that results in a faster step response then has additional applications in patient-included closed-loop feedback control using pharmacokinetics and pharmacodynamics, target-controlled anesthesia, time course delivery, etc.[52–54] These closed-loop autonomous systems have been shown to result in better control over the delivery of anesthesia with significant reduction in dose overshooting and undershooting.[55]

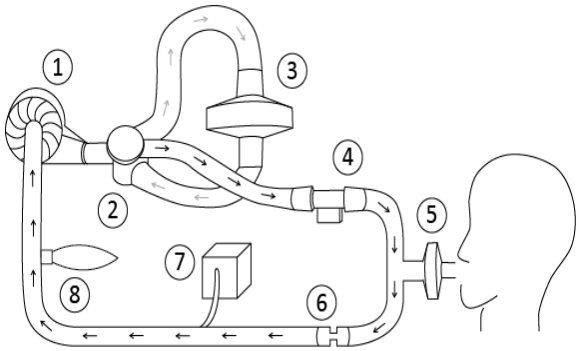

Figure 2.1-1 *A radial blower (1) passes air through a variable valve (2) which can be actuated to scavenge anesthetic from the circuit through a filter (3). A differential pressure flow sensor measures changes in flow and density (4), while a test lung (5) is ventilated by changes in pressure caused by changed in flow from the blower and a fluid resistor (6). Isoflurane can be injected into the system using a custom vaporizer (7) and a reservoir bag (8) adds extra volume to ventilate the test lung.*

II. METHODS

Sensor Fusion for Anesthetic Concentration Sensing

A custom anesthesia machine was created, consisting of a fresh oxygen inlet, anesthetic vaporizer, charcoal scavenging outlet, and custom rebreathing circuit. The custom rebreathing circuit consisted of a radial turbine with fluid resistor and differential pressure sensor anteriorly. The fluid resistor enabled flow changes from the radial turbine to yield pressure changes in that leg of the circuit, allowing for the ventilation of a mechanical lung simulator (TTL Michigan Testlung, Michigan Instruments, Grand Rapids, MI). Finally, posterior to the radial turbine was a reservoir bag (Figure 2.1-1). Data was collected from the radial turbine tachometer and differential pressure sensor, both serving as indicators of gas flow. Several tests were performed to characterize the behavior of these sensors in various conditions. This included steady state flow tests ranging from 2-60 liters per minute to calibrate both sensors using a standard gas flow bench (VT-Plus Gas Flow Analyzer, Fluke Corp., Everett, WA), cyclical tests to determine and correct for hysteresis between the tachometer and the differential pressure sensor, and verification tests to ensure the tachometer's independence in measured flow with the presence of isoflurane. Once a baseline with no anesthetic gas had been

determined, the radial turbine was set to ventilate a test lung at 12 breaths per minute, with a tidal volume of 500 milliliters. Isoflurane was then introduced into the system at concentrations ranging from 0-3.0%, which was measured using a standard infrared gas bench (Datex-Ohmeda, Helsinki, Finland). The difference in flow measured by the differential pressure sensor from the turbine tachometer was attributed to changes in the gas density, and therefore isoflurane concentration. This difference was then passed through a simple alpha-beta filter and used to estimate the isoflurane concentration. This result was then compared to the infrared gas bench. All sensors were sampled at 20 Hz.

Sorption Isotherm of Porous Materials with Anesthetic gases

Two generalized tests were performed to better understand the general behavior of activated charcoal and anesthetic gases. The first test consisted of a 5 L/min flow of oxygen containing 5% isoflurane (Piramal Healthcare Limited, Andhra Pradesh, India) to be passed through a cylindrical vessel containing 42 grams of activated charcoal (Oxpure 1220C-75, Oxbow Activated Carbon, West Palm Beach, FL) until 0.5% isoflurane pushed through (approximately 10 minutes). The vessel was sealed and weighed to determine the amount of anesthetic gas adsorbed onto the surface of the charcoal. Next, a gas flow containing pure oxygen was pushed through the vessel at a rate of 2 L/min and the concentration of anesthetic gas leaving the vessel was measured. The same process was repeated with non-porous beads as a control. A second test consisted of a smaller vessel containing 10 grams of partially-saturated activated charcoal (total weight of 14 grams) placed between the Y-piece of an anesthesia circuit and a mechanical lung simulator (TTL Michigan Testlung, Michigan Instruments, Grand Rapids, MI). This test lung was then driven using a ventilator and 100% oxygen, with the concentration of isoflurane between the vessel and test lung being monitored. A control was performed with non-porous beads.

