

## Comparative Study Between Halothane and Isoflurane on Hypoxic Pulmonary Vasoconstriction and its Reflection on Tissue Oxygenation During One Lung Anesthesia

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### ABSTRACT

**Purpose:** There is a high incidence of hypoxemia and hypercapnia during one lung anaesthesia in patients undergoing pulmonary surgeries for lung cancer. Many factors are claimed to affect oxygenation during one lung anaesthesia. In our work, we studied the effect of halothane and isoflurane on hypoxic pulmonary vasoconstriction (HPV) as an important factor affecting tissue oxygenation during one lung ventilation (OLV).

**Materials and methods:** Forty patients are randomly divided into two equal groups A and B:

Group A: Patients are going to receive halothane anaesthesia.

Group B: Patients are going to receive isoflurane anaesthesia.

The effect of halothane and isoflurane on HPV was studied on both groups as reflected by systemic, pulmonary hemodynamics and blood gases. In spite of the fact that isoflurane is known to abolish the HPV by its vasodilator effect.

**Results:** No marked difference was noticed between both groups as regard tissue oxygenation. so, both isoflurane and halothane can be used safely during OLV.

**Key Words:** *Isoflurane - Halothane - Hypoxic vasoconstriction.*

### INTRODUCTION

The most common indication for thoracotomy in adults is lung malignancy. Surgeries for lung cancer now are done by one lung anaesthesia technique to give easy convenient surgical approach.

During OLV, close monitoring of oxygenation is essential [19]. Previous studies suggested that HPV is considered to be an important mechanism by which blood flow is diverted away from atelectatic or hypoxic regions of the

lung to the better ventilated normoxic regions [9].

This blood flow diversion minimizes venous admixture and increases arterial oxygen tension. Maintenance of normal arterial CO<sub>2</sub> pressure is also mandatory during OLV [9,19].

This work is done to compare between the effect of halothane and isoflurane on HPV as reflected by blood gases, pulmonary and systemic hemodynamics during OLV.

### PATIENTS AND METHODS

Forty ASA-physical status II, III patients undergoing elective thoracotomy for lung resection in the National Cancer Institute fasted overnight after their written informed consent was obtained.

Patients with fever, anaemia or history of chronic exposure to drugs known to affect the systemic and pulmonary haemodynamics were excluded from participation.

Patients were randomly assigned to receive halothane or isoflurane in 100% oxygen. The patients were classified into two groups:

Group A: Included 20 patients (halothane group).

Group B: Included 20 patients (isoflurane group).

Routine general examination and investigation were done with special concern to chest X-ray and blood gases and PFT (Pulmonary function tests).

*Premedication:*

Was carried out with morphine 0.1 mg/kg IM, 30-90 minutes before surgery and midazolam 3 mg IV in operating room.

*Preoperative preparation:*

ASA standard monitors were applied on admission to the operating room using Hewlett Packard monitor model 645.

5 leads ECG monitor is established in operating room. All patients had radial artery catheter placed for systemic arterial blood pressure and blood gases. Pulse oximetry and capnography for measurement of oxygen saturation and end tidal CO<sub>2</sub> respectively.

Central venous access with central venous pressure (CVP) was introduced in every patient for fluid management. Pulmonary artery catheter 4 lumen into a 7F. catheter 110 cm long with polyvinyl chloride body was introduced [5]. Insertion of the pulmonary artery catheter was done through the central venous access with Seldinger's technique through the internal jugular vein.

After attaining a pulmonary artery position minimal catheter advancement resulted in pulmonary capillary wedge wave form. The pulmonary tracing reappeared when the balloon was deflated.

*Induction:*

Anesthesia was induced by sodium thiopental 2.5%, 3-4 mg/kg and fentanyl 2 µg/kg. Pancuronium as I.V. bolus of 0.1 mg/kg after 3 min pre oxygenation. Patients were ventilated via face mask with halothane or isoflurane in 100% oxygen left or right sided double lumen tube was introduced and its position was confirmed by auscultation before and after the patient was placed in the lateral decubitus position.

