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Vapor Pressures of Anesthetic Agents at Temperatures below Zero Degrees Celsius and a Novel Anesthetic Delivery Device

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Abstract

At room temperature, the vapor pressures of desflurane, isoflurane, and sevoflurane are well above the clinically useful range. We hypothesized that therapeutic concentrations of these agents could be achieved at temperatures below zero, but the vapor pressure-temperature relationship is unknown below zero. Secondly, we hypothesized that this relationship could be exploited to deliver therapeutic-range concentrations of anesthetic vapor. We therefore set out to determine the low temperature-vapor pressure relationships of each anesthetic agent thereby identifying the saturated vapor concentration of each agent at any temperature below zero. To test our hypothesis, we measured the saturated vapor concentration at 1 atmosphere of pressure for temperatures between -60°C and 0°C thus developing an empiric relationship for each agent. There was consistency in repeated experiments for all three agents. To test the empiric data we constructed a digitally-controlled thermoelectric anesthetic vaporizer, characterized the device, and used it to deliver anesthetic vapor to laboratory mice. We report, for the first time, the temperature-vapor pressure relationship at temperatures below 0°C for desflurane, isoflurane, and sevoflurane as well as the T_{MAC} of these agents: the temperature at which the vapor pressure is equal to the minimum alveolar concentration. We describe the construction and limited validation of an anesthetic vaporizer prototype based on this principle. We conclude that clinically relevant concentrations of volatile anesthetics may be achieved at low temperatures.

The temperature-vapor pressure relationship for desflurane, isoflurane, and sevoflurane is well described above 0 degrees Celsius (°C)^{1,2}, but has not been described at temperatures below 0°C. The vapor pressures of anesthetic agents above 0°C are much higher than those used in the clinical setting; therefore they are mixed with medical gases to reduce concentration prior to delivery to the patient. Because a decrease in temperature leads to a decrease in vapor pressure, existing variable-bypass vaporizers are temperature-compensated and contain thermal mass or other design features to prevent inconsistency in the rate of vapor production caused by changes in fresh gas, ambient, and vaporizer temperatures.

We hypothesized that clinically relevant concentrations of anesthetic vapor could be achieved at very low temperatures (less than 0°C), and that in this range, for each agent a mathematical relationship could describe the temperature-vapor pressure relationship. In other words, cooling an anesthetic vapor to a specified temperature would result in delivery of a particular anesthetic concentration. We used the term " T_{MAC} " to refer to the temperature of an anesthetic agent at which the minimum alveolar concentration (MAC) of the agent is delivered. We further hypothesized that once the temperature-vapor pressure relationship at clinical concentrations was determined, this information could be used to construct a prototypical anesthetic vaporizer that used digital temperature control to deliver clinical (i.e. therapeutic-range) anesthetic concentrations.

METHODS

Experiments involving laboratory mice were performed in accordance with the National Institutes of Health guidelines for the care and use of animals in research and approved by the Institutional Animal Care and Use Committee, Oregon Health & Science University, Portland, Oregon.

To determine temperature-percent relationships, a volatile anesthetic agent was placed in a glass Erlenmeyer flask, which was partially submerged in a dry ice bath. A fresh-air inflow line (with a flowmeter) provided a constant flow of 1 liter/minute through the liquid anesthetic, and waste vapor was exhausted into a fume hood. A gas sample line drawing from above the surface of the liquid anesthetic agent at a rate of 150 mL/min was connected to an anesthesia gas monitor (POET II, Criticare Systems, Inc., Waukesha, WI) to determine anesthetic concentrations. The anesthesia gas monitor (AGM) was calibrated by a qualified service technician per manufacturer specification prior to experimentation, and the functionality of the auto-calibration of the AGM was confirmed prior to use. A new water trap, oxygen cell, carbon dioxide absorber, and tubing were used for experimentation, and tubing length was minimized. Agent temperature was measured with a thermometer, and anesthetic concentrations were recorded at intervals of 1°C as the agent was slowly cooled. Trials were performed using desflurane, isoflurane, and sevoflurane, and experiments were repeated 5 times for each agent.

To mathematically model temperature-percent curves for the anesthetic agents, third-order polynomial curves were fit utilizing Prism 6 statistical software (GraphPad Software, La Jolla, CA) and evaluated using the least squares (ordinary fit) setting. After determining temperature-percent curves for each of the three agents, an anesthetic vaporizer prototype was constructed that delivered a user-set anesthetic concentration determined by the temperature of the agent. In this design, fresh gas is bubbled through the agent in the vaporizer chamber. Using a temperature sensor, digital microcontroller, and custom software, the vaporizer actively controlled the temperature of the volatile agent reservoir using pulse-width-modulation of current delivered to a Peltier thermoelectric cooling device.