Anesthetic Gas Scavenger-Vaporizing Device Test

An initial proof-of-concept prototype was demonstrated and fitted within the rebreathing circuit of a current anesthesia. This system consisted of a housing with two chambers, one fitted with a charcoal cartridge, and the other open to free gas flow. A gear with a semicircular opening was actuated externally to determine which chamber, or combination of chambers, had fresh gas traveling through from the anesthesia machine to the simulated lung. In addition, differential pressure sensors were attached at both chambers to detect inhalation and exhalation. Anesthetic gas concentration measurements from a standard infrared gas bench was used for basic feedback control. A microcontroller controlled the orientation of the gear valve to titrate the anesthetic concentration based on breath detection, anesthetic gas concentration, and a user input for desired anesthetic concentration using a rudimentary hysteresis controller.

III. RESULTS

A. Anesthetic Concentration Sensing

The mean difference in measured isoflurane concentration to estimated isoflurane concentration was -0.025% volume, with a standard deviation of 0.091% volume. In a total of over 26,000 measurements, 95% of the estimated isoflurane concentrations fell within 0.2% volume of the measured isoflurane concentration, which is within the accuracy limitations of the infrared gas bench itself (Figure 3.1-1). No statistically significant difference was found in estimating the isoflurane concentration in pure oxygen versus room air.

B. Sorption Isotherm of Porous Materials

Isoflurane was released at concentrations suitable for anesthesia maintenance for a significant amount of time, approximately 10 minutes (Figure 3.2-1). Ventilation was also tested to investigate more dynamic conditions where the device was ventilated with a test lung (Figure 3.2-2). Once saturated, the activated charcoal had absorbed approximately 60% of its total weight in isoflurane and was capable of repeatedly reflecting 10% of its

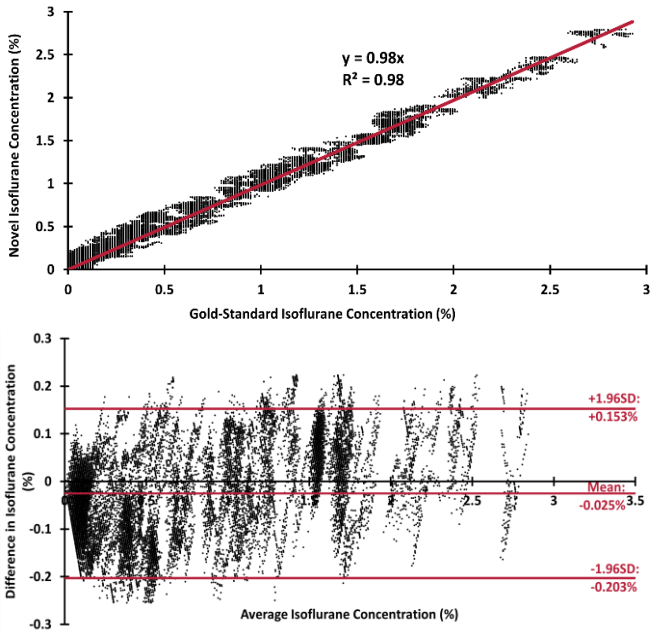

Figure 3.1-1 *Plot of the measured anesthetic concentration versus the estimated anesthetic concentrations (top) along with a Bland-Altman analysis of the two sensors against each other (bottom).*