*Maintenance:*

Anaesthesia was maintained by halothane (0.5-1) MAC in oxygen in group A and with isoflurane (0.5-1) MAC in oxygen in group B. Both groups were supplemented with intermittent doses of fentanyl (2 µg/kg) and pancuronium 0.01-0.02 mg/kg.

*Ventilation:*

After introduction of the double lumen and checking of its position, ventilation was con-

trolled by a volume-cycled ventilator at a rate of 12 cycles/min and tidal volume of 12 ml/kg. These rates were readjusted to maintain acid-base status and PaCO<sub>2</sub> within physiological limits.

*The following parameters were recorded:*

- Systemic hemodynamics including mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), Cardiac output (CO) and systemic vascular resistance (SVR).
- Pulmonary hemodynamics including mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR).
- Arterial blood gases including blood pH, oxygen partial pressure (PaO<sub>2</sub>), carbon dioxide partial pressure (PaCO<sub>2</sub>) and hemoglobin oxygen saturation (SaO<sub>2</sub>).

These hemodynamics and blood gases parameters were obtained at the following intervals of the surgical procedures:

T1 → 10 min after induction.

T2 → After occlusion of the double lumen tube.

T3 → After clamping of the pulmonary artery.

T4 → One hour after clamping the pulmonary artery.

T5 → At the end of anaesthesia.

Systemic vascular resistance and pulmonary vascular resistance were calculated in dyne/cm<sup>2</sup>/sec using this equation.

$$SVR = (MAP - CVP) / CO \times 80$$

$$PVR = MPAP - PCWP / CO \times 80$$

*Recovery:*

Patients received neostigmine (40-80 µg/kg) and glycopyrolate 1 µg/kg for reversal of neuromuscular blockade after the surgical procedure and before emergence of anaesthesia.

*Statistical analysis:*

Data were processed and analyzed using the statistical package SPSS for windows version 8 on an IBM compatible computer. Numerical data presented as means + standard deviation, and categorical data as frequency distribution. Comparison between different reachings within

each group of patients was done using freedman 2 way A NOVA test followed by wilcoxin matched pairs tests.

Mann-Whitney test was used to compare the readings of the 2 groups Chi-Squared test was used to compare categorical data of the 2 groups.

## RESULTS

This study was conducted on 40 patients having lung malignancy. They were subjected to pulmonary resection with OLV.

Group A: Included 20 patients all received halothane anaesthesia.

Group B: Included 20 patients all received isoflurane anaesthesia.

From Table (1), we have all the patients demographics and operative characters. This includes age, weight, height and operation time.

There were no differences as regards the four demographic variables between both groups.

Table (2) shows the systemic hemodynamics, namely mean arterial blood pressure (MAP), heart rate (HR), central venous pressure (CVP) cardiac output (CO) and systemic vascular resistance (SVR) in the five intervals mentioned before. Comparison between halothane and isoflurane groups.

From the table, we noticed that MAP was found to be significantly higher with isoflurane than with halothane at T2 and T5. In isoflurane group, SVR was 1003.6, 998.3, 1045.5 and 1101 dyne/cm sec in comparison to halothane (1117.4, 2057.5, 1075.9, 1427.1). The difference was significant at T2 and T3.

Heart rate was found to be higher also with isoflurane than with halothane at T1 through T4 (88.90, 78.80, 80.80 and 78.40 b/min) in isoflurane group compared with (73.20, 73.30, 77.80 and 77.80 b/min) with halothane group. However, it was lower with isoflurane than halothane at T1. The higher values of HR at T1 and T2 were significant.

CVP was also found to be higher with isoflurane than with halothane at all the time intervals (11.60, 15, 13.30, 11.10 and 12.20 cm H<sub>2</sub>O) in isoflurane group, compared with

(10.30, 11.00, 10.30, 10.80 and 9.40 cm H<sub>2</sub>O) in isoflurane group.

CO showed significantly higher values with isoflurane than halothane at all time intervals (6.80, 6.81, 6.44, 6.33 and 6.64 L/min) in isoflurane group, compared with (5.24, 5.63, 5.46, 5.63 and 5.93 L/min) in the halothane group. As regards SVR, it was lower in isoflurane group than halothane group at T2-T5. It was (1003.6, 998.3, 1045.5 and 1101.0 dyne/Scm) in isoflurane group. In comparison to halothane (1117.4, 1057.5, 1075.9, 1427, dyne/Scm<sup>-5</sup>). The difference was significant at T2 and T3).