The prototypal vaporizer consisted of three subsystems:

1. An insulated vessel for the liquid anesthetic, which featured a fresh gas inlet, a mixed gas outlet, and a temperature probe.
2. A thermoelectric refrigeration system to cool the vessel. This system consisted of the thermoelectric device, a coupling apparatus ensuring efficient transfer of heat with the vessel, a cooling bath to remove heat from the hot side of the thermoelectric device, and a power source supplying current that was controlled by pulse-width modulation by an electronic controlling device.
3. An electronic controlling device with custom software implementing a user interface which allowed the user to set the desired agent concentration, and reverse-calculated from the derived curve the necessary temperature to achieve the set concentration, and controlled the thermoelectric cooling device to

maintain the set temperature using a high-precision proportional-integral-derivative algorithms.

To characterize the performance of the vaporizer, liquid sevoflurane was cooled using the prototype vaporizer from room temperature to the temperature determined from the temperature-percent relationship previously derived. Starting at a temperature of 0°C and ending at the set temperature, cooling rates were recorded. Once the desired temperature/concentration was reached, the vaporizer maintained the same temperature for one hour at two different concentrations and flows ranging from 0.5 to 5.0 liters/min. The electronic controlling device was connected to the anesthesia gas monitor via an analog data-out port, and converted the concentration data to a digital reading of sevoflurane concentration 14 times per minute. Multiple readings within a minute were averaged to produce 60 concentration data points for each hour-long validation experiment. These 60 data points were used to determine the average sevoflurane concentration maintained by the vaporizer during characterization.

To test the functionality of the vaporizer, twelve mice (female c57bl/6) were assigned in random order to 30 minutes of sevoflurane anesthesia with either a variable-bypass vaporizer or the digital low-temperature control vaporizer. After chamber induction, mice were connected to the anesthesia circuit where they received 3% sevoflurane at a flow rate of 1 liter/minute delivered from the variable bypass vaporizer. Mouse temperature was monitored using a rectal probe and heart rate was monitored using a biotachometer with needle electrodes. Following preparation, at experimental time zero, mice either continued with variable bypass sevoflurane anesthesia, or were switched to receive sevoflurane via the already-running temperature controlled vaporizer (3% sevoflurane, 1 L/min for both vaporizers). Heart rate, respiratory rate, rectal temperature, sevoflurane concentration, gas flow rate, and circuit gas temperature were measured at Time 0 and every five minutes for 30 minutes total. At the conclusion of the experiment mice were deeply anesthetized with isoflurane and killed via transcardial exsanguination. Mouse blood was then centrifuged (5000 RPM for 5 minutes) and the serum analyzed using an enzymatic autoanalyzer (Abaxis Medical Diagnostics, Union City, CA).

RESULTS

Temperature-percent Determination

Isoflurane, sevoflurane, and desflurane were each cooled to a temperature of less than -50°C. (Figure 1) The cooling-concentration relationship was consistent in multiple trials. Curves were fit and the temperature (C)-vapor pressure relationship was $y = 0.0002x^3 + 0.0301x^2 + 1.6018x + 31.605$ for desflurane ($r^2=0.98$), $y = 0.0001x^3 + 0.0137x^2 + 0.6706x + 11.9598$ for isoflurane ($r^2=0.991$), and $y = 0.00008x^3 + 0.0093x^2 + 0.4024x + 6.48$ for sevoflurane ($r^2=0.999$). In addition to the third order polynomials, exponential and logarithmic relationships were explored, and equations are listed in Table 1. Using established MAC values for individuals aged 30-60 years (desflurane 6.6, isoflurane 1.17, and sevoflurane 1.8; partial pressures expressed as percent of one atmosphere)³ and solving for “x” in the above equations yielded the T_{MAC}. Thus the temperature at which the saturated vapor of the three

widely available volatile anesthetics has concentration equal to MAC (T_{MAC}) is -26.4°C for desflurane, -32.8°C for isoflurane, and -17.9°C for sevoflurane.

Use of Derived Relationship to Deliver Anesthetic

After the prototype temperature-controlled vaporizer was constructed (figure 2), the vessel was filled with sevoflurane and the desired anesthetic temperature was set to -17.9°C , the T_{MAC} of sevoflurane. Anesthetic concentrations and temperatures were recorded over a one-hour period to determine whether the vaporizer was able to maintain the delivery of the desired anesthetic concentration, and the experiment was repeated 3 times. The vaporizer delivered $2.2\% \pm 0.02\%$ sevoflurane ($n=3$ experiments) for 1 hour at -17.9°C . (Figure 3)

To ensure that consistent delivery was not restricted to a single concentration or flow, and in preparation for use in animal experiments, we tested the consistent delivery of anesthetic vapor at a concentration relevant to anesthesia in the mouse using multiple flow rates. We chose a single concentration (3.0%), slightly below the published MAC of sevoflurane in mice (3.22)⁴ as there was no significant surgical stimulation during our experimental procedure. The temperature-controlled vaporizer output for this setting was measured at multiple fresh gas flow rates. The vaporizer maintained a constant delivery of 3% of sevoflurane for flow rates ranging from 0.5-5 L/min. for 60 minutes ($n=3$ experiments for rates ≤ 3 liters/min, and $n=1$ experiment for rates $=4$ and 5 liters/min, each experiment representing a total of over 800 independent measurements of concentration and temperature), illustrated in figure 4.

