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Effects of an opioid on respiratory movements and expiratory activity in humans during isoflurane anaesthesia☆

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ABSTRACT

Opioids increase abdominal muscle activity during anaesthesia. We proposed that opioid activity during anaesthesia would change chest wall size and movement, and contribute to ventilation. Using an optical system to measure chest wall volume, we studied 10 patients during isoflurane anaesthesia, first under the influence of an opioid and then after reversal with naloxone. Measurements were made during quiet breathing and with carbon dioxide stimulation. Airway occlusion pressure was measured to assess inspiratory and expiratory muscle activity. Chest wall volume decreased with the onset of spontaneous breathing, and decreased further when breathing was stimulated by carbon dioxide. Reversal of opioid activity increased chest wall volume. Breathing movements were predominantly abdominal. Opioid action affected the timing and amplitude of breathing but the pattern of abdominal movement was not affected. Since opioids augment abdominal muscle action during expiration, the unchanged pattern of movement can be attributed to both diaphragm and abdominal activity displacing the abdominal wall reciprocally, in the inspiratory and expiratory phases of the respiratory cycle, respectively.

1. Introduction

1.1. Opioid effects during clinical anaesthesia

Opioid agents are frequently administered in the course of general anaesthesia, primarily to reduce autonomic and motor responses to stimulation. Opioids have profound effects on breathing. Opioids prolong expiration and thus reduce breathing frequency (Drummond, 1983; Lalley, 2003), reduce responses to stimuli such as carbon dioxide (Rigg et al., 1981), and activate expiratory muscles (Freund et al., 1973; Howard and Sears, 1991). The primary cause of some of these effects is unclear: for example, if an opioid reduces respiratory rate, the cause of increased tidal volume and altered muscle activation may be the result of hypoventilation and the resulting hypercapnia (Ferguson and Drummond, 2006).

1.2. Muscle action with opioid administration

Abdominal muscle activation after opioid administration may reduce lung volume (Chawla and Drummond, 2008; Wyche et al., 1973) and impair gas exchange (Drummond and Lafferty, 2010) as well as augment respiratory depression. Although the effects of general anaesthetics such as halothane on muscle activity and chest wall movements have been studied (Warner et al., 1995; Warner and Warner, 1995) the effects of opioids on chest wall volume and respiratory movements have not been formally assessed. In circumstances such as exercise, abdominal contraction can augment ventilation. The activation of abdominal muscles by opioids during anaesthesia (Drummond et al., 2011) may have similar effects.

1.3. Study aims

We set out to compare breathing movements in the presence and absence of opioid activity, using an optical method to characterise chest wall size and movement. We studied anaesthetised subjects, breathing spontaneously. In addition we used occlusion of inspiration to assess possible chest wall distortion, and occlusion of expiration to quantify the force generated by the expiratory muscles. To assess these features under different conditions, we

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antagonised the activity of the opioid with naloxone, and stimulated respiration with carbon dioxide.

2. Methods

2.1. Subjects

The study was approved by the appropriate French ethical and regulatory authorities (Comité Consultatif de Protection des Personnes se Prêtant à la Recherche Biomédicale de l'Hopital Henri Mondor, dossier 95-038) We recruited patients about to undergo superficial or peripheral surgical procedures (for details, see Section 3) We did not recruit patients who were obese or gave a history or had clinical evidence on routine testing of either cardiac or respiratory disease. The patients provided written consent after being given full information about the study.

2.2. Anaesthesia

Anaesthesia was induced with propofol and maintained with nitrous oxide, isoflurane, and intravenous fentanyl, which were clinically appropriate agents at the time of the study. The trachea was intubated. Vecuronium or atracurium were used for neuromuscular block, carefully monitored by train of four stimulation of the ulnar nerve. After the surgical procedure was complete, we placed the patient on a measurement board with the body, from shoulders to hips, supported by a plastic bead mattress that was then made rigid by removing the air within it (Vac Pac, Howmedica, Newbury, UK). We made sure that the lumbar spine and flanks were fully supported. The head rested on a pillow and the lower body on a folded cotton sheet, adjusted to support the legs and protect the heels. The arms were covered in non reflective material.

2.3. Measurements

Respiratory gas flow was measured with a pneumotachograph (Mercury FC10, Mercury Instruments, Glasgow, UK) and differential transducer (Furness FC044, Bexhill-on-Sea, UK) calibrated with flows of 70% nitrous oxide in oxygen. The flow signal was used only to measure the timing of respiration. Volume changes were measured by the optical system described in Section 2.4. Pressure at the airway opening was measured with a Validyne DP 45 transducer (Northridge, CA, USA). Patients breathed from a custom made breathing system designed to keep airway pressure close to ambient (Drummond et al., 2011). Large bore taps placed in the inspiratory and expiratory tubing, close to the valve, were used to intermittently occlude single episodes of inspiration or expiration. Gas was sampled from the centre portion of the valve for continuous analysis of carbon dioxide (Normocap 200) and isoflurane concentration (Normac, both Datex Instrumentation, Finland). Gas sampling was discontinued during occlusion manoeuvres. The inspired and expired gas tubing was connected via wide bore sidearms so that when the fresh gas supply to the inspiratory tubing was reduced, partial rebreathing of exhaled gases could occur. Thus excessive fresh gas flows were not required when ventilation was stimulated by adding carbon dioxide to the inspired gas, to facilitate induction of a stable state of hypercapnia.

