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Minimal fixed flow anesthesia for off-pump coronary artery bypass surgery: A parallel randomized trail

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A B S T R A C T

Objectives: The aim of the present study was to test a safety of a fixed minimal (0.5 l/min) fresh gas flow (FGF) anesthesia as a method ensuring adequate oxygenation during off-pump coronary artery bypass grafting operations.
Design: A randomized, prospective study.
Setting: Single-center clinical hospital affiliated with a university.
Participants: 208 patients underwent off-pump coronary artery bypass surgery.
Interventions: All patients received endotracheal inhalational anesthesia with fixed minimal FGF. Half of them were anesthetized by sevoflurane and another half by isoflurane. The fresh (carrier) gas was pure oxygen in the control groups and a mixture of medical air and oxygen (FiO_2 0.8) in the trial groups.
Measurements and main results: In the control groups inhaled oxygen concentration changed minimally during the operation. In the trial groups in 28.8 % of cases inhaled oxygen concentration dropped below preliminary margin (0.4). Body surface area (BSA) ($B = 38.7$; $p = 0.002$) and patient's age ($B = -0.47$; $p = 0.004$) were retained into final logistic regression model as independent predictors. We divided BSA into subcategories and analyzed data by survival cox regression with Forward LR method. Patients with BSA>2.3 (Exp.B = 183) and BSA [2.2–2.3] (Exp.B = 59) had high chance to get less than 0.4 of inhaled oxygen concentration compared to the patients with BSA <2.0 ($p < 0.001$).
Exp(B) or OR for the patients' age as independent predictor tested in multiple logistic regression was 0.628 In other words, for every year less the patient had 1/0.628 = 1.6 times more chance to reach the preliminary low margin (0.4) of oxygenation.
Conclusions: Fixed minimal FGF 0.5 l/min with FiO_2 0.8 may not be sufficient for the younger patients with BSA >2.0 to maintain inhaled oxygen concentration above 0.4. Using pure oxygen as a carrier gas during fixed minimal flow long term anesthesia is much safer and more reliable.

1. Introduction

Fresh gas flow (FGF) is one of the main instruments used by anesthesiologists to provide a patient with proper breathing mixture ensuring inhalational anesthesia. Reducing FGF has many beneficial effects. Minimal flow anesthesia is associated with better preservation of airway moisture and less heat loss [1–3]. Decreased gas waste also reduces costs [4–7]. The total amount of vaporized anesthetics is reduced and thus risk for unnecessary work place contamination is decreased as well as the amount released into the atmosphere and subsequent impact on the global ecosystem [5,8–10]. But, low fresh gas flow means increased rebreathing of exhaled gases [11,12]. Thus, some risk of hypoxic gas mixture formation appears [13]. Fresh gas vaporizing inhalational anesthetic is called a

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carrier gas. Carrier gas composition acquires high importance. If pure oxygen (FiO_2 1.0) is used as a carrier gas, adequate oxygenation for patient must be ensured [7]. However pure oxygen delivering will rise arterial oxygen partial pressure (PaO_2). So, we have to consider the degree of hyperoxemia. Using oxygen and air mixture as a carrier gas gives us possibility of maintaining blood oxygen level in more physiologic range. According to Jan A. Baum, using oxygen and air mixture as a carrier is a gold standard [13]. But in case of low fresh gas flow, steady oxygen concentration in breathing circuit is not guaranteed [14], especially with fixed flow. Baum recommended high initial fresh gas flow for denitrogenation. But this recommendation especially refers to the inhalational anesthesia when a carrier gas mixture contains nitrous oxide N_20. High flow phase may be shortened when air/oxygen mixture is used as a carrier gas [15]. By using pure oxygen as a carrier gas, denitrogenation can be omitted at the start of inhalational anesthesia, because nitrous oxide does not have to be washed in. The advantages of rebreathing systems can therefore be used right from the start. An initial high fresh gas flow is only briefly needed or not at all [7]. Maria Horwitz and Jan G Jakobsson studied sevoflurane and desflurane wash-in times with fixed minimal (0.5 L/min) and low (1 L/min) flow settings using oxygen/air mixture (FiO_2 0.5) as a carrier gas [16]. Bahar, S. et al. in their study aimed to evaluate the efficacy and practicability of fixed low-flow (1 L/min FGF FiO_2 0.5) during both the wash-in and maintenance periods of desflurane anesthesia [17]. In this study, FiO_2 did not fall below 0.3 in any patient. Arslan et al. tried to answer the question: Are high fresh gas flow rates necessary during the wash-in period in low-flow anesthesia?" They compared the efficiency, safety and the consumption of desflurane in low flow anesthesia (LFA) using constant FGF (1 L/min) and conventional LFA using high FGF (4 L/min) during the wash-in period. Wash-in was accomplished with 1 L/min FGF (50 % O2, 50 % air) and 18 % desflurane in group 1; and by 4 L/min FGF (50 % O2, 50 % air) and 6 % desflurane in group 2. Throughout the surgery, the vaporizer was adjusted to maintain 0.6 to 0.8 minimum alveolar concentration (MAC). They concluded, that the efficiency of anesthesia in both the first hour and in total was higher in group 1 ($P < 0.001$) and it is safe, more efficient and economical to use 1 L/min FGF during the wash-in period in LFA [18]. We hypothesized, that fixed minimal fresh gas flow (0.5L/min) composed with medical air and oxygen (FiO_2 0.8) might decrease oxygen concentration in inhaled mixture more intensively compared with a pure oxygen as a carrier gas. The focus of our study was to test fixed minimal flow (0.5 L/min) with FiO_2 0.8 during off-pump coronary arterial grafting operations ($\geq$3 h) as a safe method ensuring adequate oxygenation. We were interested, if it would be sufficient to keep inhaled oxygen concentration ($FinspO_2$) above 0.4. For safety reasons we appointed this preliminary margin (0.4) and if $FinspO_2$ dropped below it, FiO_2 was raised up to 1.0 to improve oxygenation. We did two parallel 2 arm trial for isoflurane and sevoflurane anesthesia separately. As we used fixed minimal flow, we were interested to study "wash-in" time for both inhalational anesthetics.