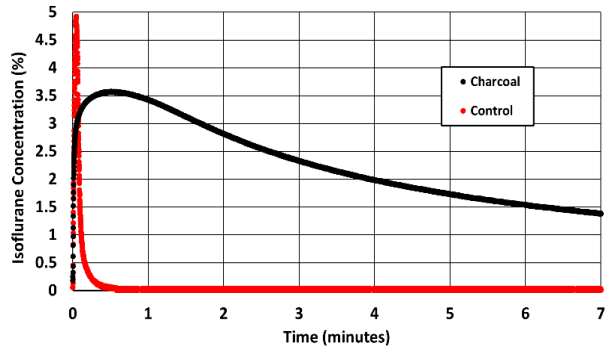

Figure 3.2-1 *The observed concentration of isoflurane leaving the vessel containing 40 grams of saturated activated charcoal as the flow was reversed at 2 liters per minute. The activated charcoal (black) allowed for the gradual released of isoflurane compared to the control (red) containing no activated charcoal.*

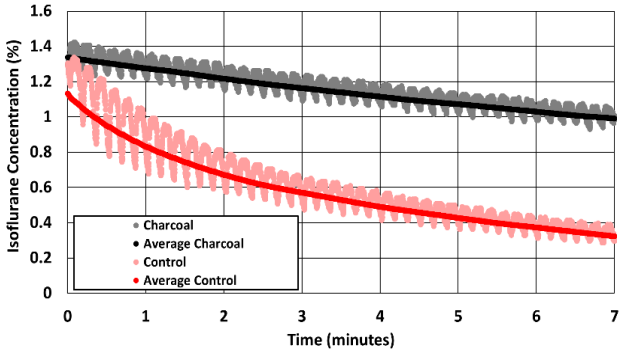

Figure 3.2-2 *The observed concentration of isoflurane during ventilation between 10 grams of activated charcoal and the test lung. Activated charcoal (grey) allowed for the gradual released of isoflurane compared to the control (pink). A running average is shown for both the activated charcoal (black) and control (red).*

total weight in isoflurane or about 3.2 mL of liquid isoflurane. This volume of isoflurane capable of being reflected is the equivalent of anesthesia maintenance at 1 MAC for 1 hour at a fresh gas flow rate of 1 liter per minute.

C. Prototype Device Design

A prototype was successfully created and could perform the basic desired functions. Specifically, inspiratory and expiratory flows were detected and a basic "bang-bang" feedback control was implemented to achieve the desired concentration. Once the charcoal had been saturated from a mock anesthesia induction, the controller was able to maintain average isoflurane concentrations within 0.2% by volume of the user set point (1.2% by volume).

IV. DISCUSSION

Activated carbon has been shown to readily absorb and release anesthetic gases. Creating a system using this material would allow for the implementation of an activated carbon reflector that absorbs, holds, and releases anesthetic gases back to the patient. Not only would this remove the need for an anesthetic scavenging system, but it would also significantly decrease the cost of anesthetic maintenance by reducing the amount of gas vaporized. Preliminary data has shown that 40-mesh activated carbon can capture anesthetic gases and release them with reversed flow at a concentration high enough for sedation. By combining this material with a novel breathing circuit design, we will remove the need for a scavenging system and expand the environments in which anesthesia can be used. Success in this research will ultimately reduce the cost, infrastructure, and expertise needed to deliver general anesthesia. By doing this, the global access to anesthesia and surgical will be greatly increased, reducing the suffering in the world.