2.4. Optical measurements

Chest wall movement was measured using an optical measurement system (Drummond and Duffy, 2001). Briefly, a narrow beam of red laser light is spread by a cylindrical lens into wide beam that forms a narrow line when it falls on the measured surface (Fig. 1). With a precisely controlled mirror, the beam is rapidly moved to a series of known pre-set positions on the surface. The shape of these lines of light depends upon the contour of the body surface, and is detected by a video camera placed in an accurately known position above the subject. We used subdued green ambient lighting and a filter specific for HeNe laser light on the video camera, so that the red laser light showed up brightly in the video picture. By use of the scanning process of the video picture system, the light beam position in the video image can be measured extremely rapidly. The exact vertical contour of the line of illumination, measured as the distance above the reference surface, is calculated. These vertical contours are then assembled to form sections of the object. The horizontal position of the light strips is known from the degree of movement of the mirror galvanometer. From the contour of the vertical plane and the distance between each contour, changes in chest wall volume are computed and the changes in volume during respiration are calculated. These measures of respired volume are unaffected by drift, which is a weakness of systems that use flow integration. Before each patient study the system calibration was checked by scanning a test object of known volume, placed on the reference surface.

2.5. Measurement procedure

On each subject, we set line positions between which we expected to detect movement, to define the limits of the chest wall (Fig. 1). The top line was placed at the manubrium, at the junction of the first rib, and the bottom line at a level midway between a line joining the anterior superior iliac spines and the cranial margin of the pubic bone. The interface between the rib cage and abdomen was defined by a middle line placed 2 cm below the caudal tip of the xiphisternum (in Fig. 1, this middle line is also labelled Ab1, RC5). For scans of the complete chest wall, from manubrium to pubis, lines were placed equidistant between top and middle lines, and between middle and bottom lines, and these 5 lines were used to scan the movements of the whole chest wall. For scans of the rib cage, three lines were placed equidistant between the top and middle lines, so that the section of chest wall between the top and middle lines could be scanned using 5 lines. For a scan of the abdomen, three lines were placed equidistant between middle and bottom lines so that the abdominal part of the chest wall was scanned with 5 lines. The middle line was included as the most caudal line in scans of the rib cage and as the most cranial line in scans of the abdomen. The central lines of the ribcage and abdomen scans were the same lines as those used in the scan of the complete chest wall (Fig. 1). Those lines that were common for scans of the whole chest wall, rib cage, and abdomen, were used to assess the repeatability of the measurements during mechanical ventilation. During a measurement sequence, a profile was measured at each individual line position every 20 ms, so that all five lines were measured in 0.1 s. During subsequent data analysis, the areas in the intervening periods for each line were estimated by linear interpolation between the successive values, to allow calculation of the chest volume each 20 ms, and provide synchronous data. Each successive volume was thus derived from 1 contemporary and 4 time-adjusted interpolated values.

2.6. Data management

For quantitative measures, volumes of the scanned surface were calculated using data from separate scans of the rib cage, abdomen, and the entire chest wall, using the distance between adjacent line positions and the area under each measurement line. For qualitative purposes, such as plotting the pattern of movement of the chest wall, scans of rib cage and abdomen were