2. Materials and methods

This study was approved by ethical review board of Tbilisi 5th clinical hospital in 2019 (# CS01-019). Informed consents were obtained from all individuals. The study was conducted from March 2019 to January 2022.

Two hundred and eight patients were randomly equally distributed into four parallel groups (two controls and two trials separately for sevoflurane and isoflurane anesthesia) with 1:1 allocation ratio (52 patients in each). The patients in the control groups were receiving pure oxygen as a carrier gas and the patients in the trial groups were receiving oxygen and medical air mixture (FiO_2 0.8). We used minimal fixed fresh gas flow (0.5L/min) for both Sevoflurane and Isoflurane groups. For avoiding low oxygenated inhaled mixture creation, we appointed the preliminary margin of inhaled oxygen concentration ($FinspO_2$) as 0.4. In the control group the fresh gas was pure oxygen (FiO_2 1.0) and there was minimal risk that $FinspO_2$ would drop below the preliminary margin 0.4. In the trial group the fresh (carrier) gas was air/oxygen mixture (FiO_2 0.8) and we hypothesized that the mentioned risk would be higher compared with the control group. We calculated sample size with α (two-tailed) = 0.05, $\beta = 0.2$ assuming risks in the control and trial groups as 0.01 and 0.20 respectively. Sample size was calculated at http://sample-size.net and it was equal to 51. Randomization was done by online program "Research randomizer". (https://www.randomizer.org/).

Inclusion criterium to involve patients in our study was the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II. To create homogenous groups with relatively low preoperative risk, only "EuroScore <5" patients were included. We used preoperative pulse oximetry (SpO_2) as exclusion criterium. Patient with arterial oxygen saturation less than 97 % were excluded.

All patients received intravenous access and were induced with midazolam 2 mg/kg, fentanyl 5mcg/kg and pancuronium 0.1 mg/kg. Intubation of trachea was performed following 5 min mask manual ventilation with FGF 6–8 L/min FiO_2 1.0. After the patient was intubated and airway secured, FGF was set at 0.5L/min and the vaporizer opened fully at 8 % and 6 % for sevoflurane and isoflurane accordingly. The patients were ventilated with anesthetic machine "Drager Primus" in VCV mode: Vt 8 ml/kg, f 10–12/min, I:E 1:2, PEEP 2–3 mbar. As soon as the anesthetic concentration reached to 1.2 MAC, the vaporizer setting was adjusted to keep the concentration at 1.1–1.2 MAC during the operation. Mechanical ventilation settings also were further adjusted to maintain normocapnia ($EtCO_2$ 34–35 mmHg). We used fentanyl infusion 2mcg/kg/h for analgesia with intermittent boluses 1 mcg/kg as needed. We added pancuronium 0.01 mcg/kg in every hour after induction for muscle relaxation. Hemodynamics were stabilized by α- and β-mimetic and blocker agents. We used dobutamine and norepinephrine via infusion and metoprolol and urapidil via boluses as needed. Heart rate, invasive arterial pressure and central venous pressure data were recorded per 5 min. Either average or median values of hemodynamic data were calculated and compared between groups as well as the medications consumed during operation.

We observed oxygen concentration changes in breathing circuit. Inhaled mixture oxygen concentration ($FinspO_2$) was recorded per 5 min. If $FinspO_2$ dropped below preliminary margin (0.4), fresh gas flow settings were changed (FiO_2 was raised up to 1.0) and the patient was transferred into the subgroup "dropped-out". Arterial blood gas sampling was done mandatory after 30 min from the beginning of mechanical ventilation and at the end of the operation. At these points of time, we compared both $FinspO_2$ and PaO_2 between groups. Oxygen uptake was calculated by formula: [FinspO2 -FexpO2 (%)] x MV (L) x 10. We studied how oxygen uptake data correlated with $FinspO_2$ dropping. Minimal $FinspO_2$ values were compared between groups. We tried to reveal the independent factors,

Table 1
Demographic data of 208 patients distributed equally into the control and trial groups.

	Control	Trial	
Age (y)	66.5 ± 8.4	65.9 ± 9.1	P = 0.624
Sex (F/M)	29/75	26/78	P = 0.753
Weight (kg)	87.5 ± 17.0	87.2 ± 16.3	P = 0.907
BSA (m^2)	2.01 ± 0.23	2 .03 ± 0.22	P = 0.682