Future designs will include a dual column system that oscillates between a vaporizing column and a recovering column (Figure 3.2-3). The system is designed so that it can be used with the circle breathing system and ventilator of a typical anesthesia machine. In this system one column

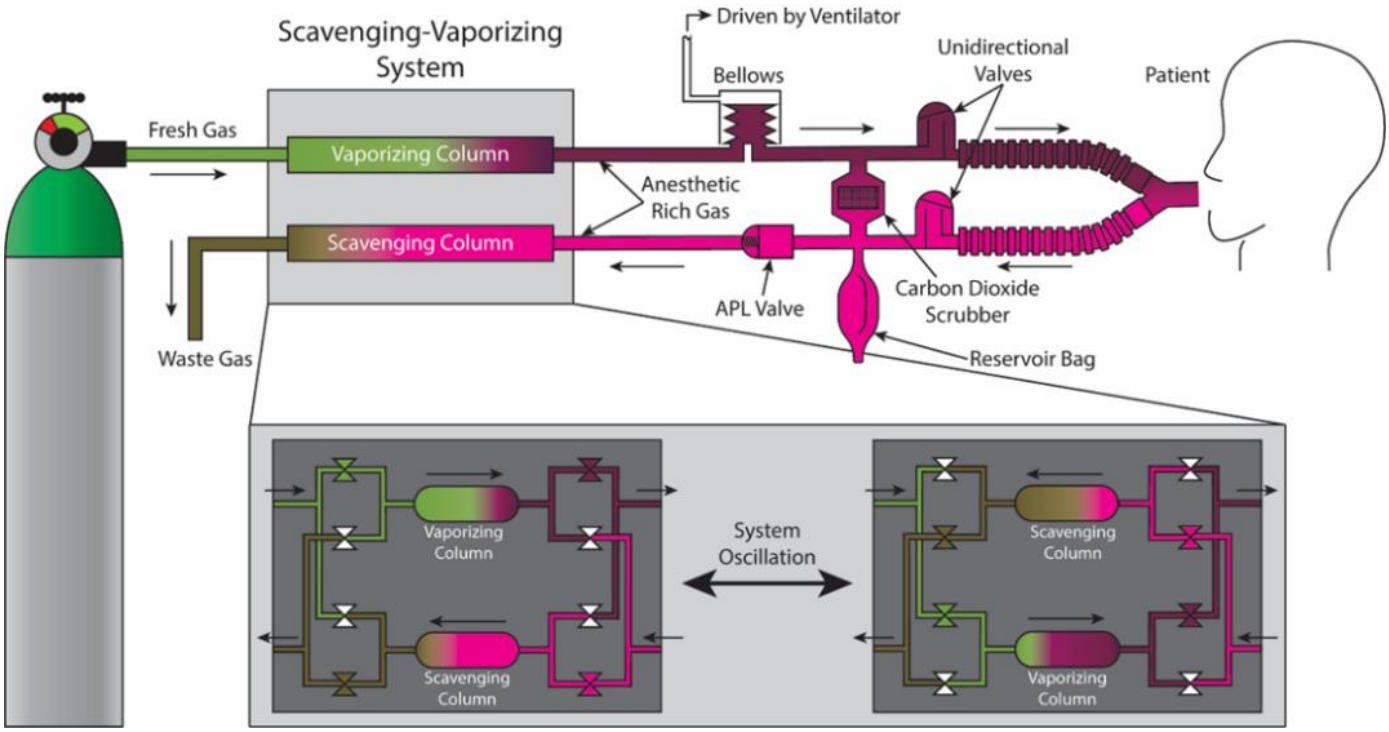

Figure 3.2-3 *Schematic of the proposed Scavenging-Vaporizing System and how it functions with a commercial ventilator. Within the system exists two columns alternating in function between vaporizer and scavenger. These roles are determined through the actuation of valves. Not shown is an anesthetic gas reservoir used if neither column can deliver the set concentration of anesthetic, as well as a fresh gas bypass for when no anesthetic is needed.*

