

# Pressure-controlled ventilation could decrease intraoperative blood loss and improve airway pressure measures during lumbar discectomy in the prone position: A comparison with volume-controlled ventilation mode

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## Abstract

**Background and Aims:** Prone positioning may induce alterations of hemodynamic and airway pressure parameters that may affect intraoperative (IO) blood loss. Pressure-controlled ventilation (PCV) may modify these alterations. To observe the relation between ventilation mode and hemodynamic, airway pressure changes, and blood loss during lumbar discectomy performed in the prone position.

**Material and Methods:** Volume-controlled ventilation (VCV) patients were using tidal volume (TV) of 8–10 ml/Kg, but for pressure-controlled ventilation (PCV) patients peak inspiratory pressure (PIP) was adjusted to provide the same TV according to ideal body weight. Respiratory and hemodynamic parameters were recorded in supine (T1), on turning to prone (T2), and on returning to the supine position (T3). Primary outcome included amount of IO blood loss; Secondary outcome included need for blood transfusion, IO hemodynamics, and airway pressure changes.

**Results:** IO blood loss and central venous pressure (CVP) were significantly higher with VCV than PCV patients. Heart rate and blood pressure were significantly reduced in the prone position with little impact of ventilation mode. Prone positioning resulted in significant increase of P-peak and non-significant decrease of P-mean pressure with VCV, while with PCV resulted in a significantly increased airway pressures. P-peak pressure was significantly lower with PCV in supine and prone positions than VCV. P-mean pressure was significantly lower in supine but significantly higher in the prone position with PCV than VCV.

**Conclusions:** Prone positioning and VCV were associated with increased CVP and IO blood loss, while PCV could lessen these effects and significantly improve airway pressures.

**Keywords:** Airway pressure measures, intraoperative blood loss, lumbar position, ventilation mode

## Introduction

Lumbar disc herniation may lead to radiculopathy causing back pain.<sup>[1,2]</sup> There is very little evidence of pressure-controlled

ventilation (PCV) efficacy over volume-controlled ventilation (VCV) in the adult population.<sup>[3]</sup>

Prone positioning may induce alterations of hemodynamic<sup>[4]</sup> and airway pressure parameters<sup>[5]</sup> that may affect intraoperative (IO) blood loss. Thus, the current study hypothesized that PCV may modify these alterations.

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Our study aimed to observe the relation between ventilation mode and hemodynamic, airway pressure changes, and blood loss during lumbar discectomy performed in the prone position.

Our primary outcome was the amount of IO blood loss. Secondary outcome included frequency of patients required a blood transfusion, number of transfused units, operative time, IO changes of HR, blood pressure, CVP, and airway pressures including P-peak and P-mean.

## Material and Methods

After obtained approval of our institutional ethical committee (110/3/13), the current prospective, comparative study was conducted since June 2016 till March 2018. Patients classified by American Society of anesthesiologists as ASA grade I or II, aged 20–70 years were enrolled in this study for further evaluation for inclusion and exclusion criteria. The study included 119 eligible patients; 27 were excluded and 92 assigned for one-level lumbar discectomy underwent the intervention [Figure 1]. Exclusion criteria included obese patients with body mass index >30 kg/m<sup>2</sup>, patients with a history of expected difficult intubation, multiple level lumbar disc prolapse, previous chest surgery, restrictive pulmonary diseases, bleeding diathesis, asthmatic bronchitis, cardiac, hepatic or renal compromise, allergy to anesthetics or drugs planned to be used. Patients younger than 20 years, older than 70 years, or those attended as emergency cases were also excluded from the study.

Preoperative assessment included determination of demographic data, clinical evaluation, and determination of ASA grade.

