Effect of propofol on twitch diaphragmatic pressure evoked by cervical magnetic stimulation in patients

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Background. Several studies have demonstrated the inhibitory effect of propofol on diaphragmatic contractility in laboratory animals, but there have been few studies in humans. We have investigated the effect of a single bolus injection of propofol on twitch diaphragmatic pressure (TwPdi) evoked by cervical supramaximal magnetic stimulation, and its impact on diaphragmatic contractility.

Methods. In 16 patients scheduled for elective operation, TwPdi was evoked bilaterally at the cervical phrenic nerves with supramaximal magnetic stimulations using a 140 mm diameter magnetic coil. Changes of TwPdi were monitored dynamically before and during general anaesthesia induced by single bolus of propofol 2 mg kg⁻¹. During the study, all patients breathed 100% oxygen by a face mask, maintaining SpO₂ ≥ 99% and PEco₂ 4.6–5.2 kPa.

Results. TwPdi declined after administration of propofol with gradual recovery. Compared with baseline [20.6 (6.0) cm H₂O], TwPdi decreased by 23.3% (P<0.001) to [15.8 (6.4) cm H₂O]. When the patients regained awareness, TwPdi returned to [19.1 (6.1) cm H₂O], close to baseline (P=0.063). The time from starting the propofol infusion to the lowest TwPdi was [240 (86) s]. Total time course of stimulation lasted [363 (89) s].

Conclusions. A single bolus propofol depressed TwPdi evoked by cervical magnetic stimulation, demonstrating inhibitory effects of propofol on diaphragmatic contractility in patients during general anaesthesia.

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The diaphragm is the most important respiratory muscle in humans, accounting for 60–80% of function in all inspiratory muscles.¹⁻⁵ Twitch diaphragmatic pressure (TwPdi) is an objective measure for assessing diaphragmatic contractility.⁶⁻⁸ Supramaximal electrical or magnetic stimulation of the phrenic nerves bilaterally is the most acceptable method for measuring TwPdi.⁹⁻¹² As a technique for stimulating the phrenic nerves, magnetic stimulation is reported to be safe, painless, and relatively simple.

Several animal studies have demonstrated the inhibitory effect of propofol on diaphragmatic contractility.¹³⁻¹⁷ However, there have been few studies on its effect in humans. We have investigated the effect of propofol on TwPdi evoked by cervical supramaximal magnetic stimulation in patients to assess the influence on diaphragmatic contractility of a single bolus of propofol.

Methods

This protocol was approved by Ethical Committee of the First Affiliated Hospital of Guangzhou Medical College. All subjects (patients) gave written informed consent. Sixteen patients (eight males) undergoing elective surgical procedures under general anaesthesia were enrolled. All cases were ASA grades I and II, aged 18–63, with normal cardiac, pulmonary, hepatic, and renal function, absent of neurological or muscular diseases. None was premedicated.
Oesophageal and gastric balloon catheters were used to measure TwPdi. These were two 2.5 mm OD and 2.0 mm ID polythene tubes with a thin-walled latex balloon sealing the distal hole and four side holes. These tubes were connected to a pressure collecting and analysing system (Mircocal Origin Co., USA). Twitch oesophageal pressure (TwPoes) and twitch gastric pressure (TwPgas) were measured by two separate pressure transducers (Vigg-Spectramed Pte Ltd, USA). TwPdi was calculated as: TwPdi = TwPgas – TwPoes.6–8 Cervical magnetic stimulation was with a Magstim 200 magnetic stimulator (Magstim Co. Ltd, UK) with a 14 cm diameter coil, the maximal output was 2.0 T.