vaporizes anesthetic gas into the fresh gas flow, while the other column simultaneously scavenges exhaled anesthetic gas from the waste stream. When either the vaporizing column begins to deplete, or the scavenging column begins to fully saturate, a series of valves reverse the roles of each column and continue the process indefinitely. A fresh gas bypass will also be included to both titrate the vaporizing column accordingly and allow for pure oxygen delivery when anesthetic gas is no longer needed. A feedback controller based off an anesthetic gas concentration sensor at the inspiratory limb of the proposed system will further control the fresh gas bypass for increased accuracy and stability. By placing the feedback sensor in the inspiratory limb, the patient remains out of the feedback loop, thereby avoiding regulatory hurdles associated with patient-included feedback control systems like target-controlled infusion. If both columns are depleted and can no longer maintain set anesthetic gas concentrations, a reservoir of anesthetic gas separate from the columns will be used to deliver anesthetic gas and re-saturate the entire system. This system will not require any additional work from the clinician as it will be designed to maintain an anesthetic gas concentration set by the clinician, similar to conventional anesthetic gas vaporizers. However, unlike conventional anesthetic gas vaporizers, this system limits clinicians to a single volatile anesthetic for each case and requires that each column be replaced between cases. While there will still be some remaining volatile anesthetic gas in each discarded column, the overall anesthetic gas used will remain substantially lower.

