

Endogenous Gas Formation—An In Vitro Study with Relevance to Gas Microemboli during Cardiopulmonary Bypass

Lena Lindholm, PhD, ECCP; Karl Gunnar Engström, PhD, MD

Heart Centre, Cardiothoracic Surgery, Department of Surgery and Perioperative Sciences, University of Umeå, Umeå, Sweden

Presented at the annual meeting of SATS/Scansect, August 26, 2010, Oslo, Norway.

Abstract: Gas embolism is an identified problem during cardiopulmonary bypass (CPB). Our aim was to analyze the potential influence from gas solubility based on simple physical laws, here called endogenous gas embolism. Gas solubility decreases at higher temperature and gas bubbles are presumably formed at CPB warming. An experimental model to measure gas release was designed. Medium (water or blood retrieved from mediastinal drains, 14.6 mL) was incubated and equilibrated with gas (air, 100% oxygen, or 5% carbon dioxide in air) at low temperature (10°C or 23°C). At warming to 37°C, gas release was digitally measured. Also, the effect of fluid motion was evaluated. At warming, the medium became oversaturated with dissolved gas. When fluid motion was applied, gas was released to form bubbles. This was exemplified by a gas release of .45% (.31/.54, medians

and quartile range, volume percent, $p = .007$) and 1.26% (1.14/1.33, $p = .003$) when blood was warmed from 23°C or 10°C to 37°C, respectively (carbon dioxide 5% in air). Consistent findings were seen for water and with the other types of gas exposure. The theory of endogenous gas embolization was confirmed with gas being released at warming. The endogenous gas formation demonstrated a dynamic pattern with oversaturation and with rapid gas released at fluid motion. The gas release at warming was substantial, in particular when the results were extrapolated to full-scale CPB conditions. The interference from endogenous gas formation should be considered in parallel to external sources of gas microemboli. **Keywords:** cardiopulmonary bypass, gas embolization, microemboli, gas solubility, temperature. JECT. 2012;44:126–133

Embolism is a known and feared risk in cardiac surgery and during cardiopulmonary bypass (CPB) and may explain a major part of postoperative morbidity and mortality. Atherosclerotic debris becomes dislodged at aortic manipulation (1), lipids from the wound contaminate retrieved cardiotomy blood (2), and gas bubbles are known to occur (3). Arterial gas embolization during CPB remains a problem despite considerable efforts both scientifically and technically. Modern CPB equipment includes bubble detectors, which have improved the safety of cardiac surgery but not helped in eliminating gas microemboli. Potential sources for gas bubbles have been proposed, including vacuum-assisted venous drainage, air leakage at the venous cannulation site, air introduced at drug administration, insufficient deairing

in the venous reservoir, minibypass circuits without a venous reservoir, or damaged oxygenator fibers (3–8).

Previous science in this field had attention on technical issues with a presumed external origin of gas. In this study we focused on an endogenous formation of gas embolism based on physical mechanisms. It is a well-known fact that the gas solubility in liquids decreases at higher temperature. This phenomenon has obvious implications during CPB with gas being saturated and transported at various temperatures. At CPB warming, gas bubbles are to be expected by simple principles of gas solubility. This issue was discussed in the early days of CPB development, although the exact magnitude of formed gas during warming remained unknown (9). The phenomenon has its parallel in daily living when a glass of cold tap water warms up at room temperature during which gas bubbles become obvious.

The aim of the present investigation was to confirm the phenomenon of endogenous gas formation as a potential and contributing mechanism behind gas embolization during CPB. For this purpose, an experimental digital in vitro model of gas solubility was designed to measure the volume of released gas at warming. The phenomenon was analyzed in retrieved mediastinal drain blood or in

Received for publication December 14, 2011; accepted June 15, 2012.
Address correspondence to: Lena Lindholm, PhD, ECCP, Heart Centre, Cardiothoracic Surgery, Department of Surgery and Perioperative Sciences, University of Umeå, S-901 85 Umeå, Sweden. E-mail: lena.e.lindholm@vll.se

The senior author has stated that authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

water, equilibrated with various types of gas, applying two different temperature spans, and also evaluating the effect of fluid motion.

MATERIALS AND METHODS

Experimental Materials

Gas solubility was tested in two different media: blood and water. The blood was from mediastinal drains retrieved in the first postoperative morning from patients who had undergone routine cardiac surgery ($n = 21$). The patients had a median age of 70.6 years (quartile range 63–79 years) and 86% were men. The hematocrit of this blood was approximately 15% (2). Patient identity was not disclosed at sampling nor documented within the study. With the collected blood, information about gender, age, and type of surgery was recorded only. This sampling procedure does not require ethical approval according to Swedish legislation, a procedure that was confirmed and agreed by the local ethical review board at Umeå University.

