

Original Article

Effect of chronic obstructive pulmonary disease on washout time of sevoflurane anesthesia: a placebo controlled randomized trial

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Abstract: Background: Respiratory functions and gas exchange deteriorates in patients with COPD. In our study, we aimed to investigate if there is any relationship between the washout time of sevoflurane and chronic obstructive pulmonary disease (COPD). Method: Sixty patients, American Society of Anesthesiology (ASA) 1-3 status; aged between 18-60 years old who underwent general anesthesia for an operation were enrolled in our study. Patients were divided into two groups: Group N (non-COPD n = 33), group COPD (patients with COPD, n = 33). Two patients were excluded from the study, a total of 31 patients in Group COPD. Pre-operative respiratory function tests were performed and standard monitoring was provided in the operation room. Both groups received propofol 2 mg/kg, fentanyl 1.5-2 mcg/kg and rocuronium 0.6 mg/kg intravenously, and an oxygen-air mixture of 50%/50% with a tidal volume of 6 ml/kg (ideal body weight) and sevoflurane of 1 MAC. Remifentanyl was administered at 0.05-0.1 mcg/kg/min intravenously in the maintenance of anesthesia. All patients were monitored by an anesthesia machine until extubation. A sevoflurane vaporizer was closed at the end of the operation and the measurement time was started. FiO_2 , Fi_{ins} , Fi_{exp} of sevoflurane, End-tidal CO_2 were recorded during the operation and F_{ins} (Sevo)/ F_{exp} (Sevo) ratio, MAC1, MAC2, MAC3, MAC4, extubation times were recorded. Fi_{ins} 1: percentage of sevoflurane filiation in inspirium before closing 1 MAC vaporizer. Fi_{exp} 1: percentage of sevoflurane filiation in expirium before closing 1 MAC vaporizer. Fi_{ins} 2: percentage of sevoflurane filiation in inspirium after closing 0.1 MAC vaporizer. Fi_{exp} 2: percentage of sevoflurane filiation in expirium after closing 0.1 MAC vaporizer. Results: There was no significant relationship between the respiratory function tests of individuals with or without COPD and MAC1, MAC2, MAC3, MAC4 and extubation time ($P > 0.05$). The cut-off criterion for MAC4 was determined to be 210 seconds. Conclusion: Although there was no difference between the washout and extubation times of both groups, increased BMI and decreased intraoperative hemoglobin values should be carefully considered during anesthetic management in the COPD group.

Keywords: Sevoflurane, COPD, washout time, gas exchange, anesthesia

Introduction

Diagnosis of airway obstruction and COPD can be defined as FEV1/FVC ratio measured with a spirometer after administration of a bronchodilator agent below 70% according to GOLD criteria [1-5]. This ratio is also defined as the criterion for the diagnosis of COPD independently from age according to ATS-ERS and NICE guidelines [5]. COPD is diagnosed based on medical history, physical examination and radiological

examinations, and should be verified using values measured by a spirometer [6].

FEV1/FVC ratio can easily be measured, does not require reference equivalence and significantly decreases in those aged over 60 years old [6]. Elimination of the inhalational anesthetic agents affected by pathologies that disturb width and quality of gas exchange surface in the airways. Washing lungs with 100% oxygen during wake-up period decreases the concen-

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tration and partial pressure of inhalational anesthetic gasses in the alveoli. This causes their increased diffusion into the alveoli through the tissues, and thus causes wake-up. Sevoflurane is a safe volatile anesthetic [2, 7]. Gas transportation is affected by three factors including surface area of the alveolar capillary membrane, thickness of the membrane and repellent pressure caused by the difference of pressure between the alveolar oxygen gas pressure and oxygen in venous blood [8].

Departing from the fact that the delayed excretion of inhalation agents from the lungs may affect the quality of gas exchange, this study aims to compare the washout and extubation times of sevoflurane between patients with and without COPD.