Table (3) shows a comparison between the two groups as regard changes in pulmonary hemodynamics. Three pulmonary hemodynamic parameters were assessed, namely, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR) at five time intervals.

MPAP were found to be higher with isoflurane than with halothane. The difference was significant at T2 and T4 (28.90 and 26.10 mmHg) in isoflurane and (26.80 and 23.10 mmHg) in the halothane group.

PCWP were found to be higher with isoflurane than with halothane. The difference was significant at T2 and T4 (18.00 and 16.00 mmHg) in isoflurane group compared with (15.70 and 13.50 mmHg) in halothane group.

On the other hand (PVR) showed significant decrease in isoflurane group as compared to halothane at all time intervals (139.00, 119.00, 129.60, 128.90 and 131.70 dyne/scm<sup>-5</sup>), isoflurane group and (156.20, 132.30, 141.00, 115.70 and 141.50 dyne/scm<sup>-5</sup>) in halothane group.

From Table (4), we notice that pH was found to be significantly higher with isoflurane than halothane at T1, T2, T3 and T5 (7.41, 7.38, 7.39 and 7.34) in isoflurane and (7.36, 7.33, 7.34 and 7.32) in halothane group. There was no difference at T4.

As regard PaO<sub>2</sub>, no significant difference could be elicited at all time intervals between both groups. Both decrease PaO<sub>2</sub> significantly at T2-T3 compared to T1.

PaCO<sub>2</sub> showed higher values with isoflurane than halothane at all time intervals. The differences were statistically significant at T1, T3, T4

and T5 (41.90, 43.90, 42.90 and 45.20 mmHg) in the isoflurane group and (40.20, 40.40, 38.00 mm and 41.40 mmHg) in the halothane group. However, the still higher value at T2 could not reach significant.

On the other hand, oxygen saturation (SaO<sub>2</sub>) showed decrease in both halothane and isoflurane at T2-T3 intervals, but the decrease is more significant in halothane than isoflurane group.

Table (1): Patient demographics and operative characters.

Variable	Group A		Group B	
	Mean	St. dev	Mean	St. dev
Age	61.10	±7.73	60.70	±6.60
Weight	76.70	±7.21	83.60	±7.03
Height	169.10	±4.45	172.60	±4.92
Operation time	2.91	±0.5	2.62	±0.23

Data are: Mean & S.D.  
\* Significant ( $p < 0.05$ ).

Table (2): Systemic haemodynamic: Comparison between group A (halothane) and group B (isoflurane).

Variable	Time	Group A		Group B		p value
		Mean	St. dev	Mean	St. dev	
MAP (mmHg)	T1	83.30*	±10.42*	100.40*	±9.48*	0.00*
	T2	78.50*	±14.08*	96.00*	±7.12*	0.00*
	T3	76.90*	±6.28*	85.40*	±6.94*	0.00*
	T4	79.50*	±8.45*	86.40*	±6.05*	0.00*
	T5	89.30*	±10.19	92.30	±7.28*	0.29
HR (beat/min)	T1	3.20*	±7.85*	88.90*	±5.55*	0.01*
	T2	73.70*	±8.74*	78.80*	±5.59*	0.03*
	T3	77.80	±5.00	80.80	±5.16*	0.06
	T4	77.80	±5.78	78.40	±5.43*	0.73
	T5	89.20*	±11.72	80.40	±5.49*	0.00*
CVP (cm H <sub>2</sub> O)	T1	10.30	±2.83	11.60	±2.25	0.11
	T2	11.00*	±3.94*	15.00*	±1.89*	0.00*
	T3	10.30*	±2.79	13.30*	±2.05*	0.00*
	T4	10.80	±2.50	11.10	±1.68*	0.65
	T5	9.40*	±3.01*	12.20*	±2.33*	0.00*
CO (l/min)	T1	5.24*	±0.37*	6.80*	±6.41*	0.00*
	T2	5.36*	±0.61*	6.81*	±0.42*	0.00*
	T3	5.46*	±0.40	6.44*	±0.32*	0.00*
	T4	5.63*	±0.42*	6.33*	±0.33*	0.00*
	T5	5.93*	±0.46*	6.64*	±0.37*	0.00*
SVR (dyne-cm <sup>2</sup> /sec <sup>-5</sup> )	T1	1201.90*	±27.02	1127.70*	±5.76*	0.00*
	T2	1117.40*	±84.91*	1003.60*	±6.34*	0.00*
	T3	1057.50*	±95.82*	998.30*	±17.21*	0.00*
	T4	1075.90	±89.49	1045.50	±5.79	0.13
	T5	1427.10	±89.77	1101.00	±8.05*	0.11