Experimental Model

The in vitro method aimed at analyzing gas release at warming. Two temperature differentials and three different gas settings were tested. The design had an ambition to simulate the situation at CPB rewarming from deep hypothermia. The experimental model is shown in Figure 1. The medium was placed inside an incubator made from a modified glass pipette that filled 14.6 mL. The medium was saturated with gas inside the incubator at low temperature (10°C or 23°C). Three gases were tested: air, oxygen (O₂), and carbon dioxide 5% mixed in air. The inlet gas was

humidified and was delivered through a peristaltic pump (2.6 mL/min) and allowed to bubble through the medium. During this procedure the incubator was vertically positioned and gas escaped through a top vent. After gassing, the incubator was topped up to completely fill the enclosed space and the top vent was sealed. The incubator was then turned to a horizontal position for the continued experiment. All equipment and tubes were of gas-tight materials. Air was ambient, whereas the two other gases were of analytical grade.

The flow rate and duration of gas exposure were calibrated to ensure proper presaturation within the incubator. The calibration was based on a series of blood gas measurements (not shown), allowing 10 minutes for experiments with air and 30 minutes for the two other gases. The discrepancy regarding air was because of the pre-existing equilibration of the medium with ambient air. These experiments were for calibration only, not followed by gas release analyses. The calibration experiments were made before the main study.

During the experiment, the sealed incubator with medium had direct fluid communication with a collector open to ambient air (Figure 1). Both the incubator and the collector were at the same hydrostatic level, and therefore the experiments were conducted at constant atmospheric pressure. The collector was positioned on a digital balance (Mettler PM460, Mettler Toledo AG, Greifensee, Switzerland). The balance communicated with a computer at 2-second intervals. The computer was programmed to signal and control the different experimental phases. At warming, released gas was entrapped inside the incubator and the gas displaced an equal amount of medium toward the collector.

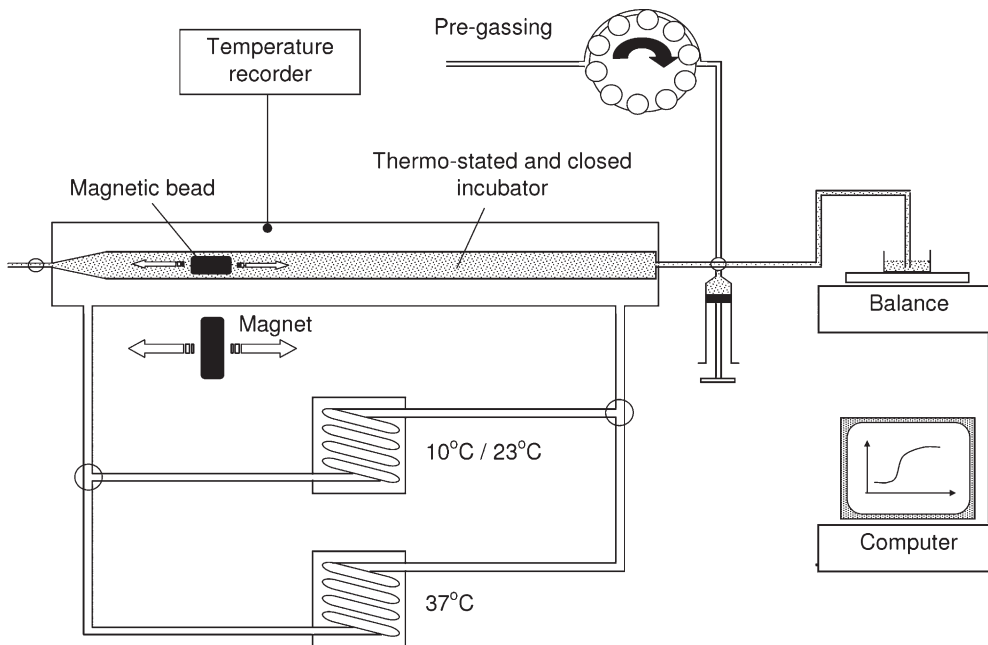


Figure 1. Schematic illustration of the experimental model. See text for details and principles.