Methods

Upon approval of a non-invasive research from the ethical committee of Düzce University (Date: 13/09/2012, Decision Nr: 2012/302) (ClinicalTrials.gov Identifier: NCT02209883) patient consent was taken. Sixty-six patients were included in this comparative case-control study, diagnosed with ASA (American Society Of Anesthesiologists Classification) Status 1-3 with or without COPD. They were aged between 18 and 60 years old and scheduled to have general anesthesia for an operation. The subjects, who have an allergy to the drugs used in the study, have been smokers for the last 2 years, have clinically significant cardiovascular endocrine, neurological, metabolic hepatorenal disease, restrictive-type pulmonary disorder, have previously undergone a lung operation, have gastroesophageal reflux, are obese (body mass index: BMI over 30), hepatic, renal failure, pulmonary hypertension and pregnancy. All patients underwent a pre-operative respiratory function test (RFT) and their results were recorded.

The patients in the study were randomized into two groups by a care provider: Group N (Control group patients, n = 33), Group COPD (patients with COPD, n = 33). Two patients in Group COPD were excluded from the study due to intraoperative hemodynamic instabilization. Standard monitoring was performed in the operation room, which included systolic, diastolic and mean blood pressure, 3-lead ECG, oxygen saturation (SpO₂). Both groups received propofol 2 mg/kg, fentanyl 1.5-2 mcg/kg, rocuronium 0.6

mg/kg via intravenous (IV) route for general anesthesia induction. All patients were connected to the same type of anesthesia device (Datex Ohmeda S/5 Avance, Datex Ohmeda Inc. USA). During maintenance, a 50% oxygen-air mixture 6 L/dk with tidal volume of 6 ml/kg (ideal body weight) and sevoflurane of 1 MAC, remifentanyl was administered at 0.05-0.1 mcg/kg/min via iv infusion. The anesthesia device was set for tidal volume: 6-8 ml/kg, frequency: 10-12 respiration/minute, end-tidal CO₂: 35-40 mmHg, SpO₂: 95% and more. No PEEP was applied.

Patients were monitored with a mechanical ventilator until extubation. A sevoflurane vaporizer was closed at the end of the operation and the measurement time was started. Infusion of remifentanyl IV was stopped when sevoflurane reached a Minimum Alveolar Concentration (MAC) of 0.1. Administration of muscle relaxants was discontinued 30 minutes before the end of the operation and neostigmin (1.5 mg) and atropine (0.5 mg) iv were administered to the patient to restore neuromuscular block after observing two twitches in TOF response before discontinuing sevoflurane. The time period for data collection was approximately 30 minutes. Outcomes were assessed blindly by a statistician.

Fi_{ins} 1: percentage of sevoflurane filiation in inspirium before closing 1 MAC vaporizer; Fi_{exp} 1: percentage of sevoflurane filiation in expirium before closing 1 MAC vaporizer; Fi_{ins} 2: percentage of sevoflurane filiation in inspirium after closing 0.1 MAC vaporizer; Fi_{exp} 2: percentage of sevoflurane filiation in expirium after closing 0.1 MAC vaporizer; FiO₂, Fi_{ins} (Sevo), Fi_{exp} (Sevo), end-tidal CO₂ were recorded during the operation and Fi_{ins} (Sevo)/Fi_{exp} (Sevo) ratio, MAC1, MAC2, MAC3, MAC4.

MAC1: time between 1 MAC and 0.3 MAC (seconds); MAC2: time between 0.3 MAC and 0.1 MAC (seconds); MAC3: time between 1 MAC and 0.1 MAC (seconds); MAC4: time between 0.1 MAC and extubation (seconds).

Extubation Time: Time to extubation after closing vaporizer (seconds); End of the operation, MAC1, MAC2, MAC3, MAC4, extubation time was recorded; Primary outcome: We aimed to determine if there is any relationship between the washout and extubation times of sevoflurane and COPD.

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Table 1. Demographical data of two groups

	Group N (n = 33)	Group COPD (n = 31)	P
Age (year)*	45.03±13.43	56.00±11.52	0.001
Weight (kilogram)#	75.00 (57.00-120.00)	70.00 (50.00-177.00)	0.375
Height (centimeter)#	170.00 (150.00-184.00)	172.00 (95.00-180.00)	0.588
Body mass index#	26.89 (18.90-37.04)	24.07 (17.93-196.12)	0.209
Hemoglobin (mg/dl)#	14.20 (11.10-16.30)	15.00 (10.10-16.70)	0.043
Haematocrit (%)#	43.40 (33.70-51.00)	43.00 (4.00-49.20)	0.541
Operation time (min)#	110.00 (45.00-340.00)	95.00 (45.00-225.00)	0.532

*Mean ± Standard Deviation; #Median (Minimum-Maximum).

