

Original Article

Variable lung protective mechanical ventilation decreases incidence of postoperative delirium and cognitive dysfunction during open abdominal surgery

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Abstract: Background: Postoperative cognitive dysfunction (POCD) is a subtle impairment of cognitive abilities and can manifest on different neuropsychological features in the early postoperative period. It has been proved that the use of mechanical ventilation (MV) increased the development of delirium and POCD. However, the impact of variable and conventional lung protective mechanical ventilation on the incidence of POCD still remains unknown, which was the aim of this study. Methods: 162 patients scheduled to undergo elective gastrointestinal tumor resection via laparotomy in Ningbo No. 2 hospital with expected duration >2 h from June, 2013 to June, 2015 were enrolled in this study. Patients included were divided into two groups according to the scheme of lung protective MV, variable ventilation group (VV group, n=79) and conventional ventilation group (CV group, n=83) by randomization performed by random block randomization. The plasma levels of inflammatory cytokines, characteristics of the surgical procedure, incidence of delirium and POCD were collected and compared. Results: Postoperative delirium was detected in 36 of 162 patients (22.2%) and 12 patients of these (16.5%) belonged to the VV group while 24 patients (28.9%) were in the CV group (P=0.036). POCD on the seventh postoperative day in CV group (26/83, 31.3%) was increased in comparison with the VV group (14/79, 17.7%) with significant statistical difference (P=0.045). The levels of inflammatory cytokines were all significantly higher in CV group than those in VV group on the 1st postoperative day (P<0.05). On 7th postoperative day, the levels of IL-6 and TNF- α in CV group remained much higher compared with VV group (P<0.05). Conclusions: Variable vs conventional lung protective MV decreased the incidence of postoperative delirium and POCD by reducing the systemic proinflammatory response.

Keywords: Postoperative cognitive dysfunction, mechanical ventilation, variable ventilation, conventional ventilation, open abdominal surgery

Introduction

Researchers have investigated postoperative cognitive changes in elderly patients for over a century, and proved that anesthesia is a possible cause of this problem [1]. It has been reported that the incidence of postoperative confusion and cognitive problems in elderly patients (≥ 65 years) is much higher than younger patients and the problems can be categorized as postoperative delirium, postoperative cognitive dysfunction (POCD), and dementia [2]. POCD is a subtle impairment of cognitive abilities (including memory, concentration, and information processing) and can manifest on different neuropsychological features in the early postoperative period, which is distinct

from delirium and dementia [3]. As POCD can't be defined as a formal psychiatric diagnosis, we always consider it to be a mild neurocognitive disorder. The mechanisms of POCD still remain poorly understood and only the neuropsychological battery tests can detect the severity of cognitive decline before and after the surgery [4]. Anesthesia and surgical have been proved to cause cognitive decline especially in elderly patients with unknown molecular mechanisms underlying cognitive disorders [5]. Coping strategies that may avoid POCD over time as a result of preoperative and perioperative factors should be very important.

Mechanical ventilation (MV) is very often used in patients undergoing gastrointestinal surger-

Mechanical ventilation; postoperative cognitive dysfunction

Table 1. Inclusion and exclusion criteria for patients in this study

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Patients scheduled to undergo elective gastrointestinal tumor resection via laparotomy with expected duration >2 h • ASA class 2 and 3 • Ages ≥60 years • Informed consent to participate in the study signed by patients 	<ul style="list-style-type: none"> • With cognitive impairment characterized by MMSE <24 • History of dementia • Chronic lung disease • Allergy against one of the drugs administered during the study • BMI >24.5 kg/m² • Any disease of the central nervous system • History of surgery within 6 weeks • Mechanical ventilation within 1 month • Low patient compliance • Inability to read, or serious hearing or vision loss • Poor comprehension of the Chinese language • Recent cerebrovascular accident (<6 months)

ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; BMI, Body Mass Index.