Then, all patients underwent radiologic workup and laboratory investigations including kidney and liver function tests, complete blood count [to record preoperative hemoglobin (Hb) concentration and hematocrit (HCT) value], and coagulation profile for assurance of inclusion and exclusion criteria. In addition, patients were examined immediately before anesthesia for baseline (T0) hemodynamic data including heart rate, blood pressure (BP) measures; systolic (SAP), diastolic (DAP), and calculation of mean arterial pressure (MAP). Ideal body weight (IBW) was calculated according to the following equation:  $IBW = [(height\ in\ inches - 60) - 2.2] + 50$  for men or 45 for women.<sup>[6]</sup> Patients fulfilling inclusion criteria were asked to sign a written fully informed consent concerning the study plan detailed all needed interventions and were randomly, using sealed envelopes prepared by blinded assistant and chosen by the patient him/herself, divided into two groups according to controlled ventilation mode as follows:

- VCV group (46 Patients): after intubation, mechanical ventilation was initiated with 100% oxygen using volume-controlled mode (VCM) for a tidal volume (TV) of 8–10 ml/kg and positive end-expiratory pressure (PEEP) at 5 cmH<sub>2</sub>O with the respiratory rate (RR) was set to maintain an end-tidal CO<sub>2</sub> (ET<sub>CO<sub>2</sub></sub>) of 30–35 mmHg, with inspiration/expiration (I/E) ratio = 1:2, without adjusting peak inspiratory pressure (PIP)
- PCV group (46 patients): Same ventilation settings except that PIP was adjusted for a flow rate to provide volume calculated according to IBW to achieve TV of 8–10 ml/kg with PEEP at 5 cmH<sub>2</sub>O.

The attending anesthesiologist used the standard anesthesia regimen in the study protocol, but he was blinded to the

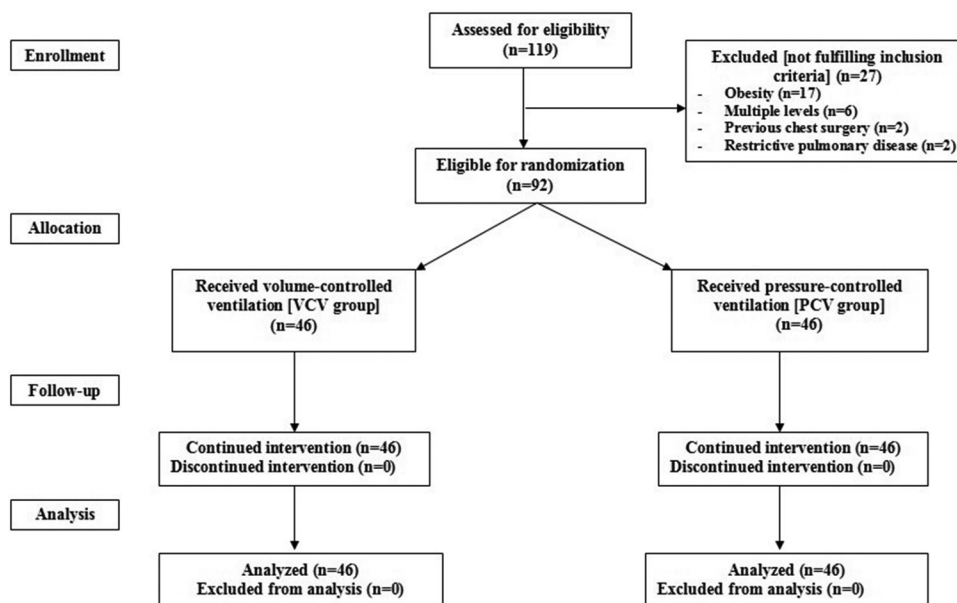


Figure 1: Consort flow sheet

study protocol details. One of the authors was responsible for measuring and recording the data and changes and was blinded to the study protocol details and he did not share in patient care. All surgeries were performed by the same team of surgeons, and both surgeons and nurses who were providing patient care were blinded to the study protocol details.