Table 2. Identifier values of the respiratory function tests

	Group N (n = 33)	Group COPD (n = 31)	P
FEV1 (L)	5.56±14.11	1.98±0.68	< 0.001
FVC (L)	5.96±11.90	3.08±0.85	0.001
FEF25-75 (L/s)	6.74±21.79	1.22±0.60	< 0.001
FEV/FVC (%)	80.85±9.33	63.32±8.18	< 0.001

Table 3. Gas quantities in inspirium and expirium air

	Group N (n = 33)	Group COPD (n = 31)	P
Fi _{ins} 1 (%)	2.25±0.39	2.26±0.38	0.981
Fi _{ins} 2 (%)	0.12±0.18	0.30±0.50	0.149
Fi _{exp} 1 (%)	1.97±0.19	1.77±0.64	0.538
Fi _{exp} 2 (%)	0.32±0.16	0.22±0.12	0.021
Fi _{ins} 1-Fi _{exp} 1 ratio	1.13±0.16	1.18±0.16	0.919
Fi _{ins} 2-Fi _{exp} 2 ratio	0.36±0.62	1.44±2.12	0.182

Fi_{ins} 1: Percentage of sevoflurane gas in inspirium before closing 1 MAC vaporizer, Fi_{ins} 2: Percentage of sevoflurane gas in inspirium after closing 0.1 MAC vaporizer, Fi_{exp} 1: Percentage of sevoflurane gas in expirium before closing 1 MAC vaporizer, Fi_{exp} 2: Percentage of sevoflurane gas in expirium after closing 0.1 MAC vaporizer.

Power analysis: In order to achieve a clinical significance with 80% power and 5% significance based on the literature, the number of subjects required to be included in each group was determined as 30 (n = 30) as a result of Power analysis [9, 10].

Statistical assessment

The descriptive statistics (mean, standard deviation, median, minimum, maximum, percentage) of all variables in the study were calculated. The normality assumption for quantitative variables was examined with Kolmogorov-

Smirnov and Shapiro Wilk tests. Independent t test samples and a Mann-Whitney U test were used in the group comparisons. Repeated Measures ANOVA (post hoc Tukey HSD test) was used in comparison of the measured time-dependent variables. In addition, Parametric and Nonparametric Repeated Measures ANCOVA (post hoc Fisher LSD test or Dunn test) were used to compare the related variables between the groups by excluding the effect of a confounding factor (covariate). ROC analysis was used to determine the thresholds for biochemical measurements in both patient and control groups. The relationships between the quantitative variables were assessed using a Spearman correlation test. The relationships between the categorical variables were investigated using a Pearson chi-square test. SPSS 22 software was used for statistical assessments and P < 0.05 was assumed as statistically significant.

Results

Seventy-five patients were assessed for eligibility. Nine patients were excluded (eight patients did not meet the inclusion criteria and one patient's operation was cancelled). Sixty-six patients were included in the study. Two patients discontinued the intervention because of hemodynamic instability in the COPD group.

It was determined that gender is not a confounding factor during comparison of the groups in terms of the variables investigated. Therefore, comparisons were made by using age as the only variable and confounding factor. The results of comparisons were obtained by adjusting age.

As presented in **Table 1**, the average age of patients in the COPD group was significantly higher than the control group. A significant neg-

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Table 4. Comparison of hemoglobin and hematocrit values as well as targeted time to reach MAC (seconds) and extubation times between Group N and Group COPD

		Group N		Group COPD	
		Hemoglobin (mg/dL)	Haematocrit (%)	Hemoglobin (mg/dL)	Haematocrit (%)
MAC1 (second)	R	.357	.268	.133	.057
	P	.041	.132	.476	.760
	N	33	33	31	31
MAC2 (second)	R	.333	.248	.157	.062
	P	.058	.165	.398	.740
	N	33	33	31	31
MAC3 (second)	R	.487	.365	.007	-.057
	P	.004	.037	.970	.762
	N	33	33	31	31
MAC4 (second)	R	-.427	-.308	-.394	-.342
	P	.013	.082	.028	.060
	N	33	33	31	31
Extubation time (second)	R	.123	.246	-.332	-.249
	P	.494	.168	.068	.176
	N	33	33	31	31

MAC1: Time between 1 MAC and 0.3 MAC. MAC2: Time between 0.3 MAC and 0.1 MAC. MAC3: Time between 1 MAC and 0.1 MAC. MAC4: Time between 0.1 MAC and extubation.

ative relationship was determined between the age of patients with COPD and F_{exp1} measured before closing 1 MAC vaporizer ($r = -0.462$, $P = 0.009$).