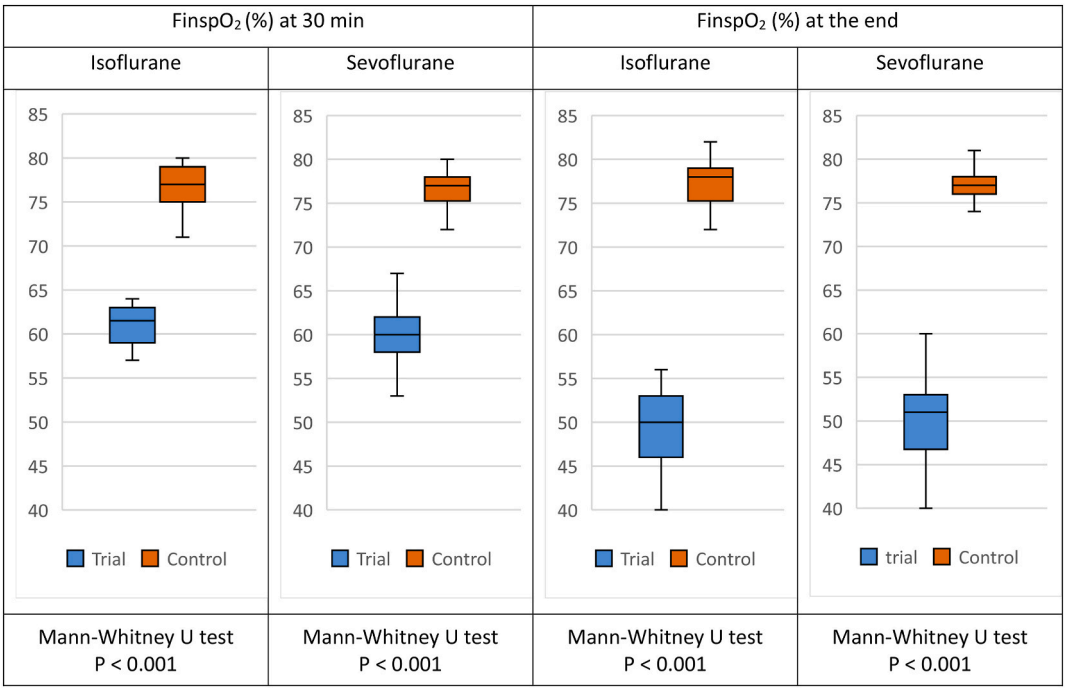

Fig. 1. Inhaled mixture oxygen concentration ($FinspO_2$) at start and end points of operations in the trial and the control groups.

that might have an effect on oxygen uptake. The main focus of our study was to test safety of the minimal fixed flow (0.5L/min) anesthesia as a method ensuring adequate oxygenation during long term (≥3h) operations.

We evaluated blood lactate, creatinine and cardiac troponin I levels. Blood sampling for lactate and creatinine was done after 30 min from tracheal intubation, at the end of the operation, on the first and the second postoperative morning. We evaluated cardiac troponin I level after 12 h from the end of the operation.

Statistical analysis of acquired data was performed by the program IBM® SPSS® Statistics 23. According to exploring data distribution normality, values are presented either as mean and standard deviation or median with interquartile range. Comparison of normally distributed values were done by Student's t-test and paired *t*-test. Variables not following a normal distribution were compared by non-parametric tests (Mann-Whitney *U* test; Wilcoxon signed rank test). The Chi-Square test was used to examine whether or not two nominal (categorical) variables had a significant connection. We tested possible independent predictors affecting on $FinspO_2$ dropping below preliminary margin (0.4) by multiple logistic and survival cox regressions.

3. Results

The demographic data of the patients distributed into the control and trial groups are shown in Table 1.

In trial groups $FinspO_2$ was significantly low than in control groups. 104 patients were enrolled in trail groups. Fixed minimal flow anesthesia with 0.5L/min FiO_2 0.8 fresh gas was not found as safe enough to ensure adequate oxygenation during long term operations. In 30 patients (16 patients from isoflurane and 14 patients from sevoflurane groups) $FinspO_2$ dropped below preliminary margin (0.4). Those patients were excluded from trial groups and transferred into the subgroup "dropped-out". So, 74 patients (36 patients in sevoflurane group and 38 patients in sevoflurane group) were retained in trial groups. Minimal mean $FinspO_2$ value was 48.3 ± 3.7 % in isoflurane and 48.5 ± 4.7 % in sevoflurane group. None of the patients from control groups were excluded. $FinspO_2$ remained high in all cases of control groups. We found fixed minimal flow anesthesia with 0.5L/min pure oxygen fresh gas (FiO_2 1.0) as the safe method avoiding oxygen concentration dropping in breathing circuit. Minimal median $FinspO_2$ (%) value was 75.5 [73–77] in

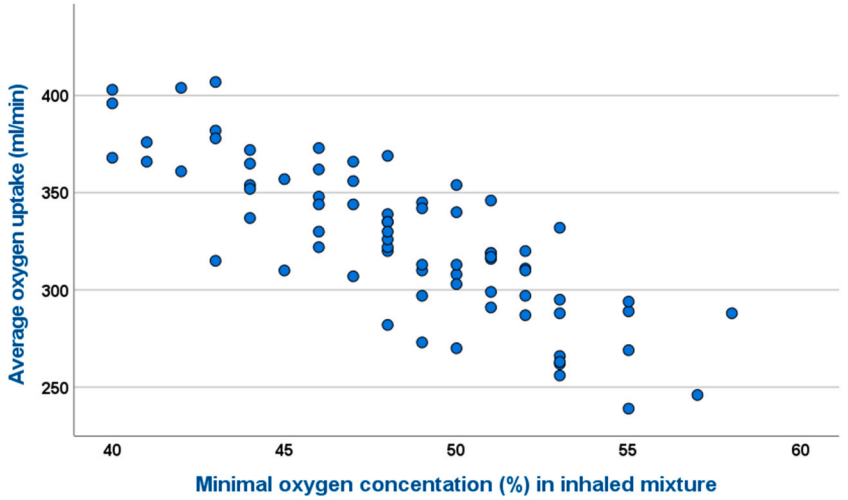

Fig. 2. Correlation between average oxygen uptake and minimal inhaled oxygen concentration in the trial groups.