Data are Mean, S.D. and comparison between the two groups.  
\* Significant ( $p < 0.05$ ).

Table (3): Pulmonary hemodynamics: Comparison between group A (halothane) and group B (isoflurane).

Variable	Time	Group A		Group B		p value
		Mean	St. dev	Mean	St. dev	
MPAP (mmHg)	T1	24.10	±3.50	23.90	±3.16	0.85
	T2	26.80	±4.51	28.90*	±3.56*	0.11*
	T3	24.10	±2.95	26.10	±3.35	0.05
	T4	23.10*	±2.77*	26.10*	±3.35*	0.00*
	T5	25.00	±3.11	25.10	±3.35	0.92
PCWP (mmHg)	T1	14.10	±2.53	14.20	±2.66	0.90
	T2	15.70*	±3.24*	18.00*	±3.04*	0.02*
	T3	14.20	±3.03	16.00	±3.04	0.06
	T4	13.50*	±3.25*	16.00*	±3.04*	0.01*
	T5	13.40	±2.39	14.90	±3.16	0.09
PVR (dyne cm/sec <sup>-5</sup> )	T1	156.20*	±17.34*	139.00*	±6.63*	0.00*
	T2	132.30*	±17.63*	119.00*	±6.63*	0.00*
	T3	141.00*	±16.00*	129.60*	±7.15*	0.00*
	T4	115.70*	±8.44*	128.90*	±6.70*	0.00*
	T5	141.50*	±17.73*	131.70*	±7.03*	0.02

Data are Mean, S.D., comparison between the two groups.

\* Significant ( $p < 0.05$ ).

Table (4): Blood gas changes: Comparison between group A (halothane) and group B (isoflurane).

Variable	Time	Group A		Group B		p value
		Mean	St. dev	Mean	St. dev	
PH	T1	7.39*	±0.03*	7.41*	±0.02*	0.00*
	T2	7.33*	±0.04*	7.38*	±0.02*	0.00*
	T3	7.34*	±0.02*	7.39*	±0.03*	0.00*
	T4	7.38	±0.12	7.38	±0.02	0.08
	T5	7.32*	±0.02*	7.34*	±0.02*	0.01*
PaO <sub>2</sub> (mmHg)	T1	349.30	±94.88	302.30	±183.46	0.31
	T2	226.70	±75.55	180.60	±90.26	0.08
	T3	226.70	±61.23	211.50	±62.15	0.80
	T4	297.20*	±83.07*	345.00*	±50.35	0.01*
	T5	291.80*	±84.60*	318.40*	±42.36*	0.00*
PaCO <sub>2</sub> (mmHg)	T1	40.20*	±2.04*	41.90*	±2.26*	0.01*
	T2	41.20	±3.27*	42.80	±4.95	0.18
	T3	40.40*	±2.43*	43.90*	±2.73*	0.00*
	T4	38.00*	±2.20*	42.90*	±2.61*	0.00*
	T5	41.40*	±3.89*	45.200*	±2.19*	0.00*
SaO <sub>2</sub> (%)	T1	98.74*	±0.74	99.35*	±0.73*	0.01*
	T2	96.66*	±2.45*	98.29*	±0.70*	0.00*
	T3	96.58*	±1.71*	97.99*	±0.86*	0.00*
	T4	98.12*	±1.20*	99.13*	±0.69*	0.00*
	T5	98.15*	±0.98*	99.03*	±0.69*	0.00*

Data are Mean, S.D., comparison between the two groups.