As presented in **Table 1**, the distribution of sex was found to be significantly different between the two groups ($P = 0.009$).

Demographical data are shown in **Table 1**.

No significant difference was found between the groups in terms of MAC1, MAC2, MAC3, MAC4 and extubation time measured after closing the sevoflurane vaporizer, corrected for age ($P > 0.1$).

As shown in **Table 3**, it was determined that there was no significant difference between groups in terms of $F_{i_{ins}1}$, $F_{i_{ins}2}$, $F_{i_{exp}1}$, $F_{i_{ins}1}/F_{i_{exp}1}$ ratio and $F_{i_{ins}2}/F_{i_{exp}2}$ ratio measured before closing the 1 MAC vaporizer, corrected for age.

It was determined that $F_{i_{exp}2}$ values, measured after closing 0.1 MAC vaporizer, corrected for age, were significantly different between the groups listed in **Table 3**.

There was no significant relationship between the respiratory function tests of individuals

without COPD and the times measured after closing the sevoflurane vaporizer ($P > 0.05$).

In this group, there was no significant relationship between the values measured before closing the 1 MAC vaporizer and after closing 0.1 MAC vaporizer and the respiratory function tests.

There was no significant relationship between the values measured before closing the 1 MAC vaporizer and after closing the 0.1 MAC vaporizer and the respiratory function tests of patients with COPD.

There was a significant negative relationship between MAC3 time measured after closing the sevoflurane vaporizer and the BMI values of individuals without COPD ($r = -0.354$, $P = 0.043$).

There was a significant positive relationship between the BMI values of patients with COPD and the extubation time measured after closing the sevoflurane vaporizer ($r = 0.395$, $P = 0.028$).

There was a significant negative relationship between F_{exp2} value measured after closing the 0.1 MC vaporizer and BMI values of individuals without COPD ($r = -0.392$, $P = 0.024$).