The recorded weight equaled that of the displaced medium volume with a presumed density of 1.00 for both blood and water. The displaced volume hence equaled that of the released gas at atmospheric pressure. The computer processed and stored the recorded data for further analysis. Each experiment consisted of 900 weight recordings.

To induce fluid motion, a magnetic bead was positioned inside the incubator. The bead could be operated from the outside by a movable magnet. The bead moved along the incubator from one end to the other at a periodicity of approximately 2 seconds per cycle. For temperature control, the incubator was positioned inside a transparent tube that served as a heat exchanger. The heat exchanger was fed by two separate thermostated water baths for low and high temperature, respectively. The medium inside the incubator reached its target temperature within 60–120 seconds depending on temperature settings. This was digitally measured (Thermostat type 601-40; Intercontrol A/S, Hvidovre, Denmark) and calibrated in a series of control experiments. The temperature outside of the incubator was continuously recorded in all experiments (Figure 1). The rapid temperature increase of the medium was also evident from the data presentation with a corresponding volume expansion being obvious at temperature increase.

The experiment had seven phases (Figure 2): 1) low temperature (10°C or 23°C) and steadiness (2.5 minutes); 2) low temperature and fluid motion (7.5 minutes); 3) low temperature and steadiness (2.5 minutes); 4) temperature change (5 minutes); 5) high temperature (37°C) and steadiness (2.5 minutes); 6) high temperature and fluid motion (7.5 minutes); and 7) high temperature and steadiness (2.5 minutes). A minimum of 10 experiments were conducted per setting, and overall, 131 experiments were performed.

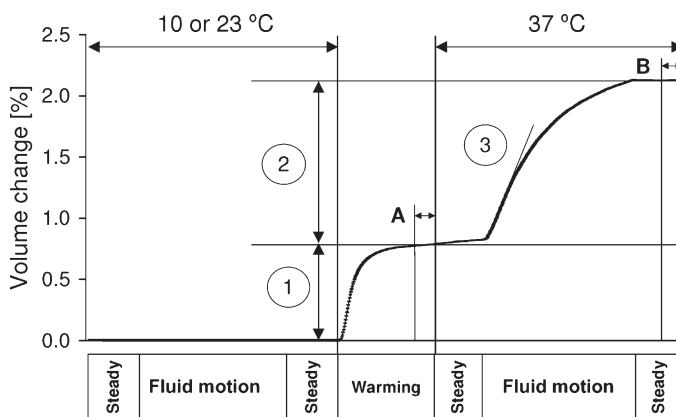


Figure 2. Schematic illustration for how key parameters were extracted: 1) acute volume increase at warming; 2) volume expansion resulting from gas release at 37°C; 3) calculated slope of volume expansion over time resulting from gas release at induced fluid motion at 37°C. Baseline measurement after temperature shift and before the experimental phase at 37°C. The presented curve represents a typical experiment.

Theoretical Calculation of Volume Expansion in Response to Temperature Change

The empirically observed volume expansion at temperature increase was compared with that calculated theoretically. At temperature shift, the volume of a medium changes according to the following equation (10):

$$dV = \beta V_0 dT \quad (1)$$

The volume change (dV) of a predefined volume (V_0) is the function of coefficient (β) and the temperature change (dT). For water, the coefficient β is not constant. From tabulated technical data, the coefficient β could here be approximated for the used temperature span and was calculated according to the following second-order equation. The term (T) refers to the absolute temperature in degrees Celsius:

$$\beta = -0.1083 * T^2 + 15.368 * T - 57.742 \quad (2)$$

The theoretical volume expansion was solved by numerical integration. These calculations were restrained to water only because of the unknown coefficient (β) of blood. These calculations have no influence on the results other than to explain the instant volume increase at warming.

Data Evaluation and Statistics

Data were exported to Excel (Microsoft Inc., Redmond, WA), and relevant information from each experiment was extracted by macro programming. The seven experimental phases were separated to calculate the incremental volume of gas release over time (e.g., slope) but also the mean values for defined time periods. These values were expressed in relation to the volume of medium contained inside the incubator (e.g., volume percent of gas release). The slope values (gas volume percent per second) were multiplied by 1000 for easier overview in the tables. The selected key parameters are schematically presented in Figure 2. An instant volume expansion at warming was evident, which stabilized at 37°C. The mean value during the last minute of the warming period served as a reference for the changes occurring during the high-temperature period.