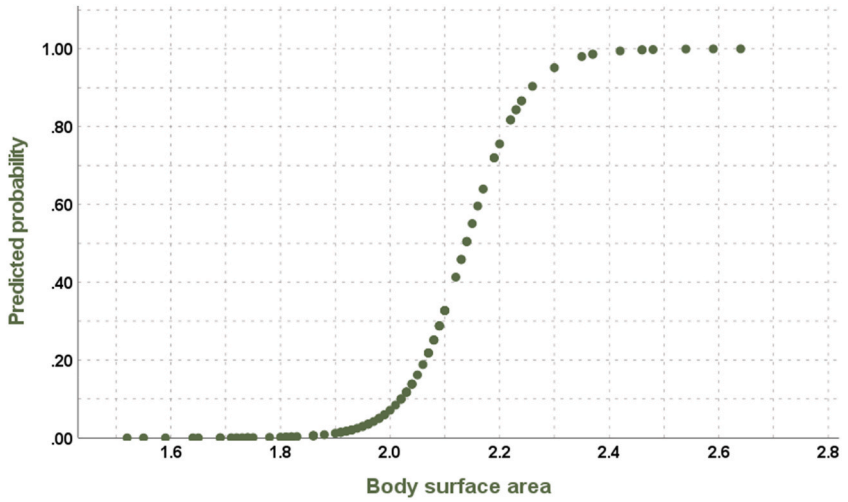

Fig. 3. Predicted probability of $FinspO_2$ dropping below 0.4 according to patients' BSA.

isoflurane control group and 75 [73–77] in sevoflurane control group. Difference of minimal $FinspO_2$ between trial and control groups is statistically highly significant. Mann-Whitney test $P < 0.001$.

In trial groups at 30 min passed after intubation median $FinspO_2$ (%) was 61.5 [59–63] (isoflurane group) and 60 [58–62] (sevoflurane group). At the end of the operation $FinspO_2$ decreased to 50 [46–53] (isoflurane group) and 51 [47–53] (sevoflurane group). In control groups inhaled oxygen concentration remained high throughout the operation. At 30 min it was 77 [75–79] (isoflurane group) and 77 [75–78] (sevoflurane group). At the end of the operation $FinspO_2$ did not change practically in control groups: 78 [75–79] (isoflurane group) and 77 [76–78] (sevoflurane group). (Fig. 1).

In trial groups $FinspO_2$ minimal value highly correlates with average oxygen uptake. Pearson correlation r = - 811; $p < 0.001$. (Fig. 2).

We compared average oxygen uptake mean values between trail groups and the subgroup "dropped-out". The mean oxygen uptake in "retained patients" was 326 ± 39 ml/min while in "dropped-out patients" _ 436 ± 25 ml/min. The mean difference is remarkable (110 ml/min) and statistically highly significant ($p < 001$).

The independent predictors that might affect on oxygen uptake were tested by multiple logistic regression. Patients' age, sex, body surface area (BSA), preoperative cardiac ejection fraction (EF), operation duration and the inhalational anesthesia agent were used as the independent predictors. The multiple logistic regression was done with the method "Forward LR". Only BSA ($B = 38.7$; $p = 0.002$) and patient's age ($B = -0.47$; $p = 0.004$) were retained into final regression model as independent predictors. (Fig. 3), (Fig. 4).

We transformed BSA as the continuous variable into the ordinal variable by making subcategories: BSA <2.0; BSA = [2.0–2.1]; BSA = [2.1–2.2]; BSA = [2.2–2.3]; BSA>2.3. Each of the 30 patients, that were dropped out from the trial groups, reached preliminary low

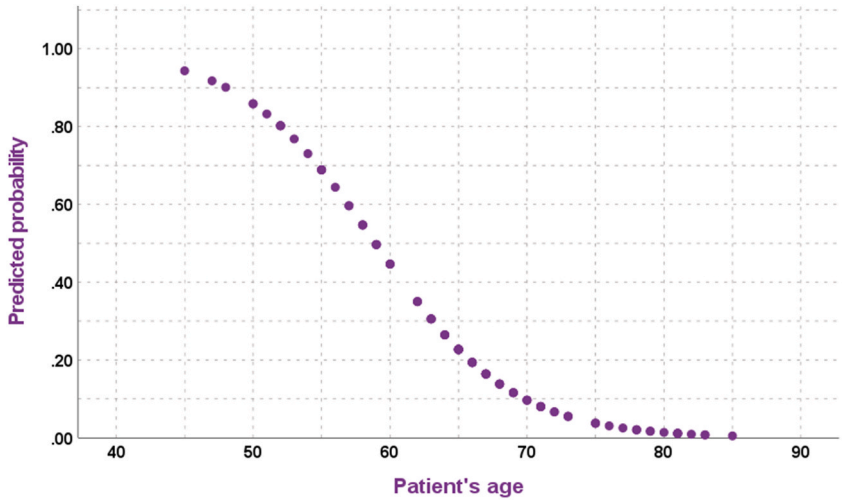

Fig. 4. Predicted probability of FinspO_2 dropping below 0.4 according to patients' age.

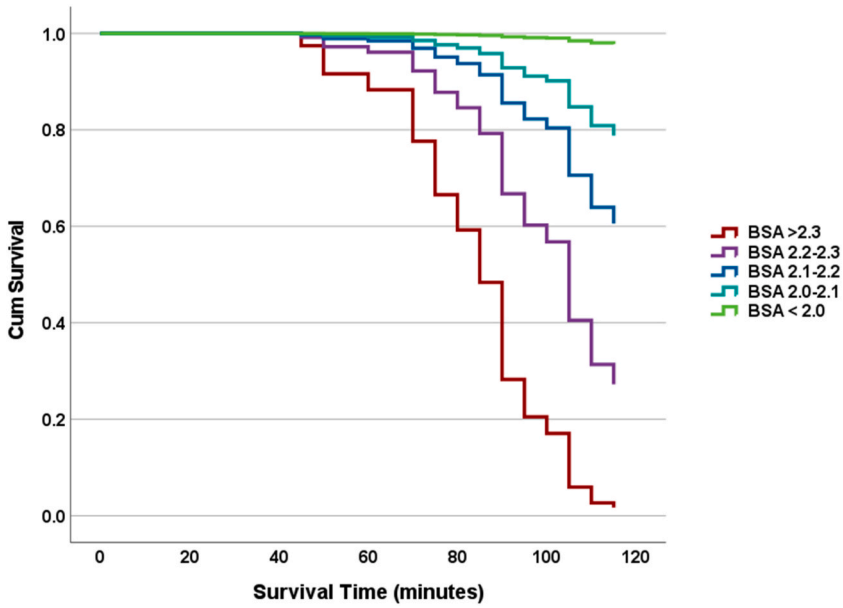

Fig. 5. Survival function for BSA subcategories.