Patients of both groups received the same anesthetic protocol including premedication using intravenous (IV) midazolam 2 mg, then the central venous catheter was inserted through the right internal jugular vein after local anesthetic infiltration for central venous pressure (CVP) measurement and fluid administration. Proper central venous catheter insertion was ascertained on C-arm fluoroscopy. In addition, the arterial cannula was inserted in the left radial artery after local anesthetic infiltration for invasive BP monitoring. Induction of anesthesia by fentanyl 2 µg/kg and propofol 2 mg/kg followed by atracurium 0.5 mg/kg to facilitate tracheal intubation. Patients were maintained on controlled mask ventilation with 100% O<sub>2</sub> until adequately relaxed within 3–5 min and then endotracheal armored tube was inserted. Incremental doses of fentanyl (0.5–1.0 µg/kg) and atracurium (0.1 mg/kg) were given according to needs, in addition to isoflurane 2% as an inhalational anesthetic agent in a mixture with O<sub>2</sub> and air by 1:1 ratio. Standard monitoring for all patients included invasive monitoring for blood pressures, CVP, and urine output and non-invasive monitoring of HR using 5-lead ECG, Sp<sub>O<sub>2</sub></sub>, and ET<sub>CO<sub>2</sub></sub>.

After stabilization of ventilation, respiratory and hemodynamic parameters were recorded in supine position (T1 measures). Then, patients were turned to a prone position and another reading for evaluated parameters was obtained (T2 measures), then, the surgical procedure was started. Total fixed amount of normal saline solution (200 ml) was used for intermittent wash of the surgical field for all patients in both groups to remove blood clots, clarify surgical field, and secure hemostasis; the resultant wash fluid was removed by suction in the suction canister and in the wet gauze intraoperatively and in the surgical drain postoperatively, and its amount was subtracted from the total IO and postoperative (PO) blood loss to get the actual amount of IO plus 24 h PO blood loss. At the end of surgery and reversing patients to supine position, the same parameters, together with IO haemoglobin (Hb) concentration and haematocrit (HCT) value were recorded (T3 measures). Then, all anesthetics were stopped, trachea was extubated when patients were recovered, and patients were transferred to post-anesthetic care unit and hemodynamic measures were re-determined (T4 measures). IO blood loss was calculated as the sum of the amount of blood collected in the suction canister and in the calculated net weight of gauze swabs. Total blood loss was calculated as the sum of IO and PO blood loss for 24 h PO. Blood transfusion regimen followed the hospital

protocol to transfuse whole blood or packed red blood cells when the HCT value dropped below 30%; Hence, HCT value below 30% was the trigger used for IO and PO blood transfusion. In patients with HCT values more than 30%, blood loss was replaced by the administration of intravenous fluids with urine output monitoring to establish and preserve stable hemodynamic status. Postoperatively, Hb and HCT values were rechecked and recorded after 24 h.

Our primary outcome was the amount of IO blood loss. Secondary outcome included frequency of patients required a blood transfusion, number of transfused units, operative time, IO changes of HR, blood pressure, CVP, and airway pressures including P<sub>-peak</sub> and P<sub>-mean</sub>.

### Statistical analysis

As regard statistical analysis, the sample size was calculated according to Rosner<sup>[7]</sup> based on a power of 80%, an alpha of 0.05, and the assumption that 30% of patients in VCV group would have increased IO blood loss that may require blood transfusion; a sample size of ≥40 patients per group was needed to detect a 20% decrease in rate of patients who may require blood transfusion in PCV group. Results were analyzed using paired and Student t test and Chi-square test (X<sup>2</sup> test). Possible relationships were investigated using Pearson's linear regression. Statistical analysis was conducted using IBM SPSS (Version 23, 2015) statistical package.  $P < 0.05$  was considered statistically significant.

### Results

The study included 119 eligible patients; 27 patients were excluded for not fulfilling inclusion criteria, whereas the remaining 92 patients assigned for one-level lumbar discectomy were undergoing the intervention [Figure 1]. Preoperative data of the enrolled patients showed the non-significant difference ( $P > 0.05$ ), [Table 1].