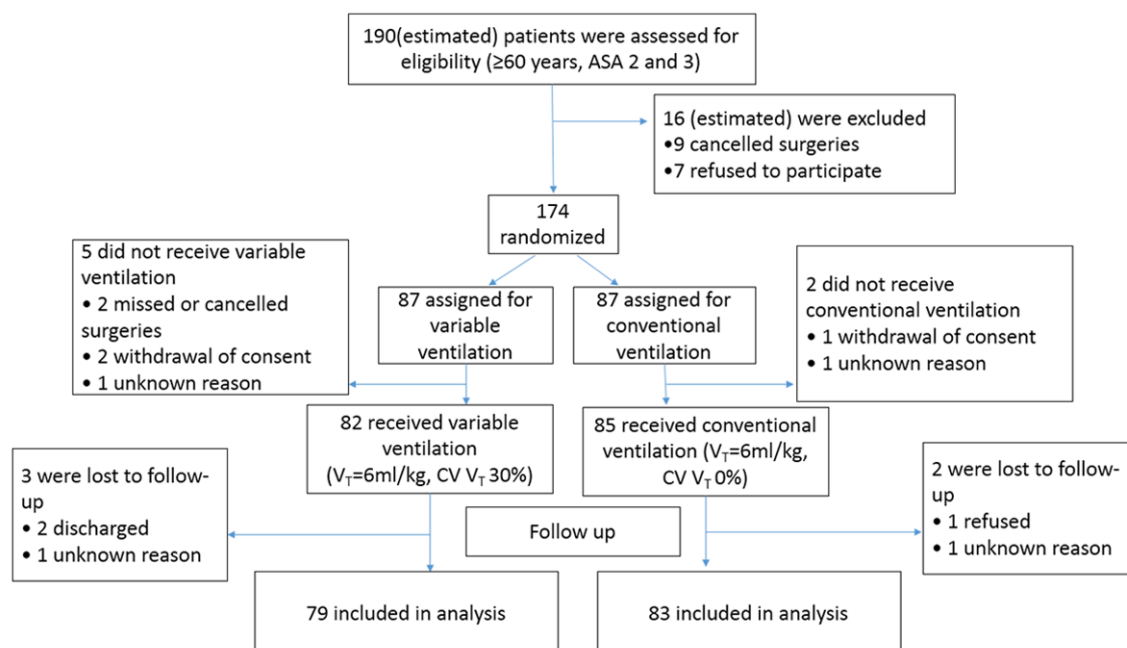


Figure 1. CONSORT diagram of patient enrollment, allocation, follow up and analysis V_T , tidal volume; CV V_T , coefficient of variation of tidal volume.

ies under general anesthesia [6]. It has been proved that the use of MV increased the development of delirium [7]. The incidence of delirium is reported to be up to 74%-83% in patients with intubation and positive-pressure ventilation and 20%-48% in non-intubated patients [8]. Pulmonary atelectasis occurs commonly under general anesthesia especially during open abdominal surgery, mainly due to the application of muscle paralysis [9]. Although the use of positive end-expiratory airway pressure (PEEP) combined with lung recruitment

maneuvers is effective to improve the lung function and reduce atelectasis, increasing risk of barotrauma and deterioration of hemodynamics is also concomitant [10]. Both experimental and clinical studies have pointed out that variable ventilation can improve the lung function and it doesn't affect pulmonary inflammatory response status and cause structural damage of the lung [11, 12]. However, the impact of variable and conventional lung protective mechanical ventilation on the incidence of POCD still remains unknown. Therefore, the

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Table 2. Baseline characteristics of the patients included

	VV group (n=79)	CV group (n=83)	P- value
Age (year)	67.8±6.8	67.1±7.7	0.54
Gender			
Male	33 (41.8%)	30 (36.1%)	
Female	46 (58.2%)	53 (63.9)	0.46
ASA physical status			
II	42 (53.2%)	50 (60.2%)	
III	37 (46.8%)	33 (39.8%)	0.36
BMI (kg/m ²)	22.3±2.4	22.1±3.0	0.64
MMSE (score)	28.8±1.7	28.9±1.8	0.72

ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; BMI, Body Mass Index; VV, variable ventilation; CV, conventional ventilation. *P*-values were calculated by Chi-square test or Mann-Whitney U-test.

aim of our present study was to compare the influence of these two lung protective mechanical ventilation schemes on the POCD in elderly patients one week after open abdominal surgery.