Finally, physiologic parameters were compared between mice anesthetized using a variable-bypass vaporizer compared to the temperature-controlled vaporizer (design of the apparatus for this experiment is summarized in figure 5). Rectal temperature, heart rate, and respiratory rate were similar amongst mice anesthetized using the variable-bypass vaporizer and the temperature-controlled vaporizer (figure 6). Following experimentation, mouse serum samples were used to obtain electrolyte, kidney function, and liver function laboratory values and data were similar amongst mice anesthetized with a variable-bypass vaporizer and those anesthetized with the temperature-controlled vaporizer. (Table 2)

DISCUSSION

For the first time, we described the temperature-vapor pressure relationship at clinical concentrations for desflurane, isoflurane, and sevoflurane. Using this data, we established the temperature-percent relationship and the temperature-percent at MAC, or “ T_{MAC} ” for each of the three agents. The consistent relationship between mathematical modeling and observed data suggests the observed relationships represent underlying physical characteristics of halogenated hydrocarbons with differing structures, such as intermolecular forces. We found that it is possible to exploit the temperature-vapor pressure relationship in order to deliver volatile anesthetics using technology that is distinct from currently available devices.

We constructed a laboratory prototype anesthetic vaporizer to determine whether it was possible to use the derived temperature-vapor pressure relationships to deliver a clinically

relevant anesthetic concentration. This prototype vaporizer delivered a clinical anesthetic dose over a range of fresh gas flows. Because of conservation of mass, the mixed gas retains the same concentration of vapor after warming as immediately on exit from the vaporizer, and therefore could be delivered to experimental animals without additional physiologic burden. Delivery of a clinical concentration of anesthetic vapor to laboratory animals using a prototype novel device was pursued in order to test the hypothesis in this investigation, but also may suggest a novel method for delivery of clinical anesthetics. Some further work would be required to demonstrate the practicality of such an approach. Contemporary variable bypass vaporizers for sevoflurane and isoflurane have many advantages, including low- or zero power consumption, and an excellent safety and reliability profile. A digital temperature-controlled low-temperature vaporizer based on the principles elaborated here could be compatible with multiple agents, highly reliable, and highly portable, as no excess thermal mass is required, potentially rendering such a device attractive in austere environments.

Our work has several limitations. We tested the derived relationship between temperature and vapor pressure at low temperatures using a digitally controlled prototype vaporizer which is not intended for clinical use. Our testing of vaporizer stability at multiple flows is limited to one concentration slightly below the MAC for sevoflurane in mice, and to flows between 0.5 and 5 LPM. A limitation of the design of challenge for the low-temperature digitally-controlled vaporizer is the high power requirement, a consequence of thermoelectric temperature control. An additional challenge is that if used for multiple agents, there is the possibility of mismatch between the agent as set by the user and the agent actually present in the chamber. Enhancements to the design could prevent this, since the vaporizer itself could measure the specific heat of the substance in the chamber and determine which agent was being used, rendering this multi-agent device resilient to this historical source of error in anesthesia, although such measurements would likely require very high precision, assuming the difference in specific heat between fluorinated hydrocarbons is small. Another potential drawback of the vaporizer is that, as currently designed, it is possible that unrecognized failure of temperature control could deliver a dangerous or even lethal anesthetic partial pressure. Finally, we conducted all of our experiments at 1 atmosphere of pressure and we do not know how results would differ at different altitudes. Based on the physics of liquid vaporization it is likely that consistent partial pressures can be delivered from vaporizers of this type for all agents including desflurane. This is important because it is believed that anesthetic partial pressure is the measure that determines depth of anesthesia.

This work describes the relationship between the vapor pressures of volatile anesthetics and temperatures below zero degrees Celsius, and establishes the temperature-concentration and T_{MAC} , a previously undefined physical property, of desflurane, isoflurane, and sevoflurane. Using this information, we were able to develop a novel digital temperature-controlled vaporizer prototype capable of reliable delivery of inhalational anesthetics at clinical concentrations.

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Figure 1.

Anesthetic vapor concentration is dependent on temperature. A. Each point represents the average of 5 experiments, and error bars represent the standard deviation. Curves were fitted using third-order polynomials with the full equation presented in the text. B. To facilitate evaluation of the temperature-concentration relationship from a functional perspective, data from 1A is plotted as the inverse of 1A curves.