Table 2
Comparison of patients' age and BSA between trial groups and the subgroup "dropped-out".

	Retained in trial groups	Dropped out	P value
BSA (m2)	1.93 ± 0.16	2.26 ± 0.18	P < 0.001
Age (years)	69 ± 8	58 ± 7	P < 0.001

Abbreviations: BSA, body surface area.

margin of oxygenation (FinspO_2 0.4) at different times (85 ± 18.5 min) after applying fixed minimal flow anesthesia. Tested by Survival Cox regression, we found out that patients with BSA >2.3 (B; 5.2) had much higher chance of leaving the group, that is 183 (Exp.B) times that of those with BSA <2.0 ($p < 0.001$). For the patients with BSA [2.2–2.3]; [2.1–2.2]; [2.0–2.1] that chances were 59 (Exp.B) $p < 001$; 23(Exp.B) $p = 0.004$; 11(Exp.B) $p = 0.035$ respectively. (Fig. 5).

The patients retained in the trial groups had less BSA and higher age compared with the patients transferred into the subgroup "dropped-out" (Table 2).

Table 3
Comparison of PaO_2 between control and trial groups.

	Isoflurane groups PaO_2 mmHg			sevoflurane groups PaO_2 mmHg		
	control	trial		control	trial	
At 30 min from intubation	286 ± 55	226 ± 56	p < 0.001	285 ± 65	225 ± 45	p < 0.001
At the end of the operation	240 ± 80	128 ± 32	p < 0.001	242 ± 68	131 ± 30	p < 0.001

Abbreviations: PaO_2, arterial blood partial oxygen pressure.

Table 4
Comparison of laboratory data between control and trial groups.

	Isoflurane			Sevoflurane		
	Trial	Control		Trial	Control	
Peak Lactate (mmol/L) during 72 h	1.55 [1.31; 1.96]	1.51 [1.33; 2.08]	P = 0.808	1.57 [1.30; 1.90]	1.53 [1.33; 1.80]	P = 0.984
Creatinine increase (%) during 72 h	10.6 [5.4; 20.0]	10.9 [5.2; 24.8]	P = 0.653	13.2 [8.0; 20.5]	13.7 [8.2; 23.9]	P = 0.919
Cardiac Troponin I (ng/ml) after 12 h	0.094 [0.040; 0.338]	0.090 [0.060; 0.372]	P = 0.344	0.097 [0.052; 0.346]	0.091 [0.040; 0.325]	P = 0.535

Exp(B) or OR for the patients' age as an independent predictor tested in multiple logistic regression is 0.628 [95%CI 0.457; 0.863]. (B = −0.47; p = 0.004). So, for every year of age chance of leaving the group is 0.628 times more. In other words, for every year less the patient has 1/0.628 = 1.6 times more chance to reach the preliminary low margin (0.4) of oxygenation.

The trial and control groups differ with the level of oxemia. In the control groups arterial blood partial oxygen pressure (PaO_2) is significantly high than in the trial groups. (Table 3).

The mean PaO_2 difference between the control and the trial groups is about 60 mmHg at 30 min from intubation and 110 mmHg at the end of the operation. In our study PaO_2 level did not affect on the outcome. The control and trial groups are similar according to the laboratory data, hemodynamic profile, duration of mechanical ventilation and ICU length of stay.