Nonparametric statistics were applied throughout. Experiments had an ambition to use paired comparisons, a condition that was applied for water and for the majority of the blood-medium experiments. However, because of a few blood experiments without paired conditions, unpaired statistics were used for all between-group comparisons. Therefore, the true effects may have been somewhat underestimated in statistical terms. This potential artifact is of no importance because of the obvious and consistent results. Kruskal-Wallis test was applied for multiple between-group comparisons, (e.g., comparing the three gas types). Mann-Whitney U test with Bonferroni correction was used in post hoc mode. When only two groups were tested against each other, Mann-Whitney U test

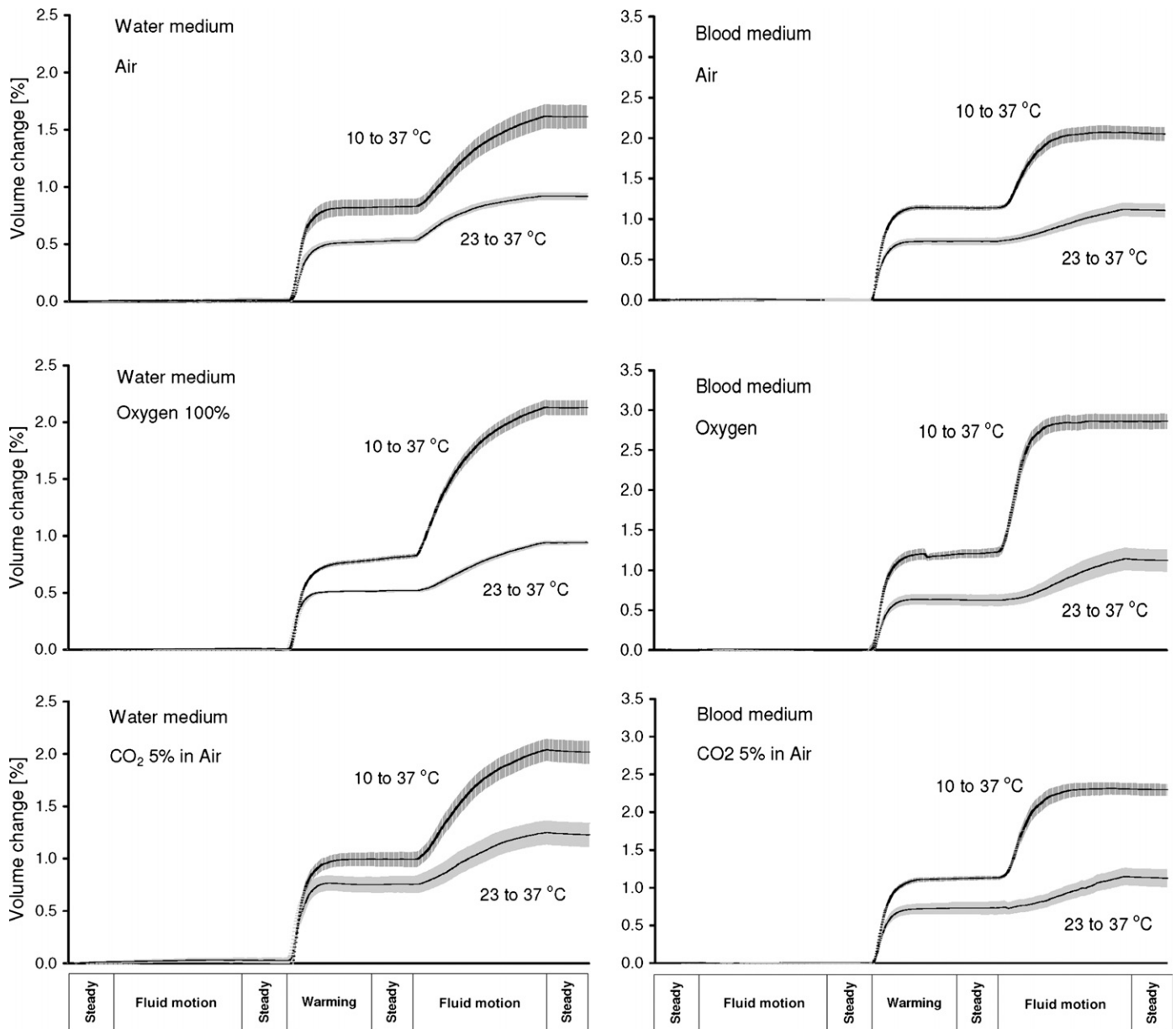


Figure 3. Effects of warming and fluid motion on gas release. The curves show different media, temperature settings, and gas types as indicated in each panel. Mean values \pm standard error of mean. See text and tables for further details.

was applied. For within-group comparisons, Wilcoxon matched-pair test was used. Median values with quartile range are presented. However, in Figure 3, mean values \pm standard errors are presented for better overview of the group differences.