Figure 2. Schematic diagram of digitally temperature-controlled vaporizer. Agent is placed in the reservoir which is contained in a thermoelectric cooling device precooled to 0°C in a cooling bath. The full volume of fresh gas inflow is bubbled through the agent. The temperature of the agent is controlled by pulse-width modulation of electric current controlled by the controller, which uses the relationship we derived for temperature-percent (see text, and figure 1) to determine the set temperature from the set concentration.

Figure 3. Temperature-controlled vaporizer validation at human therapeutic concentration. The vaporizer sustained delivery of 1 MAC of sevoflurane for 1 hour at T_{MAC} , -17.9°C .

Figure 4.

Temperature-controlled vaporizer validation at multiple flow rates. Room temperature sevoflurane was added to the agent chamber and cooled using the vaporizer to the target temperature-percent (see methods). Temperature recording began when the agent temperature crossed 0°C. Example cooling curves for 0.5, 2.0, and 4 liters/min fresh gas flow are displayed at the top of the figure. The slope of the temperature line during cooling from 0°C to target temperature varies with flow, indicating maximal output from the cooling device. At target temperature-percent, concentration recording commenced for 1h. Vaporizer output at all tested flows at 3.0% sevoflurane was stable for the 1h period as demonstrated by standard deviation <0.1 at each flow.

Figure 5.

Schematic diagram of apparatus for testing application of the temperature-vapor pressure relationship in animal experiments. Experimental apparatus was designed to allow randomly-determined switch between variable bypass and digitally temperature-controlled vaporizer at the start of the experiment. The digitally temperature-controlled vaporizer (right) mixed the full fresh gas flow into the agent reservoir (maintained at -13.7°C). Mixed gas emerging from the vaporizer is warmed in a coil with external heating set to 37°C before arriving at the common exit, where concentration and circuit gas temperature are measured prior to delivery.

Figure 6.

Circuit temperature, mouse rectal temperature, heart rate and respiratory rate during anesthesia with variable bypass and digitally temperature-controlled vaporizer. Mice were randomly assigned to receive anesthesia with a variable bypass vaporizer (control) or the prototypal digital temperature control vaporizer exploiting the low-temperature/concentration relationship derived in our experimental protocol. As shown in figure 2, mixed gas was warmed prior to administration to mice.

Table 1

Temperature (x)-Vapor Pressure (y) relationships (Temperature in Kelvins)

Mouse metabolic parameters during anesthesia with variable bypass and temperature-controlled vaporizer. Mice were randomly assigned to receive anesthesia with a variable bypass vaporizer (control) or the prototypal digital temperature control vaporizer exploiting the low-temperature/concentration relationship derived in our experimental protocol. Immediately following anesthesia, mice were killed and serum sampled for a metabolic panel.

Equation type	Isoflurane			Sevoflurane			Desflurane		
	Third Order Polynomial	Exponential	Logarithmic	Third Order Polynomial	Exponential	Logarithmic	Third Order Polynomial	Exponential	Logarithmic
Equation	$y=0.0001x^3+0.0665x^2+15.1070x-1145.036$	$y=(5.7^{*}10^{-8})_ye^{0.0705x}$	$y=-42.6035+17.9387\ln(\log(x))$	$y=0.00008x^3-0.0531x^2+12.3647x-960.6791$	$y=(6.3^{*}10^{-8})_ye^{0.0675x}$	$y=-42.8858+17.9323\ln(\log(x))$	$y=0.0002x^3-0.1410x^2+31.6058x-2368.102$	$y=(7.9^{*}10^{-7})_ye^{0.0646x}$	$y=-36.9761+15.8030\ln(\log(x))$
R2	0.99	0.99	0.99	1	1	1	0.98	0.98	0.98
Sum-of-Squares	15.27	12.79	13.03	3.4	2.84	1.73	62.6	62.34	64.42

Table 2

Serum metabolic parameters after 30 minutes of anesthesia

	Variable bypass		Digital Temperature Control	
	Mean	SD	Mean	SD
Na ⁺	142.17	4.62	144.50	1.22
K ⁺	4.88	0.88	5.42	1.61
CO ₂ ⁻	25.17	1.17	24.33	2.07
Chloride	105.83	3.31	106.33	2.16
Glucose	201.33	36.94	180.83	25.51
Calcium	8.98	0.62	8.98	0.34
Urea Nitrogen	21.00	5.69	20.67	5.32
Creatinine	0.10	0.11	0.13	0.08
Alanine aminotransferase	60.33	59.38	145.50	252.00
Aspartate aminotransferase	136.33	77.68	288.67	438.94
Total bilirubin	0.35	0.05	0.30	0.14