REFERENCES

1. Dripps, R., Lamont, A. & JE, E. The role of anaesthesia in surgical mortality. *Jama* **178,** 261–266 (1961).
2. Tiret, L., Desmonts, J. M., Hatton, F. & Vourc'h, G. Complications associated with anaesthesia - a prospective survey in France. *Can. Anaesth. Soc. J.* **33,** 336–344 (1986).
3. Arbous, M. S. *et al.* Mortality associated with anaesthesia: A qualitative analysis to identify risk factors. *Anaesthesia* **56,** 1141–1153 (2001).
4. Gibbs, N. & Borton, C. *Safety of Anaesthesia in Australia A review of anaesthesia related mortality 2000 - 2002. Report of the Committee convened under the auspices of the Australian and New Zealand College of Anaesthetists.* (2006).
5. Li, G., Warner, M., Lang, B. H., Huang, L. & Sun, L. S. Epidemiology of anesthesia-related mortality in the united states, 1999-2005. *Anesthesiology* **110,** 759–765 (2009).
6. Alkire, B. C. *et al.* Global Access to Surgical Care: a Modelling Study. *Lancet Glob. Heal.* **3,** e316–e323 (2015).
7. Bainbridge, D., Martin, J., Arango, M. & Cheng, D. Perioperative and anaesthetic-related mortality in developed and developing countries: A systematic review and meta-analysis. *Lancet* **380,** 1075–1081 (2012).
8. Khan, M. & Khan, F. A. Anesthetic deaths in a developing country. *Middle East J. Anaesthesiol.* **19,** 159–72 (2015).
9. Funk, L. M. *et al.* Global operating theatre distribution and pulse oximetry supply: An estimation from reported data. *Lancet* **376,** 1055–1061 (2010).
10. Weiser, T. G. *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* **372,** 139–144 (2008).
11. Ariyo, P. *et al.* Providing Anesthesia Care in Resource-limited Settings. *Anesthesiology* **124,** 561–569 (2016).
12. Finch, L. C. *et al.* Evaluation of a large-scale donation of Lifebox pulse oximeters to non-physician anaesthetists in Uganda. *Anaesthesia* **69,** 445–451 (2014).
13. Kingham, T. P. *et al.* Quantifying Surgical Capacity in Sierra Leone. *Arch. Surg.* **144,** 122–127 (2009).
14. Notrica, M. R., Evans, F. M., Knowlton, L. M. & Kelly McQueen, K. A. Rwandan surgical and anesthesia infrastructure: A survey of district hospitals. *World J. Surg.* **35,** 1770–1780 (2011).
15. Gatrad, A. R., Gatrad, S. & Gatrad, A. Equipment donation to developing countries. *Anaesthesia* **62,** 90–95 (2007).
16. WHO Guidelines For Health Care Equipment Donations. *World Heath Organ.* (2000).
17. Eltringham, R. J. & Varvinski, A. The Oxyvent: The anaesthetic machine designed to be used in developing countries and difficult situations. *Anaesthesia* **52,** 668–672 (1997).
18. Beringer, R. M. & Eltringham, R. J. The Glostavent: evolution of an anaesthetic machine for developing countries. *Anaesth. Intensive Care* **36,** 442–448 (2008).
19. Finks, J., Osborne, N. & Birkmeyer, J. D. Trends in hospital volume and operative. *N. Engl. J. Med.* **364,** 2128–37 (2011).
20. The Migration of Care to Non-hospital Settings: Have Regulatory Structures Kept Pace with Changes in Care Delivery. *Am. Hosp. Assoc.* (2006).
21. Bhananker, S. M. *et al.* Injury and Liability Associated with Monitored Anesthesia. *Anesthesiology* **104,** 228–234 (2006).
22. Shapiro, F. E., Jani, S. R., Liu, X., Dutton, R. P. & Urman, R. D. Initial Results from the National Anesthesia Clinical Outcomes Registry and Overview of Office-Based Anesthesia. *Anesthesiol. Clin.* **32,** 431–444 (2014).
23. Shapiro, F. E. *et al.* Office-based anesthesia: Safety and outcomes. *Anesth. Analg.* **119,** 276–285 (2014).
24. Rex, D. K., Heuss, L. T., Walker, J. A. & Qi, R. Trained Registered Nurses/Endoscopy Teams Can Administer Propofol Safely for Endoscopy. *Gastroenterology* **129,** 1384–1391 (2005).
25. Gupta, A. *et al.* Comparison of Recovery Profile After Ambulatory Anesthesia with Propofol, Isoflurane, Sevoflurane and Desflurane: A Systematic Review. *Anesth. Analg.* 632–641 (2004). doi:10.1213/01.ANE.0000103187.70627.57
26. Ashworth, J. & Smith, I. Comparison of Desflurane with Isoflurane or Propofol in Spontaneously Breathing Ambulatory Patients. *Anesth. Analg.* **87,** 312–318 (1998).
27. Eger II, E. I., Saidman, L. J. & Brandstater, B. Minimum Alveolar Anesthetic Concentration: A Standard of Anesthetic Potency. *Anesthesiology* **26,** 756–763 (1965).
28. Eger II, E. I. Characteristics of anesthetic agents used for induction and maintenance of general anesthesia. *Am. J. Heal. Pharm.* **61,** S3–S10 (2004).
29. Urman, R. D., Punwani, N. & Shapiro, F. E. Office-based surgical and medical procedures: educational gaps. *Ochsner J.* **12,** 383–388 (2012).
30. Kotob, F. & Twersky, R. S. Anesthesia Outside the Operating Room : General Overview and Monitoring Standards. *Int. Anesthesiol. Clin.* **41,** 1–15 (2003).
31. Ahmad, S. Office Based-Is My Anesthetic Care Any Different? Assessment and Management. *Anesthesiol. Clin.* **28,** 369–384 (2010).
32. Yasny, J. S. & White, J. Environmental implications of anesthetic gases. *Anesth. Prog.* **59,** 154–158 (2012).
33. Ryan, S. M. & Nielsen, C. J. Global warming potential of inhaled anesthetics: Application to clinical use. *Anesth. Analg.* **111,** 92–98 (2010).
34. Gadani, H. & Vyas, A. Anesthetic gases and global warming: Potentials, prevention and future of anesthesia. *Anesth Essays Res* **5,** 5–10 (2011).
35. Odin, I. & Feiss, P. Low flow and economics of inhalational anaesthesia. *Best Pract. Res. Clin. Anaesthesiol.* **19,** 399–413 (2005).
36. Fee, J. P. H., Murray, J. M. & Luney, S. R. Molecular sieves: an alternative method of carbon dioxide removal which does not generate compound A during simulated low-flow sevoflurane anaesthesia. *Anaesthesia* **50,** 841–845 (1995).
37. Eckelman, M. J. & Sherman, J. D. Estimated Global Disease Burden From US Health Care Sector Greenhouse Gas Emissions. *Am. J. Public Health* e1–e3 (2017). doi:10.2105/AJPH.2017.303846
38. Eckelman, M. J. & Sherman, J. Environmental impacts of the U.S. health care system and effects on public health. *PLoS One* **11,** 1–14 (2016).
39. Thiel, C. L. *et al.* Environmental Impacts of Surgical Procedures: Life Cycle Assessment of Hysterectomy in the United States. *Environ. Sci. Technol.* **49,** 1779–1786 (2015).