Material and methods

Patients

This study was approved by the Medical Institutional Ethics Committee of Zhejiang province. Patients scheduled to undergo elective gastrointestinal tumor resection via laparotomy in Ningbo NO.2 hospital with expected duration >2 h from June, 2013 to June, 2015 were enrolled in this study. The detailed inclusion and exclusion criteria was described in **Table 1** below. Patients included were divided into two groups according to the scheme of lung protective MV, variable ventilation group (VV group) and conventional ventilation group (CV group) by randomization performed by random block randomization.

Methods

After adequate preoperative anesthesia assessment, patients undergo the elective gastrointestinal tumor resection via laparotomy as planned with CV or VV respectively. The same ventilator (Siemens Elema 900C Servo, Solna, Sweden) was used in two groups with the same volume-controlled mode. The ventilator parameter settings [13] were described in details as follows: PEEP of 5 cmH₂O, fraction of inspired

oxygen (F_IO₂) of 0.35, respiratory rate (RR) adjusted to achieve normocapnia (4.6 to 6.0 kPa), tidal volumes (V_T) of 8 ml/kg and ratio of inspiratory to expiratory time (I:E) of 1:1. V_T was kept constant for patients in CV group during the mechanical ventilation, while it varied randomly on a breath-by-breath basis for patients in VV group. For VV group, the mean V_T was kept at the level of 8 ml/kg equally with CV group, the varied values followed a Gaussian distribution with coefficient of variation at 30% as previously described [11]. Blood samples were collected before, 12 hours and 7 days after the mechanical ventilation for the measurement of inflammatory cytokines including interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor alpha (TNF-α).

Cytokines measurements

The plasma levels of inflammatory cytokines including IL-6, IL-8 and TNF-α (R&D Systems, Minneapolis, MN, USA) were measured by commercially available enzyme-linked immunosorbent assays (ELISA) and performed according to the manufacturers' guidelines. The measurement of samples was all duplicated by the same technician who was blinded to this study design.

Assessment of delirium

In our present study, the medical personnel performed the delirium screening under the instruction of a psychiatrist and delirium experts. The observers were all blinded to the study design. In order to avoid bias research assistants rotated between both groups. Twice a day (morning and night) was required to assess delirium from the first to the seventh postoperative day to avoid the research bias. The diagnosis of postoperative delirium was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV).

Assessment of postoperative cognitive dysfunction

The Cambridge Neuropsychological Test Automated Battery (CANTAB, Cantab Cognition, Cambridge, UK), a touch screen computer system was used for evaluate the neuropsychological testing [14]. A pattern recognition memory test, spatial recognition memory test, a Motor Screening Test, a choice reaction time test, the visual verbal learning test and the

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Table 3. Characteristics of the surgical procedure and postoperative cognition

	VV group (n=79)	CV group (n=83)	P-value
Duration of surgery (min)	167.2±65.3	159.6±80.2	0.51
Duration of anesthesia (min)	192.4±66.4	189.3±59.9	0.76
Estimated blood loss (ml)	298.3±107.5	314.3±134.4	0.41
Duration of hospital stay (days)	10.3±3.4	10.7±3.9	0.49
Anaesthetic			
Propofol (TIVA)	30 (38.0%)	34 (41.0%)	
Volatile anaesthesia	49 (62.0%)	49 (59.0%)	0.70
Drugs			
Fentanyl	60 (75.9%)	55 (66.3%)	
Remifentanyl	19 (24.1%)	28 (33.7%)	0.17
Postoperative delirium (DSM-IV)	12 (16.5%)	24 (28.9%)	0.036*
POCD 7th postoperative day	14 (17.7%)	26 (31.3%)	0.045*