Duration of maintenance in the prone position and total anesthesia time were non-significantly ( $P > 0.05$ ) shorter in patients maintained on PCV than those maintained on VCV. The amount of IO blood loss was significantly ( $P < 0.05$ ) higher, whereas PO blood loss was non-significantly ( $P > 0.05$ ) higher with significantly ( $P < 0.05$ ) higher amount of total blood loss in patients maintained on VCV than those maintained on PCV. Seventeen patients required blood transfusion with a non-significant difference ( $P > 0.05$ ) between patients of both groups as regard a number of patients required blood transfusion or the number of transfused units. PO Hb and HCT values in VCV group were significantly ( $P < 0.05$ ) lower than those in PCV group and both (Hb and HCT) were significantly lower than preoperative values in both groups [Table 2].

**Table 1: Preoperative data of patients of studied groups**

Data	Group VCV	Group PCV	P
Age (years)	44.4±7	43.5±5.4	NS
Gender			
Male	19 (41.3%)	21 (45.7%)	NS
Female	27 (58.7%)	25 (54.3%)	
Actual body weight (kg)	80.4±5.1	81.2±5.1	NS
Body height (cm)	169.7±1.8	170.8±3.7	NS
Body mass index data			
<25 kg/m <sup>2</sup>	8 (17.4%)	5 (10.9%)	NS
≥25 kg/m <sup>2</sup>	38 (82.6%)	41 (89.1%)	
Mean (kg/m <sup>2</sup> )	27.3±1.9	27.8±1.7	NS
Calculated Ideal body weight (kg)	54.9±1.7	55.1±2.3	NS
Duration of back pain (months)			
<24	11 (23.9%)	16 (34.8%)	NS
24-36	22 (47.8%)	18 (39.1%)	
>36	13 (28.3%)	12 (26.1%)	
Mean	31.3±8	30.2±8.9	NS
Level of discectomy			
L2-3	4 (8.7%)	6 (13%)	NS
L3-4	6 (13%)	5 (10.9%)	
L4-5	15 (32.6%)	17 (37%)	
L5-S1	21 (45.7%)	18 (39.1%)	
ASA grade			
I	37 (80.4%)	33 (71.7%)	NS
II	9 (19.6%)	13 (28.3%)	

Data are presented as means±SD or numbers and percentages; NS=Indicates the non-significant difference between both groups; P<0.05 indicates a significant difference between both groups

Pearson’s correlation analysis showed a positive significant correlation between CVP measures on one side and prone positioning ( $r = 0.456, P = 0.001$ ) and the maintenance on VCV ventilation mode ( $r = 0.378, P = 0.004$ ) on the other side. Moreover, there was a positive significant correlation between high CVP and excess IO bleeding in both VCV ( $r = 0.505, P = 0.002$ ) and PCV groups ( $r = 0.414, P = 0.015$ ).

Turning patients who were maintained on VCV from supine to prone position resulted in significant ( $P < 0.05$ ) increase of P-peak, but non-significant ( $P > 0.05$ ) decrease of P-mean pressure measures. However, turning patients who were maintained on PCV from supine to prone position resulted in significant ( $P < 0.05$ ) increase of all estimated airway pressures. P-peak pressure was significantly ( $P < 0.05$ ) lower in patients maintained on PCV in both supine and prone position than the patients who were maintained on VCV. However, P-mean pressure was significantly ( $P < 0.05$ ) lower in the supine position but was significantly ( $P < 0.05$ ) higher in the prone position in patients maintained on PCV than the patients maintained on VCV [Table 3].