4. Discussion

At the moment of starting mechanical ventilation $FinspO_2$ was about 80% in both trial and control groups. At 30 min passed after intubation in control groups oxygen concentration in inhaled mixture changed minimally _ 77 [IQR 75–79] (isoflurane group), 77 [IQR 75–78] (sevoflurane group) and was maintained in this range throughout the operation. At the end of the operation, it was almost the same _ 78 [IQR 75–79] (isoflurane group), 77 [IQR 76–78] (sevoflurane group). So, it seems that in case of using pure oxygen as a carrier gas, $FinpsO_2$ is about 80% throughout the operation. According to WHO 2018 recommendations, FiO_2 0.8 is considered as safe in terms of alveolar atelectasis formation and cardiovascular side effects. At the same time, with moderate level of evidence FiO_2 0.8 appears to be effective compared with FiO_2 0.3–0.35 for reducing surgical site infection in adult surgical patients undergoing general anesthesia with tracheal intubation [19,20]. Two systematic reviews were conducted. One on the effectiveness of this intervention, which is an update of the original review performed for the 2016 WHO guidelines, and one on the safety of the use of high FiO_2 in surgical patients for the purpose of reducing the risk of SSI. Both reviews [20,21] included 17 moderate-good quality RCTs, the safety review also included two non-randomized studies. Meta-regression indicated that the method of oxygen administration modified the effect of high FiO_2 on the incidence of SSI (test of interaction, P = 0.048; proportion variance explained, 27 %). In patients under general anesthesia with endotracheal intubation and mechanical ventilation, 80 % FiO_2 reduced the incidence of SSI (RR: 0.80: 95 % CI 0.64–0.99; tau [2] = 0.051; Chi [2] test for heterogeneity, P = 0.043; I^2 = 46.7 %). No evidence of harm with high FiO2 was found for major adverse effects in the meta-analysis of randomized trials: atelectasis RR; 0.91 (95 % CI: 0.59–1.42); cardiovascular events RR: 0.90 (95 % CI: 0.32–2.54); intensive care admission RR: 0.93 (95 % CI: 0.7–1.12); death during the trial RR: 0.49 (95 % CI: 0.17–1.37). One non-randomized study reported that high FiO2 was associated with major respiratory adverse effects (RR: 1.99 [95 % CI: 1.72–2.31]). In our study in the control groups arterial blood partial oxygen tension (PaO_2) average value is less than 300 mmHg. (Table 3). In studies demonstrating negative effect of hyperoxemia PaO_2 is more than 300–400 mmHg [22–24]. The recent meta-analysis describes hemodynamic effects of hyperoxemia [25]. It includes 33 trials. According to them, hyperoxemia (PaO_2 234–617 mmHg) decreases cardiac output by 10.2 % in healthy volunteers, by 9.6 % in CAD and by 15.2 % in CHF patients. Significant changes were not found in CABG patients. Systemic vascular resistance increased by 24.6 % in patients with heart failure and by 11–16 % in healthy, CAD, CABG patients. The randomized control study compared moderate hyperoxemia with oxygen tension near physiologic level during CABG operations [26]. In control group PaO_2 was 220 [213–233] mmHg during bypass and 157 [152–161] _ in trial group. Hemodynamic data (CI, SVR) did not improve in the trial group compared with the control group. There were no significant differences between groups according to laboratory (CK-MB, cTnT, Creatinine, LIS, PaO_2/FiO_2, Lactate) data. In our study the trial and control groups differ with the level of oxemia. In the control groups arterial blood partial oxygen pressure (PaO_2) is significantly high than in the trial groups. (Table 3). The mean PaO_2 difference between the control and the trial groups is about 60 mmHg at 30 min from intubation and 110 mmHg at the end of the operation. We studied if PaO_2 level affected on the outcomes such as laboratory data, hemodynamic profile, duration of mechanical ventilation and ICU length of stay. We did not find any significant

Table 5
Comparison of hemodynamic data and used medications between control and trial groups.

	Isoflurane			Sevoflurane		
	Trial	Control		Trial	Control	
HR (min^{-1})	78.6 ± 7.1	77.7 ± 7.4	P = 0.572	76.4 ± 7.5	75.5 ± 7.9	P = 0.592
MAP (mmHg)	73.5 ± 2.7	73.2 ± 2.6	P = 0.602	76.6 ± 2.9	76.2 ± 2.8	P = 0.505
Norepinephrine (mcg/kg/min)	0.06 [0.03; 0.09]	0.07 [0.05 0.10]	P = 0.304	0.04 [0.02 0.06]	0.04 [0.03 0.08]	P = 0.422
Urapidil (mg/kg)	0.06 [0.00; 0.24]	0.05 [0.00; 0.18]	P = 0.736	0.07 [0.00; 0.22]	0.06 [0.00; 0.17]	P = 0.317
Dobutamine (mcg/kg/min)	2.02 [1.58; 2.97]	2.09 [1.32; 2.76]	P = 0.709	2.08 [1.68; 2.85]	2.07 [1.62; 2.88]	P = 0.731
Metoprolol (mg/kg)	0.02 [0.00; 0.03]	0.02 [0.00; 0.03]	P = 0.473	0.02 [0.00; 0.04]	0.02 [0.00; 0.04]	P = 0.871

Abbreviations: HR, heart rate; MAP, mean arterial pressure.

Table 6
Comparison of mechanical ventilation duration in intensive care unit between control and trial groups.

	Isoflurane			Sevoflurane		
	Trial	Control		Trial	Control	
ICU mechanical ventilation (hours)	9.2 ± 1.7	9.1 ± 1.8	P = 0.675	9.0 ± 1.8	8.9 ± 1.9	P = 0.913

Abbreviations: ICU, intensive care unit.

Table 7
Comparison of patients' ICU stay between control and trial groups.

		ICU stay ≤48 h	ICU stay >48 h	Chi-Square tests
Sevoflurane groups	Trial	37 (97.4 %)	1 (2.6 %)	P = 0.822
	Control	51 (98.1 %)	1 (1.9 %)	
Isoflurane groups	Trial	35(97.2 %)	1 (2.8 %)	P = 0.786
	Control	50 (96.2 %)	2 (3.8 %)	

Abbreviations: ICU, intensive care unit.