TIVA: total intravenous anesthesia; VV, variable ventilation; CV, conventional ventilation; POCD, Postoperative Cognitive Dysfunction; DSM, Diagnostic and Statistical Manual of Mental Disorders. P-values were calculated by Chi-square test or Mann-

Stroop Color Word interference test in three parallel versions in random order were included in the CANTAB test. Patients were required to finish the CANTAB test the evening before surgery, 7 days and 3 months after surgery. In order to eliminate the interference factors, all the test was carried out at the same time of day and in a quiet room with no others except the investigator and patient. The calculation of reliable change index (RCI) according to the recommendations of Rasmussen and colleagues was used for the definition of POCD. Either when the RCI score was <-1.96 at least on 2 tests or the combined Z score was <-1.96, POCD was defined [15].

Statistical analysis

SPSS 19.0 (SPSS, Inc.) statistical software was used in this study for statistical analysis. Data are presented as number (n) and percentage (%), or mean ± standard error (SD) as appropriate. Chi-square test and Mann-Whitney U-test are used for the statistical analysis. All statistical tests were bilateral probability and P<0.05 was accepted as statistically significant.

Results

Baselines

An estimated 190 elderly patients who undergo the elective gastrointestinal tumor resection

via laparotomy were screened for eligibility. As shown in the consort (**Figure 1**), 162 of these including 79 in VV group and 83 in CV group were finally enrolled in this study over the whole course of a 2-year period, from June, 2013 to June, 2015. The characteristics of patients in two groups were statistically similar (**Table 2**). The demographic or clinical data including age, gender, ASA physical status, BMI and MMSE score preoperative in both groups did not differ significantly (P>0.05).

Surgical procedures and postoperative cognition

As shown in **Table 3**, no difference was found between VV group and CV group with regard to the characteristics of the surgical procedure including duration of surgery, duration of anesthesia, duration of hospital stay, estimated blood loss, applications of anesthesia and drugs (P>0.05). Postoperative delirium was detected in 36 of 162 patients (22.2%) and 12 patients of these (16.5%) belonged to the VV group while 24 patients (28.9%) were in the CV group (P=0.036). Postoperative cognitive dysfunction on the seventh postoperative day in CV group (26/83, 31.3%) was increased in comparison with the VV group (14/79, 17.7%) with significant statistical difference (P=0.045).

Inflammatory cytokines

The values of pre- and postoperative inflammatory cytokines including IL-6, IL-8 and TNF-α were present in **Figure 2** for the comparison between the VV and CV groups. The levels of these inflammatory cytokines were all significantly higher in CV group than those in VV group on the 1st postoperative day (P<0.05). On 7th postoperative day, the levels of cytokines decreased significantly both in two groups. However, the levels of IL-6 and TNF-α in CV group remained much higher compared with VV group, which was consistent with a higher degree of inflammatory stress response in the CV group.

Mechanical ventilation; postoperative cognitive dysfunction

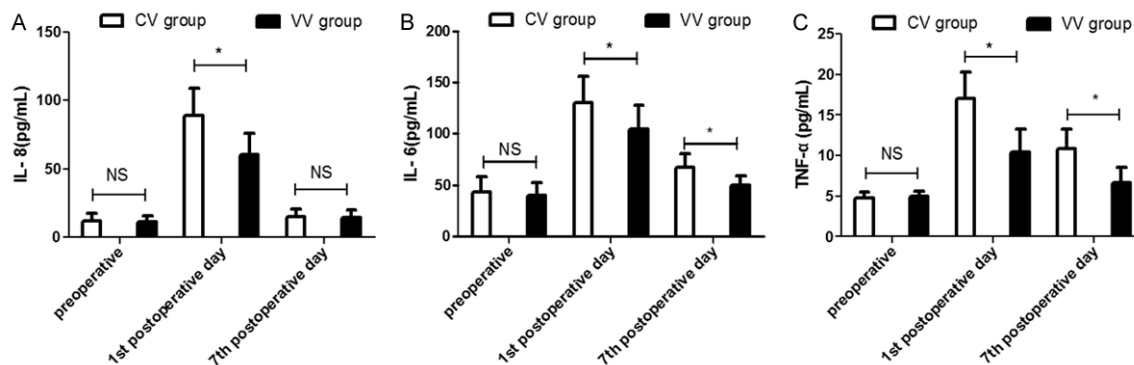


Figure 2. Time course of plasma levels of inflammatory cytokines in VV and CV groups. VV, variable ventilation; CV, conventional ventilation; NS, no significance. * $P < 0.05$.