Changing patients to prone position (T2) significantly ( $P < 0.05$ ) reduced HR and BP measures compared to measures at supine positions before turning to prone position (T1) and after return to supine position at the end

**Table 2: Intraoperative data of patients of both groups**

Data	Group VCV	Group PCV	P
Anesthesiatime (min)			
Duration in prone position	129.2±20.4	120.2±16.6	0.060
Total	153.6±22.2	143.8±21	0.068
Blood loss (ml)			
Intraoperative	539.8±125	454.1±135	0.012*
24-h postoperative	353.3±135	332.9±165	0.281
Total 24-h blood loss	893.1±170	787±145	0.004*
Fixed amount of normal saline solution used for intraoperative wash	200 ml	200 ml	
Actual Total 24-h blood loss	693.1±170	587±145	0.003*
Hematological data			
Hemoglobin concentration (Hb) (gm%)			
Preoperative	11.86±1.24	11.94±1.44	0.539
Intraoperative (at T3)	11.25±1.17	11.65±1.25	0.085
24-h postoperative	11.11±1.06	11.61±1.13	0.031*
Hematocrit value (HCT) (%)			
Preoperative	36.5±5.3	36.3±5.12	0.729
Intraoperative (at T3)	33.07±4.79	34.5±4.45	0.091
24-hpostoperative	32.58±4.52	34.41±5.13	0.023*
Need for blood transfusion			
Number of patients required	10 (21.7%)	7 (15.2%)	0.355
Number of units received by patients required (unit)	1.7±0.4	1.4±0.7	0.276

Data are presented as means±SD and numbers; P=Indicates difference between VCV and PCV groups; \*Statistically significant (P of statistical significance <0.05) T3=Time at the end of the surgery, after reversing patient to the supine position

of surgery (T3). In spite increased HR and BP measures at T3, these measures were still significantly ( $P < 0.05$ ) lower than T1 measures. However, mode of ventilation showed little impact on HR and BP measures, manifested as non-significant ( $P > 0.05$ ) difference between measures recorded in patients of both groups throughout anesthesia time. Moreover, patients maintained on VCV showed significantly ( $P < 0.05$ ) higher CVP at T1, T2, and T3 than the patients maintained on PCV [Table 4].

## Discussion

In our study, patients maintained on VCV showed significantly higher IO blood loss on one side and significantly higher CVP at T1-3 compared to patients maintained on PCV on the other side with a positive significant correlation between IO blood loss and CVP. Moreover, prone positioning showed positive significant correlation with increased CVP and IO blood loss. These findings spotlight on a fact that prone positioning and/or VCV induced increased venous engorgement resulting in increased CVP and bleeding of injured vessels during surgery. Similarly, Koh *et al.*<sup>[8]</sup> found IO blood loss was correlated with peak airway pressure changes and Malhotra *et al.*<sup>[9]</sup> detected increased mean airway pressure and IO blood loss on prone position during spine surgery. In addition, Kang *et al.*<sup>[10]</sup> reported that PCV decreased IO surgical bleeding in patients undergoing lumbar fusion surgery and this may be related to lower IO peak inspiratory pressure.

In trial to explain the relation between prone positioning, ventilation mode, increased CVP, and IO blood loss, Malhotra *et al.*<sup>[9]</sup> detected that prolonged prone positioning during surgery induces increased intra-abdominal pressure and associated increased IO blood loss. In addition, Ma *et al.*,<sup>[11]</sup> Berger *et al.*<sup>[12]</sup> and Min *et al.*<sup>[13]</sup> found short-term prone positioning may have a direct effect on cardiac function with decreased stroke volume and cardiac output. Moreover, Koprulu *et al.*<sup>[14]</sup> suggested that high frequency-low TV ventilation during general anesthesia for lumbar microdiscectomy can be useful in minimizing epidural venous engorgement and bleeding by using low peak pressure during surgery.

However, ventilation mode showed a significant impact on airway pressure as manifested by significantly lower P-peak pressure in patients maintained on PCV than the patients maintained on VCV in both supine and prone positions. Moreover, the significant difference in P-mean pressure, between both ventilation modes, on turning patients from supine to prone position illustrated the beneficial effect of PCV.