RESULTS

Model Evaluation

During the initial low-temperature period, only minor and nonsignificant changes were observed irrespective of

gas type, temperature settings, or induced fluid motion (Figure 3). These changes were not further analyzed. At warming, a distinct and rapid volume expansion occurred. The volume expansion leveled off within the dedicated 5-minute warming period.

The magnitude of volume expansion stood in proportion to the temperature differential. At 23°C to 37°C, the recorded volume expansion was .50% (.47%/.56%) (air in water medium). The corresponding magnitude at 10°C to 37°C was .76% (.72%/.78%) (Table 1). These values are to be compared with those calculated from physical laws of water expansion, suggesting .43% and .64%, respectively.

Table 1. Gas release at 37°C.

Medium	Gas Type	Temp Span	No.	Free Gas Volume			Volume Slope			Volume Expansion at Warming		
				Percent Change	Q1/Q3	<i>p</i> Value	%/s × 1000	Q1/Q3	<i>p</i> Value	Percent Change	Q1/Q3	<i>p</i> Value
Water	Air	23°C > 37°C	10	.39	.33/.43	.005	1.68	1.37/1.82	.005	.50	.47/.56	.005
Water	Air	10°C > 37°C	10	.74	.70/.77	.005	2.54	2.35/2.82	.005	.82	.70/.93	.005
Water	O ₂	23°C > 37°C	10	.42	.40/.45	.005	1.10	1.05/1.32	.005	.52	.49/.53	.005
Water	O ₂	10°C > 37°C	10	1.39	1.33/1.45	.005	5.64	5.34/6.00	.005	.79	.77/.81	.005
Water	CO ₂ 5% in air	23°C > 37°C	10	.51	.47/.57	.005	1.25	1.15/1.76	.005	.83	.73/.84	.005
Water	CO ₂ 5% in air	10°C > 37°C	13	1.05	.88/1.17	.002	4.17	3.09/4.49	.001	1.01	.92/1.12	.001
Blood	Air	23°C > 37°C	12	.39	.28/.49	.002	.69	.36/.83	.002	.76	.72/.78	.002
Blood	Air	10°C > 37°C	12	.93	.90/1.02	.002	6.19	4.37/6.98	.002	1.12	1.07/1.23	.002
Blood	O ₂	23°C > 37°C	11	.48	.32/.65	.003	.82	.36/1.05	.003	.67	.48/.75	.003
Blood	O ₂	10°C > 37°C	12	1.75	1.56/1.82	.002	12.21	10.70/13.50	.002	1.13	1.09/1.21	.002
Blood	CO ₂ 5% in air	23°C > 37°C	10	.45	.31/.54	.007	.40	.30/.83	.028	.76	.64/.86	.005
Blood	CO ₂ 5% in air	10°C > 37°C	11	1.26	1.14/1.33	.003	8.74	7.72/9.49	.003	1.12	1.08/1.18	.003

The term “free gas volume” refers to the relative volume change at the end of the 37°C period. “Volume slope” refers to the change of gas volume over time during the initial period of 2.5 minutes fluid motion at 37°C. “Volume expansion at warming” refers to the instant volume increase at the temperature shift from low to high temperature. Data refer to median values with quartile range. *p* values refer to Wilcoxon matched-pair test.

The observed volume overshoot was most likely explained by gas release occurring during the acute warming. This acute gas release is here disregarded in the calculations because the baseline was reset at the end of the warming period (compare with Figure 2). Hence, the results presented here are slightly underestimated in their true magnitude of gas release.

The model showed very consistent reactions with modest data spread in response to warming but also in terms of obtained gas release. The response to fluid motion was also consistently observed. Merged gas bubbles collected and became visible inside the incubator. No other mechanisms than gas release could explain the observations.

After warming to 37°C, the medium appeared stable with only modest changes during the initial period of steadiness. In some experiments, a statistically confirmed ($p = .005$ to $p = .021$) positive slope was recorded. This gas release was hardly visible on the volume curves and had no obvious connection to a certain type of medium, gas, or temperature span. These findings were not further analyzed but illustrated a small gas release at a situation of oversaturation. The release of oversaturated gas became evident at fluid motion.