difference between the control and trial groups according to the laboratory data (Table 4), hemodynamic profile (Table 5), duration of the mechanical ventilation (Table 6) and ICU length of stay (Table 7). So, arterial blood oxygen tension level did not affect on the outcomes. It is well known that oxygenation is impaired in almost all subjects during anesthesia. Causative mechanisms to atelectasis and airway closure seem to be loss of respiratory muscle tone and gas resorption [27]. Increasing age and body mass index impairs gas exchange by different mechanisms during anesthesia. Shunt related to atelectasis is a more important cause of oxygenation impairment in middle-aged patients, whereas low V_A/Q, likely caused by airway closure, is more important in elderly patients. Shunt but not low V_A/Q increases with increasing body mass index [28]. The patients in our study were ventilated with anesthetic machine "Drager Primus" in VCV mode: Vt 8 ml/kg, f 10–12/min, I:E 1:2, PEEP 2–3 mbar. After chest closure, we increased PEEP up to 5 mbar. The control and trial groups were similar according to the weight and age. (87.5 ± 17.0 kg vs 87.2 ± 16.3 kg; P = 0.907 and 66.5 ± 8.4y vs 66.2 ± 7.8 y; P = 0.780). During the operations PaO_2 decreased in all groups (Table 3), but more prominently in the trial groups. So, we could hardly conclude that in the control groups, where patients were ventilated with higher fraction of oxygen, atelectasis were formed more intensively. For minimalization of resorptive atelectasis formation FiO_2 is recommended not to be more then 0.8 at the moment of anesthesia induction and be kept in 0.3–0.4 range during maintenance of anesthesia [27]. Thoracic surgery is the important additional risk factor contributing atelectasis formation. Alveolar collapse may reach up to 50 % [27]. Adequative oxygenation for CABG patients requires more attention. We decided to set $FinspO_2$ 0.4 as the lower margin. If $FinspO_2$ dropped below it, FGF settings were changed (FiO_2 was raised to 1.0) to improve oxygenation. In the trial groups there were 30 patients (16 patients from isoflurane and 14 patients from sevoflurane group) when $FinspO_2$ dropped below 0.4. The patients in the trial groups received 400 ml oxygen per minute (0.5 l/min FG x 0.8). We calculated oxygen uptake by the Sykes's formula ((FiO2−EtO2) × MV). In some cases, we got values more than 400 ml/min (The mean oxygen uptake in the subgroup "dropped-out" was 436 ± 25 ml/min). But this formula does not accurately calculate oxygen consumption [29,30]. For example, a difference between displayed 45 % and 40 % is not always 5 %. It may also be 4 % (44.5–40.49 %) or 6 % (45.49–39.5 %). In real-time anesthesia, leaks and compliance within the breathing circuit and sensor drift within in the monitoring system will further reduce the accuracy of any values obtained [30]. Sykes uses total minute ventilation to calculate oxygen uptake. S. Ritchie-McLean and R. Shankar suggest, that the alveolar minute ventilation, not the total minute ventilation, should be used for this calculation. Total minute ventilation includes dead-space ventilation, which does not take part in gas exchange. Dead-space, comprising anatomical plus physiological dead-space, is approximately 150 ml in healthy adults, and will significantly affect calculations of oxygen consumption, particularly at lower tidal volumes. For example, a patient whose inspired and expired O_2 fractions are 0.6 and 0.55 respectively, with a total minute volume of 5 L, would have an O_2 consumption rate of 250 ml/min, according to Sykes' formula. Assuming the patient has tidal volumes of 500 ml at a rate of 10 breaths/min, their alveolar minute ventilation is (500-150) ×10 = 3500 ml and their calculated O_2 consumption becomes (0.6-0.55) x 3500 = 175

Table 8
Comparison of patients' hemodynamic profile and used medication between the trial groups and the subgroup "dropped-out".

	Retained in trial groups	Dropped-out	
EF (%)	49 ± 8	49 ± 7	P = 0.999
HR (min^{-1})	77.5 ± 7.4	78.0 ± 6.6	P = 0.757
MAP (mmHg)	75.1 ± 3.2	75.6 ± 2.4	P = 0.429
Norepinephrine (mcg/kg/min)	0.05 [IQR 0.03; 0.08]	0.05 [IQR 0.04 0.07]	P = 0.616
Urapidil (mg/kg)	0.06 [IQR 0.00; 0.23]	0.05 [IQR 0.00; 0.16]	P = 0.296
Dobutamine (mcg/kg/min)	2.08 [IQR 1.68; 2.88]	1.92 [IQR 1.52; 2.76]	P = 0.324
Metoprolol (mg/kg)	0.02 [IQR 0.00; 0.03]	0.02 [IQR 0.00; 0.03]	P = 0.801

Abbreviations: EF. Ejection fraction; HR, heart rate; MAP, mean arterial pressure.

ml/min, a difference of 75 ml/min, which is important when calculating O_2 requirements at low gas flows [29]. Sykes's formula is suitable for a rough estimation of O_2 consumption and, if the tidal volume (and thus the percentage of dead space) is unchanged, is a good indicator of whether O_2 consumption is rising or falling [30]. In the control groups patients received 500 ml oxygen per minute and none of them had intensive FinspO_2 dropping during the operation.

Body oxygen consumption depends on several factors. More body size requires more oxygen. Patients retained in the trial groups had less BSA, then the "dropped-out" patients (1.93 ± 0.16 m^2 vs 2.26 ± 0.18 m^2) P < 0.001 (Table 2). In the elder patient oxygen uptake may be less because of reduced metabolism. The "dropped-out" patients were younger, then the patients retained in the trial groups (58 ± 7 years vs 69 ± 8 years) P < 0.001 (Table 2). Oxygen consumption proportionally is related to the cardiac output. However, hemodynamic profile of retained and dropped-out patients was similar. (Table 8). The dosage of the medication affecting HR and MAP was similar as well. (Table 8).

The trial groups received 100 ml nitrogen per minute (0.5 l/min FG x 0.2). Nitrogen accumulation is considerable factor during long term operations. Operation time may also be the contributor for oxygen concentration dropping in the breathing circuit. The subgroup "dropped-out" and the trial groups had almost the same operation time (234 ± 38 min vs 232 ± 36 min P = 0.780). We tested the possible independent factors that might affect on FinspO_2 (Patients' age, sex, BSA, EF, operation time and used inhalational anesthetic). Only BSA (B = 38.7; p = 0.002) and patient's age (B = −0.47; p = 0.004) were retained into final regression model as the independent predictors. Among the dropped-out patients only one had BSA <2.0. We counted Risk Ratio for the BSA less and more then 2.0. For cohort status "dropped-out" RR = 0.045 [95%CI 0.006; 0.319]. In other words, patients with BSA <2.0 has 1/0.045 = 22.22 times less risk of being "dropped out" than the patients with BSA ≥2.0. In the subgroup "dropped-out" patient's mean age is 58 ± 7 years. According to the curve built by logistic regression (Fig. 4), for the patients aged less than 55 years the probability of being "dropped-out" exceeds 75 %.