**Table 3: Respiratory parameters of mechanical ventilation of patients of both groups estimated during supine and prone positions**

Parameter	Position	Group VCV	Group PCV	P
P-peak (cmH <sub>2</sub> O)	Supine position	22.7±3.1	21.1±2.5	0.031
	Prone position	24±1.8	22.45±1.6	0.001
	P <sub>1</sub>	0.033	0.026	
P-mean (cmH <sub>2</sub> O)	Supine position	12.1±1.34	11.47±1.39	0.038
	Prone position	11.6±2	12.83±1.46	0.001
	P <sub>1</sub>	0.054	0.001	
Exp tidal vol. (ml)		468.3±66.4	474.3±71.7	0.750

Data are presented as means±SD; P=Indicates a difference between VCV and PCV groups; P<sub>1</sub>=Significance of difference between measures in the supine and prone position

**Table 4: Hemodynamic findings of patients of studied groups throughout operative time**

Time	Parameter	Group VCV	Group PCV	P
T0	CVP (cmH <sub>2</sub> O)	6.01±0.7	5.91±0.8	0.763
	HR (beats/min)	78.5±4.7	79.5±4.8	0.276
	SAP (mmHg)	119.5±5.8	120.9±3.6	0.309
	DAP (mmHg)	81.1±5.5	80.9±2.8	0.836
	MAP (mmHg)	93.9±4	94.2±1.9	0.723
T1	CVP (cmH <sub>2</sub> O)	7.59±0.8*	6.95±0.7*	0.013
	HR (beats/min)	75±3.9*	74±3.8*	0.231
	SAP (mmHg)	94.4±3.8*	92.6±3.9*	0.067
	DAP (mmHg)	57.7±6.1*	58.6±5.1*	0.345
	MAP (mmHg)	70±4.5*	69.9±3.8*	0.129
T2	CVP (cmH <sub>2</sub> O)	8.32±0.53	7.72±0.6	0.018
	HR (beats/min)	72±4.3	71.1±4.2	0.287
	SAP (mmHg)	92.6±2.3	93.6±8.1	0.602
	DAP (mmHg)	58.3±6.1	57.4±5.2	0.875
	MAP (mmHg)	69.8±3.9	69.4±7	0.113
T3	CVP (cmH <sub>2</sub> O)	7.69±0.73*	7.25±0.8*	0.029
	HR (beats/min)	74.9±4.5*	73.2±3.7*	0.162
	SAP (mmHg)	93.1±3.5*	94.5±6.8*†	0.422
	DAP (mmHg)	55.4±7*	55.9±4.5*†	0.398
	MAP (mmHg)	68±5.1*†	68.7±10.3*†	0.293
T4	CVP (cmH <sub>2</sub> O)	6.25±1	5.77±1	0.106
	HR (beats/min)	77.4±4.9	76.2±5.1	0.211
	SAP (mmHg)	98±9.5	99±8.3	0.439
	DAP (mmHg)	60.6±8	62.5±7.2	0.467
	MAP (mmHg)	73.1±6.2	74.7±6.6	0.098

Data are presented as means±SD; P=Indicates a difference between VCV and PCV groups; †Significant difference versus T1; \*Significant difference versus T2

In line with these findings, Sen *et al.*<sup>[5]</sup> reported that P-peak levels during supine and prone positions were significantly higher, and P-mean and compliance levels during prone position were significantly lower with VCV than PCV. In addition, Jo *et al.*<sup>[15]</sup> found PCV provided significantly lower P-peak than VCV when the ventilator is set to deliver the same TV in patients undergoing posterior lumbar spine surgery in both supine and prone positions with a significant difference between supine and prone measurements in both groups. In addition, Liao *et al.*<sup>[16]</sup> documented that PCV

offered lower peak airway pressure and higher compliance than VCV during gynecologic laparoscopic surgery. Recently, in 2018, Tan *et al.*<sup>[17]</sup> reported that during radical resection of pulmonary carcinoma using one-lung ventilation, in comparison to VCV, PCV could reduce *P* peak. Moreover, Kothari and Baskaran<sup>[18]</sup> found PCV mode resulted in lower peak airway pressures, better compliance, and lower arterial to end-tidal CO<sub>2</sub> gradient than the VCV.