In the operating theatre, with the patients in a sitting position, nasal and pharyngeal anaesthesia was produced with 2% lidocaine, and oesophageal and gastric balloon catheters were inserted nasally for 60 cm approximately. After injection of 6 ml of air into each, the air was removed leaving 1.5 ml in the gastric balloon and 0.5 ml in the oesophageal balloon. The catheters were positioned using a pair of opposite pressure waveforms displayed on the monitor (positive pressure for the gastric balloon and negative pressure for the oesophageal balloon) when the patients sniffed.6 14 15 18 To ensure appropriate positioning of the oesophageal balloon, the following approach was used. With the oesophageal balloon in the stomach, a positive pressure waveform would appear when the patient sniffed. The catheter was pulled out gradually until a negative pressure indicated that the oesophageal balloon had entered the cardia. The standard position of oesophageal balloon was achieved then by withdrawing the catheter by 10 cm. The position could be adjusted if the heart beat interfered with the baseline oesophageal pressure.18

Then, in the supine position, 500 ml sodium lactated Ringer’s solution was instilled into the left great saphenous vein at a rate of 7–10 ml kg⁻¹ h⁻¹ before testing. Left upper arm mean arterial pressure (MAP), ECG, heart rate (HR), and peripheral oxygen saturation (SpO₂) were monitored continuously. The patients inhaled 100% oxygen through a face mask during the study and face-mask pressure ventilation was applied after administration of propofol. SpO₂ was maintained ≥99% and end-tidal partial pressure of carbon dioxide (PetCO₂) was stabilized at 4.6–5.2 kPa throughout the investigation. Temperature in the operating theatre was maintained at 26 °C.

The coil was positioned with the patient’s head forward at 30° to expose their cervical vertebrae and the coil was centred at the sixth cervical vertebra (C₆) tightly against the skin. This posture was maintained throughout the investigation with a soft pillow supporting the head. The initial magnetic stimulus was delivered at 10% of the maximum output. The coil was adjusted on the midline to find the point of maximal amplitude of TwPdi. Each stimulus was single-pulsed with duration of 50 μs. The stimulation site was marked on the skin and the coil fixed.

The patients rested for 20 min to avoid twitch potentiation before baseline twitches were elicited. When the signal became stable, the intensity of the magnetic stimulus was increased gradually, from 0.2 T up to the maximum output of 2.0 T. Intermittent supramaximal magnetic stimuli6 19 were performed when the patients were at functional residual capacity. Six consecutive TwPdis at the maximal stimulus intensity were recorded. The average value of these six pressures was determined as baseline value of TwPdis. The interval between stimulations was 20 s. Pressure tracings of TwPdi were gathered, amplified, recorded, and displayed on the monitor graphically and digitally. The pressure system was calibrated before and after each test.6 7

A single bolus of propofol (AstraZeneca Ltd, Italy) 2 mg kg⁻¹ was injected over 30 s into the left great saphenous vein. Transcervical supramaximal magnetic stimuli were applied every 20 s from the start of the injection till the end of the study. The airway was occluded through a valve connected to the face mask during stimulation. After the patients regained consciousness, opened their eyes or moved their limbs, the last stimulus was performed and the test was completed.

Statistical analysis was performed with SPSS 13.0 (SPSS Software Co., USA). Quantitative data were expressed as mean (SD). Statistic analysis was performed with a paired t-test and repeated measures analysis of variance. Statistical significance was assumed for P<0.05.

Results

All 16 patients [eight male, mean age 37.6 (range 18–63) yr, mean weight 61.1 (SD 8.1) kg, mean height 165.2 (6.6) cm] completed the study. Each patient acted as his or her own control for readings performed before and after administration of propofol. The mean (SD) baseline TwPdi was 20.6 (6.0) cm H₂O. This decreased to 15.8 (6.4) cm H₂O after propofol infusion. The maximal descending amplitude was 23.3% (P=0.001). The average time from propofol injection to TwPdi dropping to the minimum was 240 (86) s. When the patients regained awareness, the final recovery value of TwPdi [19.1 (6.1) cm H₂O] returned to baseline level (P=0.063) and the total procedure lasted 363 (89) s (Table 1).