\* Significant ( $p < 0.05$ ).

## DISCUSSION

One of the homeostatic mechanisms preserving arterial oxygenation during one lung ventilation (OLV) is active pulmonary vasoconstriction of pulmonary vessels with resultant diversion of blood flow away from the hypoxic area. It is called hypoxic pulmonary vasoconstriction (HPV) [6].

This HPV is considered to be an important mechanism by which blood flow is diverted to normoxic areas, which result in minimizing venous admixture and increasing arterial oxygen tension.

One lung ventilation is required for thoracic operations to facilitate the performance of thoracic surgery [2]. Adequate arterial oxygen tension is not achieved in some patients despite an accurately placed endobronchial tube and high inspired oxygen during OLV [20]. Minor changes in arterial oxygen tension caused by changes in the anaesthetic techniques may be important in these patients.

The effect of anesthesia and OLV on arterial oxygenation are complex and not fully understood. During OLV, adequate oxygenation can be a concern especially in supine position [4] and in patients with poor pre-existing lung function. Our work contains a well controlled study of comparison between halothane and isoflurane on HPV.

We studied forty patients undergoing elective thoracotomy for lung resection.

Patients in group 1 (n = 20) received 1 MAC halothane in oxygen and group 2 (n = 20) received 1 MAC isoflurane in oxygen. We noticed that the incidence of hypotension (MAP 40-60 mmHg) and bradycardia (HR = 50-60 b/min) were greater in halothane group compared to isoflurane group at T1 to T4 interval. This may be due to negative inotropic effects of halothane on cardiac muscle [10].

Central venous pressure remains constant in patients anaesthetized with halothane in contrast to modest but significant increase in this variable in patients anaesthetized with isoflurane. This is supported by previous results demonstrating that OLV produces small increase in CVP during isoflurane anaesthesia [8].

Cardiac output [10] was found to be higher

with isoflurane than halothane group. The decrease in CO during halothane anaesthesia due to more myocardial depressant effects of halothane than isoflurane at the same MAC.

The decrease in systemic vascular resistance with isoflurane in comparison with halothane was due to vasodilator effect of isoflurane [14,17].

Mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were higher in both groups at T2 and T4 but more with isoflurane than halothane. This may be due to sympathetic stimulation and its effect on pulmonary vasculature [1]. The decrease in pulmonary vascular resistance (PVR) in isoflurane group was due to the vasodilator effect of isoflurane.

During OLV, the presence of right to left shunt in the upper lung results in an increased measured physiological dead space and may be expected to increase in PaCO<sub>2</sub> that occurs after initiation of OLV [1,16].

This work indicates that halothane produces a decrease in arterial oxygenation in patients during OLV at T2 and T3. These changes are indistinguishable from those observed during isoflurane anaesthesia. These changes are accompanied by similar changes in oxygen saturation at the same time intervals [3,18].

The absence of difference in PaO<sub>2</sub> between halothane and isoflurane is because of better preservation of cardiac output during isoflurane anaesthesia compensating for its direct inhibition of hypoxic pulmonary vasoconstriction [7,15].

In support of this we were able to demonstrate a significantly higher cardiac output during isoflurane anaesthesia. Since all potent inhalational agents directly inhibit hypoxic pulmonary vasoconstriction [11,13] at different levels. The difference in PaO<sub>2</sub> between the various inhalational agents is related to their differential depression of cardiac output. On the other hand the presence of vascular changes, intimal fibrosis and wall thickening of pulmonary vessels due to aging, smoking or chronic hypoxia may alter the mechanism of HPV.

In conclusion, from our work, no difference had been found between halothane and isoflu-

rane on arterial oxygenation during one lung anesthesia in spite of their variable effects on hypoxic pulmonary vasoconstriction.