Thereafter, Hoşten *et al.*<sup>[19]</sup> found both PaO<sub>2</sub>/FiO<sub>2</sub> and P-mean were higher, whereas P-peak was lower at open-heart surgery with PCV than VCV, and Messeha<sup>[20]</sup> also found the use of PCV after VCV induced improvement of lung mechanics in obese patients undergoing abdominoplasty. Moreover, Jaju *et al.*<sup>[21]</sup> found AP-mean and AP-peak were significantly higher with VCV than the PCV, whereas dynamic lung compliance and PaCO<sub>2</sub> were better with PCV than VCV. In support of the beneficial effect of PCV, Ghabach *et al.*<sup>[22]</sup> reported significantly higher PIP, but significantly lower compliance with VCV than PCV and PC-volume guarantee modes with the non-significant difference between PCV and PC-volume guarantee. Recently, Kock and Maurici<sup>[23]</sup> documented low lung compliance during VCV and low oxygenation index were death-related prognostic indicators.

The results of the current study showed a deleterious effect of prone positioning on estimated hemodynamic parameters as manifested by significantly reduced HR and BP measures in prone position (T2) compared to measures at the supine positions (T1 and T3). Moreover, prone positioning affected airway pressures, with significantly higher P-peak, irrespective of ventilation mode. In line with these findings, Channabasappa and Shankarnarayana<sup>[24]</sup> reported that during emergence from anesthesia HR and MAP were significantly higher in patients in supine than in patients in the prone position and Koh *et al.*<sup>[8]</sup> detected a significant increase of P-mean and P-peak airway pressures after placement of the patient in the prone position. In addition, Al-Dessoukey *et al.*<sup>[25]</sup> detected decreased MAP by 2 and 14 mmHg on turning patients from supine to oblique supine lithotomy position and prone position, respectively. Babakhani *et al.*<sup>[4]</sup> observed significant reductions in HR and MAP accompanied by significant decreases in cerebral oxygen saturation at 30 and 60 min of prone positioning, and Picard *et al.*<sup>[26]</sup> documented that MAP decreased below the predefined threshold in about 50% of patients during elective spine surgery in the prone position.

However, ventilation mode showed a minimal impact on HR and MAP of studied patients, irrespective of patients' position. The reported negligible effect of ventilation mode on HR and MAP goes in hand with multiple studies evaluating the same

topic, where Hoşten *et al.*<sup>[19]</sup> reported that the hemodynamic effects of PC and VC ventilation modes were found to be similar, but PCV may be preferable to VCV in patients undergoing open-heart surgery, and Messeha<sup>[20]</sup> evaluated the effect of PCV before or after VCV on hemodynamic variables and reported no significant difference between studied patients groups. In addition, Jaju *et al.*<sup>[21]</sup> found hemodynamic variables were comparable between patients maintained on PCV and VCV.

Although insertion of central venous catheter and arterial cannula before induction is not a routine in our center, we decided to secure it before induction in our study. It was done before by Stuedemann *et al.*<sup>[27]</sup> who found that central vascular access for a pediatric spine patient placed the day before surgery can decrease the time from induction to skin incision, to decrease the time under general anesthesia and potentially improve patient safety, and overall value.

The study limitations included the small sample size that could be attributed to a limited number of beds for spine surgery and the hospital is not a referral to receive patients who were referred from other hospitals. The study design as a single-center study done on patients having one specific type of surgery could be another limitation to establish the obtained results.

Finally, we concluded that prone positioning and VCV were associated with increased CVP and IO blood loss, whereas PCV could lessen these effects and significantly improve airway pressures. Wider scale study is mandatory to evaluate the outcome on larger scale populations and other inclusion criteria.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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