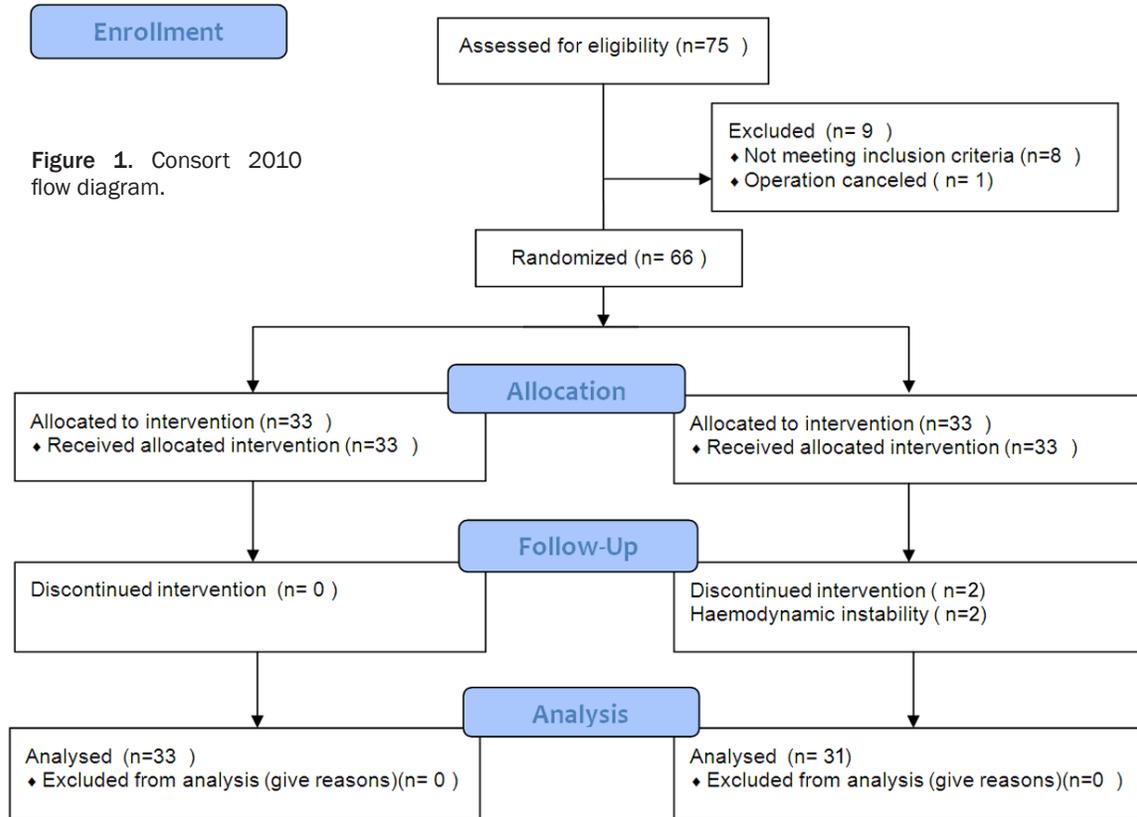


Figure 1. Consort 2010 flow diagram.

There was a significant positive relationship between the hemoglobin values of subjects in the control group and MAC1 and MAC3 values measured after closing the sevoflurane vaporizer. However, as shown in **Table 4**, there was a significant negative relationship between the hemoglobin value and MAC4 time. As a result of the statistical analysis, the cut-off criterion for MAC4 was determined to be 210 seconds (area under curve (AUC) = level 0.680; $P = 0.013$). For this value, the Sensitivity value was 74.19% (95% Confidence Interval (GA): 55.4-88.1%) and the Specificity value was 63.64% (95% GA: 45.10-79.6%). The positive estimation value was 65.7% and the negative estimation value was 72.4%. The positive likelihood ratio (LR+) was 2.04 ($LR+ < 2$) and the negative likelihood ratio (LR-) was 0.41 ($LR- < 1$). As shown in **Figure 1** it was observed that the MAC4 measurement was a good diagnosis of the test criterion between both groups.

As presented in **Table 4**, there was a significant positive relationship between hemoglobin values of the subjects in the group without COPD and MAC3 values measured after closing the sevoflurane vaporizer ($r = 0.365$, $P = 0.037$).

There was no significant relationship between operation times of the patients with COPD and MAC4 time values measured after closing the sevoflurane vaporizer ($P > 0.05$).

Time-corrected SAP values measured at different times were compared between groups. It was observed that the difference between groups did not change by SAP values measured at different times, or that the difference between SAB values were similar in both groups ($P = 0.477$).

The difference between groups did not change by DAB values measured at different times or

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that the difference between DAP values were similar in both groups ($P = 0.228$; $P < 0.01$).

Time-corrected MAP values measured at different times were compared between the groups. It was observed that the difference between the groups did not change by OAB values measured at different times, or that the difference between OAB values were similar in both groups ($P = 0.313$).

The difference between groups did not change by EtCO₂, SpO₂, FiO₂, KTA values measured at different times. The difference between EtCO₂, SpO₂, FiO₂, HR values were similar in both groups ($P = 0.380$; $P = 0.907$; $P = 0.293$; $P = 0.175$).

Discussion

No statistically significant difference was observed in sevoflurane washout and extubation times between the control group and the COPD group.

As the best indicator in the assessment of small airway diseases of our patients (peripheral airway functioning), both lung volumes and flows during FVC test were assessed. Such values include FEF 25-75, FEF50 and FEF75 [8]. In our study, FEF 25-75 values were considerably lower in the COPD group compared to the other group, which is presented in **Table 2**.

Recovery from the inhalational anesthetic agents occurs as a result of the decreased concentration of anesthetic agent in the brain tissue. This is affected by many factors, including high fresh gas inhalation, low anesthetic circulation volumes, ventilation, tissue perfusion and uptake, body mass, ratio of different organs in body composition, low absorption solubility of the anesthetic cycle, high brain blood flow and increased ventilation [11, 12]. In our study, gas flows were kept stable by alveolar ventilation. The basal values of hemodynamic parameters were kept below 20% through the use of vasoactive and vasopressor drugs.