Discussion

We found significant changes in TwPdi evoked by cervical supramaximal magnetic stimuli in patients after a single bolus infusion of propofol 2 mg kg⁻¹. After an initial decline after infusion of propofol, TwPdi returned to baseline by recovery of consciousness. These results show that TwPdi is transiently inhibited by propofol at standard induction dose. Our result is similar to that of Shaw and colleagues,19 who stimulated the phrenic nerve using...
supramaximal magnetic stimuli before and immediately after induction of propofol in 11 subjects. The change in airway pressure at the mouth (TwPmo) produced by the resulting diaphragmatic contraction was monitored instead of TwPdi, with a significant decline of TwPmo by 14.2%. In the same study, TwPdi was found to drop by 18.1% and 20.0% in two subjects studied with oesophageal and gastric balloon catheters. The descending amplitude of TwPdi in our study is consistent with that of those two subjects. It took 4 min for TwPdi to decrease to the lowest value since initiation of propofol injection. The time-point when TwPdi decreased to the lowest value signified the time when the inhibition by propofol reached its peak. Our study also showed that the recovery from inhibition by propofol took about 6 min.

Several studies in laboratory animals have demonstrated that propofol produces a decrease in TwPdi, by an inhibitory effect on diaphragmatic contractility. However, there have been very few studies on its effect in humans. Our study reflects an inhibitory effect of propofol on diaphragmatic contractility or contraction strength in humans, similar to that reported in animals. The inhibitory effect of propofol on TwPdi suggests that propofol may have a direct effect on diaphragmatic relaxation. Propofol has a transient central depressant effect on respiration reducing the ventilatory response to hypercarbia and hypoxaemia and depressing both the rate and depth of breathing. An induction dose of propofol results in a 20–30% incidence of apnoea. However, in our study, TwPdi elicited by cervical supramaximal magnetic stimulus of bilateral phrenic nerves eliminates the central depressant component of the central nervous system after propofol, indicating the effect on diaphragmatic contraction from full excitation of all fibres of the phrenic nerves. It may show a degree of neuromuscular block between the phrenic nerves and diaphragm, as these are the only two structures of motor tract involved in our study. There are no studies of the effect of propofol on the threshold of supramaximal magnetic stimulation in human peripheral nerve or its effects on the pulse delivery in peripheral nerves. Therefore, it cannot be excluded that inhibition of diaphragmatic strength by propofol is due to the direct depression of neuromuscular transmission between phrenic nerve and diaphragmatic fibres.

We believed that the depression of diaphragmatic contractility might be associated directly with a failure of diaphragmatic neuromuscular transmission. It has been reported that propofol acts presynaptically to inhibit neuromuscular transmission and at the muscle membrane to inhibit muscular contraction. In a rat isolated phrenic nerve-hemidiaphragm preparation, propofol contributed to train-of-four fade and potentiated both pre- and postsynaptic effects of the neuromuscular block. Therefore, the transient inhibitory effect on TwPdi by a bolus injection of propofol in our experiment might indicate that propofol may produce a degree of neuromuscular block in clinical practice.

A further factor to be considered is the influence of lung volume changes during propofol induction on twitch strength. We did not take into account the effect of propofol on lung volume and its impact on twitch strength. However, a similar study demonstrated that the apparent fall in diaphragm strength is not a function of the change in lung volume on induction with propofol. In some other studies, a fall in diaphragm strength leads to a fall in lung volume, and a fall in lung volume tends to an increase in twitch strength. Therefore, we do not think the depressed twitch strength in our study is caused by a fall in lung volume.

Potentiation describes the process that muscles which have contracted recently have an augmented contraction in response to a further stimulation. This phenomenon lasts for 20 min after a period of activity. Therefore, all the TwPdis used in our study were with potentiations, and

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Table 1 | Changes in TwPdis after propofol administration. Compared with baseline, *P<0.05
similar ‘twitch on twitch’ potentiations between each neighbouring contraction were reached via supramaximal stimulations at a fixed interval. Subjects in our study were rested for 20 min before baseline twitches, and there was no coughing or gagging during the investigation. Therefore, the effect of potentiation on the TwPdis was minimized and stable, and the data were valid and comparable. The mean TwPdis at the beginning and end of our study were higher than those in reported previously19 and interference from potentiation could theoretically explain such a difference.

In summary, our study has demonstrated that a single bolus injection of propofol depressed the TwPdi elicited by supramaximal magnetic stimulus, generating a transient inhibitory effect on diaphragmatic contractility. Although the underlying mechanism is not clear, it may be of clinical significance.

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References