Besides the benefits minimal flow anesthesia has also some disadvantages. Low speed flow of the carrier gas needs more time to achieve the desired alveolar concentration of inhalational anesthetic. In 2008 Hendrickx and De Wolf published an extensive review of the pharmacokinetics of inhaled anesthetics and their use with low FGF [31]. They stated that the kinetics can be assessed using routine monitoring, dialed, inhaled and end-tidal (Et) gas concentration, and that the focus should be shifted to "what combination of delivered concentration and fresh gas flow (FGF) can be used to attain the desired alveolar concentration." However, it should be acknowledged that, when a desired end-tidal concentration is maintained with a FGF that is lower than minute ventilation, rebreathing will dilute the circle gas concentration and create a discrepancy between the dialed and the concentration delivered by the anesthesia machine [32]. The discrepancy between dialed and inspired gas concentration is not uncommonly assessed as "lack of control" and is one reason why some anesthesiologists increases the FGF to ensure that the delivered gas matches the inspired concentration. Some authors recommend to start with high FGF to reduce wash-in time and then switch to low or minimal flow [7,33]. Other authors prefer "equilibration point" for switching to the low/minimal flow [34,35]. Horwitz and Jakobsson compared desflurane with sevoflurane by fixed low and minimal flow techniques. Patients were randomized to receive either desflurane or sevoflurane to maintain anesthesia with one of the two fixed FGF 0.5 L/min or 1 L/min FGF both with an inspired fraction (FiO2) 0.5 oxygen in air throughout anesthesia. No inhaled aesthetic agent was administered during induction and intubation. The FGF was adjusted in accordance to randomization following intubation of the trachea. The vaporizer was set at 18 % or 6 % for desflurane or sevoflurane, respectively, after the patient was properly intubated and airway secured. Within each of the four groups, they recorded the time from opening the vaporizer until the end-tidal aesthetic gas concentration reached 1 and 1.5 MAC. With fixed 0.5 l/min minimal flow time to reach 1 MAC anesthetic concentration was 8.5 ± 1.7 min for desflurane and 15.2 ± 2.4 min for sevoflurane P < 0.01 [16]. In our study the patients were distributed into four groups _ two trial and two control groups separately for sevoflurane and isoflurane anesthesia. All of them received fixed minimal 0.5 l/min flow from the moment of endotracheal intubation. Vaporizer was opened to maximal concentration (8 % for sevoflurane and 6 % for isoflurane) until age adjusted 1.2 MAC concentration of inhalational anesthetic was achieved. The mean "wash-in" time for control and trial groups were almost the same and about 6 min more for isoflurane.

The "wash-in" time for sevoflurane in our study is less than in Horwitz and Jakobsson's publication. The reason of getting less "wash-in" time for inhalational agents we studied may be explained by several factors. Patients' mean age in our study was more (65–67 years vs 40–46 years), our patients were of high ASA categorie (ASA III-IV vs ASA I-II) and as the population we studied were the patients with coronary artery disease undergoing OPCABG, they had less cardiac output state comparing with the general population. We have to consider, that slower the intalational agent uptake during the wash-in period, sooner its alveolar concentration is achieved. As it seems from Table 9, the fixed minimal flow of carrier gas needs some time to achieve desired MAC of inhalational anesthetic. That time is about 10.5 min for sevoflurane and about 16 min for isoflurane according to our study. The patients

Table 9
Comparison of the mean "wash-in" time of sevoflurane and isoflurane in control and trial groups.

	Sevoflurane	Isoflurane	
Trial group	10.6 ± 1.4 min	16.1 ± 2.6 min	$P < 0.001$
Control group	10.5 ± 1.5 min	16.2 ± 2.8 min	$P < 0.001$

undergoing cardiac surgery after tracheal intubation need to be prepared before the operation is started. This preparement includes central lines incertion, preoperative transesophageal cardiosonography and ect. During that period of time the patient is under anesthesia by the medications given intravenously at induction stage and alveolar concentration of inhalational anesthetic is being raised meanwhile. Although extra intravenous boluses may be administered as needed.

5. Conclusion

Minimal fixed flow anesthesia (0.5 L/min) is safe if pure oxygen (FiO_2 1.0) is used as the carrier gas during off-pump coronary artery grafting operations lasting more than 3 hours. Using oxygen/air mixture (FiO_2 0.8) as the carrier gas includes some risks for younger patients with high BSA. Minimal fixed 0.5 L/min flow anesthesia with FiO_2 0.8 fresh gas may not be suitable for the patients younger than 55 years and with BSA more than 2.0.

Arterial blood oxygen tension level is higher when using FiO_2 1.0 fresh gas. However, it does not affect on the outcomes compared with less oxemia level when FiO_2 0.8 fresh gas is used. We did not find any significant difference between the contol and trial groups according to the laboratory data, hemodynamic profile, mechanical ventilation duration and ICU length of stay.

Fixed minimal flow needs more time for vaporazing inhalational agent to achieve desired alveolar concentration. Sevoflurane as less soluble agent is more suitable for minimal flow anesthesia. The "wash-in" time for isoflurane to 1.2 MAC is 6 minutes more then for sevoflurane. The carrier gas does not affect on "wash-in" time of the inhalational anesthetics.

Fixed minimal flow has some limitations during OPCABG operations. It is not suited, if fast changing of inhalational anesthetic concentration is needed and regarding to younger patients with high BSA, FGF more than 0.5 L/min must be considered, if pure oxygen is not used as a carrier gas.

Data availability statement

Data included in article/supp. material/referenced in article.

Question	Response
Has data associated with your study been deposited into a publicly available repository?	No
Please select, why	Data included in article/supp. material/referenced in article

CRediT authorship contribution statement

Ioseb Begashvili: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Merab Kiladze:** Project administration, Supervision, Validation. **Christina Ejibishvili:** Data curation, Resources. **George Grigolia:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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