Gas Release in Water Medium

When fluid motion was applied, a vast and highly significant gas release was detected (Figure 3; Table 1). The corresponding slope values illustrated the same phenomenon (Table 1). With the 23°C to 37°C temperature differential, there was no detected difference among the three gas types (Table 2). However, at the 10°C to 37°C span, significant differences were observed among the gases (Table 2). Oxygen resulted in higher gas release compared with the other two types of gas. The gas release was more

pronounced at the 10°C to 37°C change vs. that at 23°C to 37°C, referring to both the measured volume increase and their corresponding slope values (Table 3).

Gas Release in Blood Medium

The phenomena observed with water were largely identical when blood was tested. However, the magnitudes of gas release were more pronounced with blood than with water. This is shown by the numeric values listed in Table 1 and was statistically confirmed at the 10°C to 37°C temperature differential (Table 3). For the 23°C to 37°C span, which induced smaller effects, the statistical comparisons between media were less consistent (Table 3).

DISCUSSION

The problem with gas microembolization during CPB has been extensively investigated (3–8). In these reports, an external original of gas is near exclusively presumed, and techniques to avoid external air from entering the CPB circuit have been evaluated. In view of the remaining problem with gas microembolization, gas bubble detectors and gas removal devices are appreciated in clinical practice.

In this report we introduce a new term, “endogenous” gas embolization. The gas solubility within a medium varies with the temperature and increases at cooling. When a medium is saturated at a low temperature, the excess of gas becomes released when the medium is warmed. These circumstances are expressed in basic physical laws (10) with relevance to CPB. The CPB principle includes all these aspects that makes these laws important with gas exchange inside the oxygenator and temperature variations induced by a heat exchanger. Our hypothesis readdresses findings from the early days of

Table 2. Differences in gas formation among different gas exposures.

Medium	Gas Type	Temp Span	Volume Comparisons				Volume-Slope Comparisons			
			p Value	Air vs. O ₂	Air vs. CO ₂ 5% in Air	O ₂ vs. CO ₂ 5% in Air	p Value	Air vs. O ₂	Air vs. CO ₂ 5% in Air	O ₂ vs. CO ₂ 5% in Air
				p Value	p Value	p Value		p Value	p Value	p Value
Water	Air	23°C > 37°C	.093				.096			
Water	O ₂	23°C > 37°C								
Water	CO ₂ 5% in air	23°C > 37°C								
Water	Air	10°C > 37°C	<.001	.001	.055	.004	<.001	.001	.105	.006
Water	O ₂	10°C > 37°C								
Water	CO ₂ 5% in air	10°C > 37°C								
Blood	Air	23°C > 37°C	.533				.545			
Blood	O ₂	23°C > 37°C								
Blood	CO ₂ 5% in air	23°C > 37°C								
Blood	Air	10°C > 37°C	<.001	<.001	.011	.001	<.001	<.001	.017	.001
Blood	O ₂	10°C > 37°C								
Blood	CO ₂ 5% in air	10°C > 37°C								

Statistical results from group comparison of gas exposures are listed. Reference is made to Table 1 for numeric overview. *p* values refer to the relative volume change as a result of gas release at the end of the 37°C period or slope values during the initial 2.5 minutes of fluid motion at 37°C. Kruskal-Wallis test was applied on the group level, and Mann-Whitney *U* test was used for post hoc comparisons. Bonferroni correction was applied to all post hoc analyses.

Table 3. Differences between water vs. blood medium and between 10°C vs. 23°C.

Medium	Gas Type	Temperature Span	Gas Volume	Volume Slope
			p Value	p Value
Water vs. blood	Air	23°C > 37°C	.843	<.001
Water vs. blood	O ₂	23°C > 37°C	.324	.072
Water vs. blood	CO ₂ 5% in air	23°C > 37°C	.496	.004
Water vs. blood	Air	10°C > 37°C	.015	.002
Water vs. blood	O ₂	10°C > 37°C	.007	<.001
Water vs. blood	CO ₂ 5% in air	10°C > 37°C	.040	.001
Water	Air	23°C > 37°C vs. 10°C > 37°C	<.001	.003
Water	O ₂	23°C > 37°C vs. 10°C > 37°C	<.001	<.001
Water	CO ₂ 5% in air	23°C > 37°C vs. 10°C > 37°C	<.001	<.001
Blood	Air	23°C > 37°C vs. 10°C > 37°C	<.001	.001
Blood	O ₂	23°C > 37°C vs. 10°C > 37°C	<.001	<.001
Blood	CO ₂ 5% in air	23°C > 37°C vs. 10°C > 37°C	<.001	<.001

Statistical results from group comparisons are listed. Reference is made to Table 1 for numeric overview. *p* values refer to the relative volume change resulting from gas release at the end of the 37°C period or slope values during the initial 2.5 minutes of fluid motion at 37°C. Mann-Whitney *U* test was applied.