Sevoflurane is a fluorinated inhalational agent, has a low blood/gas partition coefficient and allows fast recovery. Desflurane exceeds the maximum limit of 20% for the basal values of mean arterial pressure more frequently than sevoflurane [13]. Considering the effects of

changes in the hemodynamic parameters on washout time sevoflurane was preferred in our study.

It was observed that spontaneous recovery of inhalation and extubation was 8 minutes in cases of the administration of a sevoflurane/nitrous oxide mixture, and 13 minutes only in cases of the administration of sevoflurane [14].

Regarding studies on washout curves and recovery times performed with sevoflurane, washout curves of sevoflurane (FA/FAO) were slower in the obese group compared to the non-obese group [14-16]. It should be noted that obesity exhibits a rather restrictive pattern. The literature reports that sevoflurane did not have any effect on washout time in patients who are smokers and do not have severe pulmonary disease [16].

Additionally, positive end-expiratory pressure affects washout of nitrous oxide in patients with obstructive pulmonary disease [9]. These results suggest that patients with COPD are at risk of delay in nitrous oxide elimination.

FEV1/FVC RATIO OVER 70%:

The most striking aspect of the patients in this group was the fact that there was no significant relationship between the respiratory function tests of individuals without COPD and the times measured after closing the sevoflurane vaporizer (MAC1, MAC2, MAC3, MAC4 and extubation time) ($P > 0.05$).

There was a significant positive relationship between the hemoglobin values of subjects in the control group and MAC1, MAC3 values measured after closing the sevoflurane vaporizer. An increased hemoglobin value causes an increase in time between 1 MAC and 0.3 MAC, and thus time between 1 MAC and 0.1 MAC. This fast declining part of the curve indicates that transportation of oxygen to the related tissues may decrease the time of washout of sevoflurane. However, there is a significant negative relationship between the hemoglobin value and 1 MAC - extubation time ($r = -0.427$, $P = 0.013$). It seems 1 MAC extubation time decreases by an increase in the hemoglobin values. This may be explained by the increased partial oxygen pressure in tissues and decreased sevoflurane values.

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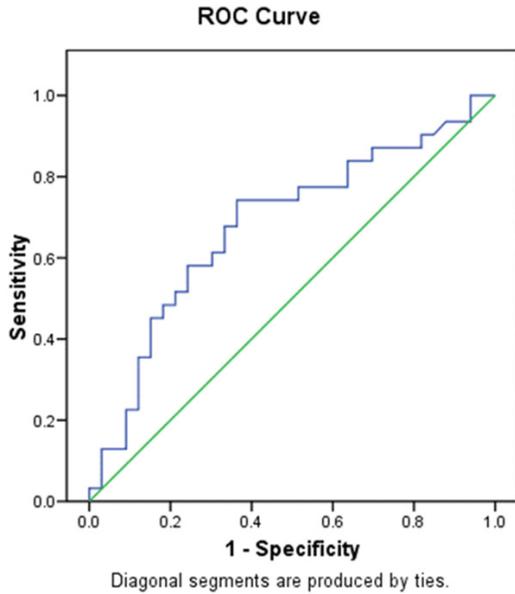


Figure 2. Statistical analysis was performed, the cut-off criterion for MAC4 was determined to be 210 seconds (AUC = level 0.680; $P = 0.013$). It was observed that MAC 4 measurement was a good diagnosis test criterion between both groups. No cut-off value was found for other measurement periods.

As a result of the investigation of the $Fi_{exp,2}$ value measured at 0.1 MAC level after closing the vaporizer, corrected for age, it was observed that a significantly higher rate of sevoflurane was present in expirium in the control group ($P = 0.021$). This suggests that the gas exchange significantly extends in patients with COPD, especially at low concentrations, and existing air trap delays the wash-up of sevoflurane. A statistical analysis was performed and the cut-off criterion for MAC4 was determined to be 210 seconds (AUC = level 0.680; $P = 0.013$). As shown in **Figure 2**, it was observed that MAC4 measurement was a good test criterion between both groups. No cut-off value was found for other measurement periods.