Discussion

It has been noticed since the 1950s that elderly patients who received anesthesia and surgery always suffer from changes of postoperative cognitive function [16]. Postoperative delirium is also a common complication especially in elderly patients and it is always associated with poor outcome [14]. In summary, POCD could be defined as the decrease of neuropsychiatric function, especially the alteration of memory and executive function [17]. Despite some common subjective tests for delirium and POCD, CANTAB is an alternative and more objective way to define the diagnosis of POCD by using a battery of tests to evaluate the immediate, short-term memory and executive function reported by previous studies [18, 19]. Some clinical and experimental studies have suggested that POCD can be caused by long-lasting neurotoxicity induced by general anesthetics [17, 20]. However, there was no direct evidence links between POCD and the operative time. Great intraoperative blood loss, advancing age, dementia, multiple comorbidities, vision and hearing impairment preoperative have been proved to be important risk factors for the occurrence of POCD [21-23]. In our present study, the age, cognitive function preoperative, the duration of MV, the operative time, estimated blood loss of patients in two groups were all with no statistical difference, which got rid of these possible factors affecting the results. A statistically lower incidence of postoperative delirium and POCD in VV group than that in CV group was observed in our study.

It was suggested that MV could raise surgery-induced cognitive impairment with poorly

understood pathogenesis [24]. The early neurological response induced by MV and the central nervous system effects related to systemic inflammation might be one of the possible mechanisms [25]. The study of VV has attracted extensive attentions during the past few years and increasing evidence have revealed the beneficial effects of VV modes for mimicking physiological variability of the respiratory system [26, 27]. VV can be used to assist spontaneous breathing instead of just control mechanical ventilation [28]. The possible mechanisms involved in the beneficial effects of VV were associated with enhanced synthesis of surfactant proteins [29], the recruitment of alveolar units closed previously [30], the improvement of ventilation/perfusion matching [31]. However, few studies have addressed the effects of VV and CV on the changes of postoperative cognitive function in elderly patients during open abdominal surgery. In recent years, a growing amount of evidence suggested that increased inflammatory response and excessive release of proinflammatory cytokines such as IL-6 and TNF- α , were associated with postoperative cognitive impairment [32]. The systemic inflammation induced by MV and apoptotic cascades response after the surgery intervention could be the most common triggers of POCD [25]. Different MV strategies could alter the level of inflammatory response at the lung, then neurotransmission in the brain, and at last affect the central nervous system [33]. So controlling the release of systemic cytokine induced by MV and surgery intervention might be beneficial for the improvement of POCD. We observed lower levels of plasma IL-8, IL-6 and TNF- α of patients in VV group at 1st postoperative day in comparison

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with patients in CV group. At the same time, patients in VV group showed significantly reduced levels of IL-6 and TNF- α inflammatory cytokines at 7th postoperative day. The reason why VV strategy was more effective than CV in controlling systemic inflammatory response may be related to the following explanation: the modulated respiratory frequency by VV strategy could improve the respiratory function and reduce histological damage to the lung compared with CV strategy [11].

Taking the correlation between inflammatory response and incidence of POCD, we concluded that variable vs conventional lung protective MV decreased the incidence of postoperative delirium and POCD by reducing the systemic proinflammatory response.

Study limitations

The sample size of this study was too small. The inclusion criteria, POCD definition, surgery interference and the statistical methods used were with debate among researchers. A long follow up and monitoring the incidence of POCD for 3, 6 months or even 1 year from hospital discharge would improve the precision and have better effects.

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Disclosure of conflict of interest

None.

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