CPB development (9). In the historic CPB era, with a bubble oxygenator ahead of a defoamer, bubbles were part of the oxygenation technique. Nevertheless, Donald et al. (9) identified the problem of gas release at warming from in vitro experiments. Their findings were of a descriptive nature to identify gas bubbles but they were unable to measure the gas volume. In animal experiments, three of five dogs died after exposure to a CPB medium that had been saturated at 20°C and then warming to 36°C (9). Forty years later, the phenomenon was readdressed by Geissler et al. (11) reporting an experiment that introduced a cold-saturated CPB medium into eight normothermic dogs. Their model simulated rapid cooling, during which gas microemboli were confirmed in the central aorta when the

temperature gradient equaled or exceeded 10°C (11). Today, with an increased confidence in CPB technology and with improved surgical methods, the problem with endogenous gas formation seems to have been neglected.

In brief, our results clearly identified the existence of endogenous gas formation of substantial magnitudes. The tested temperature spans aimed at simulating rewarming from deep hypothermia. A surprising finding was the phenomenon of gas oversaturation with the oversaturated excess gas being rapidly released at fluid motion. Although carbon dioxide is known for its high solubility, the most pronounced gas release was instead seen with oxygen. In our experiments, carbon dioxide accounted for only 5% mixed in air, whereas oxygen was tested at 100%

concentration. Nevertheless, at the 10°C to 37°C temperature span, it was confirmed that the small contribution of carbon dioxide produced higher gas release than with air alone. From the technical literature, it is known that both oxygen and carbon dioxide have higher solubility coefficients than the nitrogen of air (10). Oxygen is of interest also in perspectives of hemoglobin. For the temperature span of 10°C to 37°C, blood produced higher gas release than water. This was regardless of gas type. All gas types had oxygen in common at various concentrations. At present, the relative contribution of hemoglobin and its oxygen storage cannot be concluded about. Further experiments are needed to clarify this issue.

If our findings were scaled up for clinical comparison, a gas release of 63 mL is anticipated when blood is heated from 10°C to 37°C. This calculation was based on the most realistic experimental situation of using 5% carbon dioxide in blood and by assuming a blood volume of 5 L. In perspectives of our findings, the position of the heat exchanger in relation to the oxygenator and/or the venous reservoir becomes an important issue. Its preferred position would be before the oxygenator, which fortunately is common practice for CPB circuits of today. However, a preferred position of the heat exchanger would rather be inside the venous reservoir open to venting. This was common practice with the old-type bubble oxygenators.

The phenomenon of gas release at warming becomes a problem when blood is heated inside a closed circuit. To what extent the oxygenator is considered to be a closed circuit remains speculative. It is tempting to believe that gas bubbles are trapped and vented away over the oxygenator fibers, although this presumption is not confirmed. This interpretation also presumes that the gas has succeeded in becoming released before its passage through the oxygenator. This assumption is not supported in our experiments. The speed of blood flow and the time for passage through the heat exchanger, the oxygenator, and the arterial line is measured in a few seconds. It was here observed that the gas release was rather slow and, therefore, not expected to have reached a steady state during this short timeframe. In our model, the main gas release occurred at fluid motion provided by a magnetic bead that moved slowly. The generated Reynold number was not possible to calculate at this fluid motion, and questions about laminar vs. turbulent flow remained unanswered.

Unfortunately, the phenomenon of endogenous gas formation is not easily avoided. Gas is dissolved in the medium according to physical laws. The gas becomes released and trapped inside the circuit at warming. A medium cannot be degassed without applying negative pressure. Also, a pre-gassing routine of the CPB prime with an alternative gas is not expected to overcome the problem. In this study, a variety of gases were tested, all sharing the same problem in that oversaturated gas must escape at warming.

The natural solution would be to avoid hypothermia. At best, the temperature gradients should be kept to a minimum, in line with historic recommendations (9,11). From our experiments, this routine is anticipated to reduce the speed of gas release but not to reduce the amount of accumulated gas. Cooling protects against ischemic injuries (12), and for CPB, arrest cooling is mandatory. The risk-to-benefit circumstances around cooling must be considered, comparing endogenous gas formation with ischemic body protection.