The time periods between 1 MAC-0.3 MAC extend by the increase in hematocrit values in the control group, and the gas exchange slows down by an increase in blood viscosity ($r = 0.365$, $P = 0.037$).

It seems the quantity of sevoflurane in the expirium air after closing the 0.1 MAC vaporizer decreases by increasing the BMI in the control group ($r = -0.392$, $P = 0.024$). Therefore, it can be concluded that washout of sevoflurane at

low concentrations is delayed by an increase in the body mass index, or washout may extend due to the slow washout from the fatty tissue [13].

FEV1/FVC RATIO BELOW 70%:

Although there is no difference between the operation times and extubation times of patients in this group, it is interesting that there are many differences in the relationship level of parameters compared to the control group.

The time between 0.3 MAC and 0.1 MAC, and the time between 1 MAC and 0.1 MAC increased significantly in Group N. The gas exchanges were normal in spite of extended operation times, while no difference was observed in the COPD group. We think that this occurred due to the slowing down of the gas exchanges and air trap between the compartments in the COPD group. The statistically significant decrease in Group N and the negative correlation in the COPD group between quantities of sevoflurane ($Fi_{exp,2}$) in expirium air at 1 MAC level ($P = 0.009$; $P = 0.025$) by age, supports the fact that the infection, as well as the thickening of the membranes in alveolar membranes and respiratory bronchi, may cause difficulty in gas exchange [17, 18]. We think that the subjects with significant airway obstruction will have a longer period of wake-up from inhalational anesthesia. The air trap will also trap the inhalation agents, so return to the lungs from other compartments of the body will decrease [19]. We think that this fact is supported by the rapid decrease caused by the difference in concentration that occurred during washing of sevoflurane in the airways from 1 MAC to 0.3 MAC with 100% oxygen. This exhibited a slower decrease after 0.3 MAC, as observed on the washout curves specified in the literature and the $Fi_{exp,2}$ value measured after closing the 0.1 MAC vaporizer. This was significantly lower in the COPD group observed in our study ($P = 0.021$) [19, 20].

The extubation times increased with the increased BMI values in patients with COPD ($r = 0.395$, $P = 0.028$). In our study, it seems that body mass, the different ratio of tissues in body composition and tissue stability, which are factors that effect the inhalational anesthetic agents, affect the COPD group more [9, 10]. It was reported in the literature that slow excretion of sevoflurane from the fatty tissue may extend the wash-out time [13, 20].

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In this group, although there was no relationship between hematocrit levels and excretion times, the times between MAC 0.1 and extubation decreased by an increase in hemoglobin levels ($r = -0.394$, $P = 0.028$). The median value of hemoglobin in the COPD group was found to be significantly higher than the control group ($P = 0.043$). This suggests that oxygen transportation in these individuals exhibits a compensation mechanism in terms of optimization. Our study suggests that, in cases of anemia, excretion will be slower in patients with COPD and this may lead to delays in recovery. While the small number of cases is the negative aspect of our study, the differences between the excretion phases of the gasses and accompanying factors such as hemoglobin and BMI, which have an affect upon it, are very interesting.

As a result, no difference was found in washout times between both groups in this study. In addition, while increases in BMI and decreases in intraoperative hemoglobin levels may cause a decrease in return to the lungs from other compartments of the body, in the COPD patient group, scheduled for operation under general anesthesia, preoperative preparations should be aimed at the correction of the related parameters. In order to put forth the factors that affect excretion, we think that wider and more comprehensive studies should be performed.

Disclosure of conflict of interest

None.

Abbreviations

MAC, Minimum Alveolar Concentration; FEV₁, Forced Expiratory Volume in 1 second; FVC, Forced vital capacity; FEF 25-75, Forced Expiratory Flow at 25-75%; Hb, Hemoglobin; Htc, Hematocrit; COPD, Chronic Obstructive Pulmonary Disease; ASA, American Society Of Anesthesiologists Classification; BMI, Body Mass Index; SpO₂, Peripheral Oxygen Saturation; AUC, Area Under Curve; RFT, Respiratory Function Test; ROC, Receiver Operating Characteristic; SAP, Systolic Arterial Pressure; DAP, Diastolic Arterial Pressure; MAP, Mean Arterial Pressure.

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