40. Sherman, J., Le, C., Lamers, V. & Eckelman, M. Life cycle greenhouse gas emissions of anesthetic drugs. *Anesth. Analg.* **114,** 1086–1090 (2012).
41. Fang, Z. X., Laster, M. J., Chortkoff, B. S. & Kandel, L. Carbon Monoxide Production from Degradation of Desflurane, Enflurane, Isoflurane, Halothane, and Sevoflurane by Soda Lime and Baralyme®. *Anesth. Analg.* **80,** 1187–1193 (1995).
42. Holak, E. J. *et al.* Carbon monoxide production from sevoflurane breakdown: modeling of exposures under clinical conditions. *Anesth. Analg.* **96,** 757–764 (2003).
43. Birgenheier, N., Stoker, R., Westenskow, D. & Orr, J. Activated Charcoal Effectively Removes Inhaled Anesthetics from Modern Anesthesia Machines. *Anesth. Analg.* **112,** 1363–1370 (2011).
44. Yamazaki, S., Funaki, T., Kawashima, K. & Kagawa, T. A concentration measurement system for binary gas mixtures using two flowmeters. *Meas. Sci. Technol.* **18,** 2762–2768 (2007).
45. Youn, C., Kawashima, K. & Kagawa, T. Concentration measurement systems with stable solutions for binary gas mixtures using two flowmeters. *Meas. Sci. Technol.* **22,** 065401 (2011).
46. Kramer, A. & Paula, T. A. High-precision density sensor for concentration monitoring of binary gas mixtures. *Procedia Eng.* **47,** 44–47 (2012).
47. Masimo. ISA OR+ Multigas Monitoring. (2018). Available at: http://www.masimo.com/globalassets/image/emma/isa-or/product_information_anesthetic_gas_monitoring_or.pdf.
48. Alothman, Z. A. A review: Fundamental aspects of silicate mesoporous materials. *Materials (Basel).* **5,** 2874–2902 (2012).
49. Berton, J., Sargentini, C., Nguyen, J. L., Belii, A. & Beydon, L. AnaConDa® reflection filter: Bench and patient evaluation of safety and volatile anesthetic conservation. *Anesth. Analg.* **104,** 130–134 (2007).
50. Kolbay, P., Orr, J. & Kück, K. Reducing Volatile Anesthetic Waste Using Activated Charcoal. in *Proceedings of the 2017 Society for Technology in Anesthesia Annual Meeting* (2017).
51. Kolbay, P., Orr, J. & Kück, K. Development of an Anesthetic Reflection System. in *Proceedings of the 2018 Society for Technology in Anesthesia Annual Meeting* (2018).
52. Madhavan, J. S., Puri, G. D. & Mathew, P. J. Closed-loop isoflurane administration with bispectral index in open heart surgery: randomized controlled trial with manual control. *Acta Anaesthesiol. Taiwanica* **49,** 130–135 (2011).
53. Dussaussoy, C. *et al.* Automated titration of propofol and remifentanil decreases the anesthesiologist's workload during vascular or thoracic surgery: A randomized prospective study. *J. Clin. Monit. Comput.* **28,** 35–40 (2014).
54. Billard, V. Pharmacokinetic-pharmacodynamic relationship of anesthetic drugs: from modeling to clinical use. *F1000 Res.* **4,** 1–10 (2015).
55. Brogi, E., Cyr, S., Kazan, R., Giunta, F. & Hemmerling, T. M. Clinical Performance and Safety of Closed-Loop Systems: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Anesth. Analg.* **124,** 446–455 (2016).