The unknown effect from endogenous gas formation adds a challenge to the science of brain damage. Type II brain injury, or neurocognitive decline, is commonly discussed in conjunction with microemboli during CPB (8). The nature of neurocognitive decline most likely involves multiple mechanisms. Nevertheless, gas embolization is intuitively understood as having a negative impact on the patient.

The present study was limited to in vitro conditions only, to identify and quantify the amount of gas released at warming. For this purpose, a static model was designed without flow. During CPB, blood is warmed gradually. This may influence the amount of gas being released during each cycle of blood passage but not the accumulated volume of formed gas. An animal model or an intraoperative approach would not have allowed the necessary exactness needed here. Moreover, the comparison between types of gas and media opens up mechanistic interpretations. Retrieved mediastinal blood was used rather than venous blood, taking into account that the required volume for each set of experiments exceeded 100 mL. The unfavorable choice of blood medium may interfere with the potential influence from red blood cells. Unfortunately, a minor acute gas release at temperature increase was disregarded in our model. For water, this gas release was calculated in view of its known thermal volume expansion. The discrepancy was in the range of .1%. Moreover, our experiments reported the results at constant atmospheric pressure. This enabled the measurement of gas volume release without influence from counterbalancing pressures. The pressure varies during CPB and may have relevance for the phenomenon. In the experiments performed by Donald et al. (9), the system was pressurized. With their setup, the gas release was confirmed but the gas volume was not possible to measure.

In conclusion, the hypothesis of endogenous gas formation was confirmed. At warming, the gas solubility decreased and the excess gas formed bubbles. It was evident that a warm medium may become oversaturated with gas. The oversaturated condition became rapidly corrected at fluid motion with formation of gas bubbles. The observed gas release at warming was substantial and corresponded to 63 mL when the results were extrapolated to the CPB conditions.

ACKNOWLEDGMENTS

Supported by the Heart Foundation of North Sweden. We acknowledge the laboratory technician Berith Lundström for experimental support.

REFERENCES

1. Boivie P, Hansson M, Engström KG. Intraluminal aortic manipulation by means of intra-aortic filter, cannulation, and external clamp maneuvers evaluated versus dislodged embolic material. *J Thorac Cardiovasc Surg.* 2006;131:283–9.
2. Appelblad M, Engström KG. Fat content in pericardial suction blood and the efficacy of spontaneous density separation and surface adsorption in a prototype system for fat reduction. *J Thorac Cardiovasc Surg.* 2007;134:366–72.
3. Kurusz M, Butler BD. Bubbles and bypass: An update. *Perfusion.* 2004;19:49–55.
4. Groom RC, Quinn RD, Lennon P, et al. Detection and elimination of microemboli related to cardiopulmonary bypass. *Circ Cardiovasc Qual Outcomes.* 2009;2:191–8.
5. Lynch JE, Wells C, Akers T, et al. Monitoring microemboli during cardiopulmonary bypass with the EDAC® quantifier. *J ECT.* 2010;42:212–8.
6. Weitkempfer H-H, Oppermann B, Spilker A, Knobl HJ, Körfer R. Gaseous microemboli and the influence of microporous membrane oxygenators. *J ECT.* 2005;37:256–64.
7. De Somer F. Impact of oxygenator characteristics on its capability to remove gaseous microemboli. *J ECT.* 2007;39:271–3.
8. Borger MA, Peniston CM, Weisel RD, Vasiliou M, Green RE, Feindel CM. Neuropsychologic impairment after coronary bypass surgery: Effect of gaseous microemboli during perfusionist interventions. *J Thorac Cardiovasc Surg.* 2001;121:743–9.
9. Donald DE, Fellows JL. Physical factors relating to gas embolism in blood. *J Thorac Cardiovasc Surg.* 1961;42:772–81.
10. Poling BE, Prausnitz JM, O'Connell JP. *The Properties of Gases and Liquids.* 5th ed. New York, NY: McGraw-Hill; 2001:8.112.
11. Geissler HJ, Steven JA, Mehlhorn U, et al. Cooling gradients and formation of gaseous microemboli with cardiopulmonary bypass: An echocardiographic study. *Ann Thorac Surg.* 1997;64:100–4.
12. Lindholm L, Bengtsson A, Hansdottir V, Lundqvist M, Rosengren L, Jeppsson A. Regional oxygenation and systemic inflammatory response during cardiopulmonary bypass: Influence of temperature and blood flow variations. *J Cardiothorac Vasc Anesth.* 2003;17:182–7.