## REFERENCES

- 1- Abe K., Mashimo T. and Yoshiya I.: Arterial oxygenation and shunt fraction during one lung ventilation. A comparison of isoflurane and sevoflurane. *Anesthesia and Analgesia*, 1998, 86: 1266-70.
- 2- Benumof J.L., Augustine S.D. and Gibbons J.A.: Halothane and isoflurane only slightly impair arterial oxygenation during one lung ventilation in patients undergoing thoracotomy. *Anaesthesiology* 1987, 67: 910-5.
- 3- Benumof J.L.: Isoflurane anesthesia and arterial oxygenation during one lung ventilation. *Anesthesiology*, 1998, 64: 419-22.
- 4- Benumof J.L.: Mechanism of decreased blood flow to atelectatic lung during lateral decubitus position. *J. Appl. Physiol.*, 1988, 46: 1047.
- 5- Benumof J.L., Saudman J.L., Arkin D.B. and Diamont M.: When do pulmonary artery catheters go. *Intrathoracic distribution. Anesthesiology*, 1977, 46: 376-8.
- 6- Bjertanaes L.J.: Hypoxic induced vasoconstriction isolated perfused lungs exposed to injectable or inhaled anesthetics. *Acta. Anaesthesiologica*, 1977, 21: 133-47.
- 7- Carlsson A.J., Bindslev L. and Hedenstierna: Hypoxic induced pulmonary vasoconstriction in human lung. The effect of isoflurane anaesthesia. *Anesthesiology*, 1987, 66: 312-6.
- 8- Cohen E.: Hemodynamics and oxygenation during one lung anesthesia. Right vs left. *Anesthesiology*, 1985, 63: A566.
- 9- Domino K.B., Barowec L., Alexander C.M., et al.: Influence of isoflurane on hypoxic pulmonary vasoconstriction in dogs. *Anesthesiology*, 1986, 64: 423-9.
- 10- Eger E.I.: New inhaled anaesthetics. *Anesthesiology*, 1994, 80: 906-22.
- 11- Ishibe Y., Gui X., Uno H., Shiokawa Y. and Umeda T.: Effect of sevoflurane on hypoxic pulmonary vasoconstriction in the perfused rabbit lung. *Anesthesiology*, 1993, 79: 1348-53.
- 12- Lesitsky M.A., Davis S. and Murray P.A.: Preservation of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane anesthesia compared to the conscious state in chronically instrumented dogs. *Anesthesiology*, 1998, 89: 1501-9.
- 13- Loer S.A., Scheeren T.W., Tarnaur J.: Desflurane inhibits hypoxic pulmonary vasoconstriction in isolated rabbit lungs. *Anesthesiology*, 1995, 83: 552-6.
- 14- Malan T.P., DiNardo J.A., Ishen R.J., et al.: Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. *Anesthesiology*, 1995, 83: 918-28.
- 15- Marshall C., Lindgren L. and Marshall B.E.: Effects of halothane, enflurane, isoflurane on hypoxic pulmonary vasoconstriction in rat lungs in vitro. *Anesthesiology*, 1984, 60: 304-8.
- 16- Nomalo Y. and Kawamura M.: Pulmonary gas exchange effects by nitroglycerin, dopamine and dobutamine during one lung ventilation. *Canadian Journal of Anesthesia*, 1989, 36: 273-7.
- 17- Pagel P.S., Fu J.L., Danask M.D., et al.: Desflurane and isoflurane produce similar alteration in systemic and pulmonary hemodynamics and arterial oxygenation in patients undergoing one lung ventilation. *Anesthesia and Analgesia*, 1998, 87: 800-7.
- 18- Slinger P., McRae K., Winten T., Sandler A., Zamara J.E. and Salpeter M.J.: Arterial oxygenation during thoracic surgery: A comparison of isoflurane and sevoflurane. *Anesthesia and Analgesia*, 1998, 86: A40.
- 19- Slinger P. and Scatt W.A.C.: Arterial oxygenation during one lung ventilation; A comparison of enflurane and isoflurane. *Anesthesiology*, 1995, 32: 940-6.
- 20- Wang J.Y.Y., Russell G.N., Page R.D. and Jackson M.: A comparison of the effects of sevoflurane and isoflurane on arterial oxygenation during one lung ventilation. *British Journal of Anesthesia*, 1998, 81: 850-3.