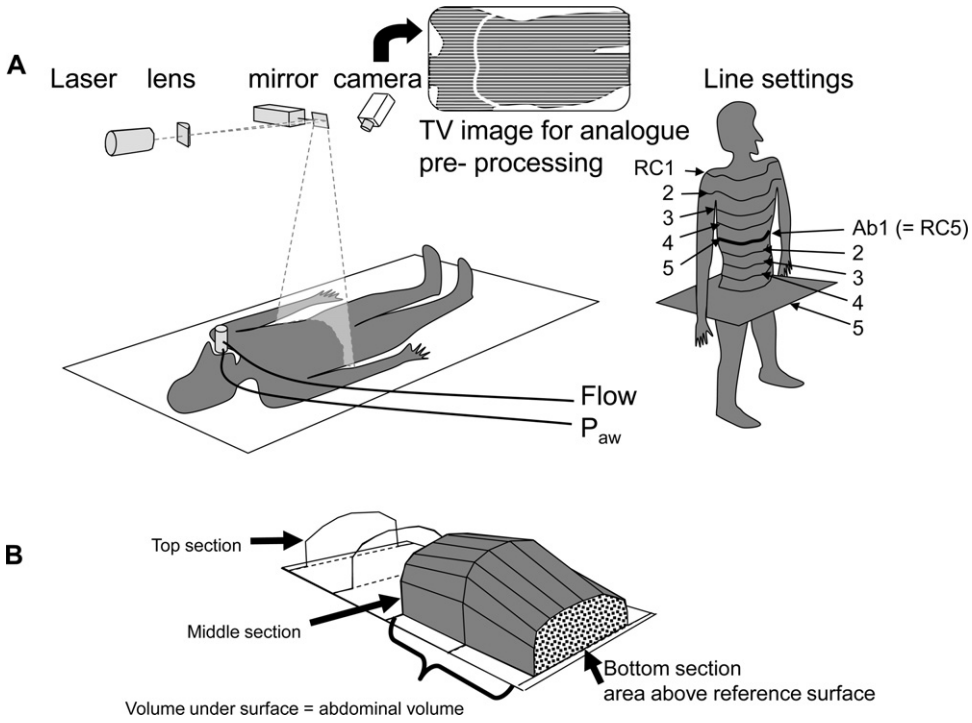

Fig. 1. Layout of the measurement system. The patient lies on an optical reference surface below an accurately positioned camera and laser projection system. The light beam position is controlled by a servo feedback mirror and moved rapidly to preset positions on the chest wall. At each position, a video frame is acquired to measure the shape of the line formed in the camera image. The dimensions of this image allow calculation of the cross-sectional area of the chest wall. Gas flow and airway pressure are measured at the endotracheal tube opening. Five lines are set to cover the rib cage and the abdomen as shown. The middle line (also labelled as Ab1, RC5) divides the ribcage from the abdomen and is common to both sets of lines. This middle line was placed 2 cm caudal to the xiphisternum.

combined by averaging the data provided by the middle line. These combinations were not used for quantitative purposes, except for deriving the passive chest wall properties. In that case, we were able to verify that the common lines yielded very similar data.

2.7. Measurement sequence

Initial measurements were made during mechanical ventilation, to measure the passive elastic properties of the relaxed respiratory system. These values were required to allow calculation of the passive component of expiratory occlusion pressure (see Section 2.8). We used a 3 l calibrated syringe (Puritan Bennett, Wilmington, MA, USA), filled with the inspired gas mixture, to deliver slow inflations of 250 and 500 ml. Inflation was timed to take 2 s, followed by a pause when there was no flow. Scans of the rib cage, abdomen, and whole thorax were taken during inflation with the two different volumes to assess the linearity of the passive elastic characteristics of the respiratory system, over the relevant range of volume changes observed. Muscle relaxant activity was then fully antagonised with neostigmine and atropine (adductor pollicis train of four was greater than 90%), and the patients allowed to breathe spontaneously from a breathing system through a low resistance one-way valve. An infusion of fentanyl was started and adjusted to maintain a stable respiratory rate close to the value present when spontaneous respiration commenced. Patients breathed 70% nitrous oxide in oxygen with inspired isoflurane (Drager Vapor 19.3) adjusted to obtain an end-tidal isoflurane concentration between 0.65 and 0.75%.

Measurements of spontaneous breathing were made when tidal volume and frequency had remained within 10% of the starting value for 10 min. Optical scanning was then started. We studied quiet breathing (Opioid, Quiet Breathing) and then reduced the fresh gas flow until rebreathing of exhaled gas was noted. Carbon dioxide was then added to the fresh gas until ventilation was approximately doubled. After stabilisation for 10 min, measurements were repeated (Opioid, Stimulated breathing). Carbon dioxide flow was then stopped, fresh gas flow was increased, the infusion of fentanyl discontinued, and naloxone 0.8 mg given iv. A further dose of naloxone 0.4 mg was given if the subsequent measurements were not completed in 20 min. When tidal volume and frequency were stable (<10% variation) a further measurement sequence was made (Naloxone, Quiet Breathing). Finally, stimulation with carbon dioxide was repeated and the last set of measurements was made (Naloxone, Stimulated Breathing).

During each condition (Opioid with Quiet Breathing, Opioid with Stimulated Breathing, Naloxone with Quiet Breathing, and Naloxone with Stimulated Breathing) scan sequences were taken to measure the rib cage, the abdomen, and the whole chest wall. These scans were taken using a set sequence, to minimise the number of times that the scan line positions had to be re-set, and reduce the time needed for the study. For example, the measurements of movements during passive inflation ended with measurements set for the complete chest wall: the first measurements during spontaneous ventilation were then also of the complete chest wall. During each scan, the inspiratory and expiratory taps were closed alternately at irregular intervals, no less than 6 breathing cycles apart, to allow flow and airway pressure to be measured before and during attempts at inspiration and expiration. Inspiration and expiration were each occluded at least four times for each scan. For each occlusion measurement, we used the preceding breath as a control for timing, flow, and volume. Measurements of breath timing were taken from airway flow, or from airway pressure changes when occlusion was present. Because the expiratory pressure generated in the airway was often not constant during the entire occlusion of expiration, we measured the mean pressure between 25 and 75% of the expiratory time.

Table 1
Patient conditions during experimental periods.

	IPPV	Opioid	Opioid + CO_2	Naloxone	Naloxone + CO_2
$F_E \cdot CO_2$ (%)					
Mean	4.8	6.7	7.6	5.3	6.6
SD	0.7	1.2	1.3	1.0	1.1
Isoflurane (%)					
Mean	0.65	0.64	0.73	0.89	0.87
SD	0.16	0.25	0.27	0.26	0.24

2.8. Passive expiratory pressure

Occlusion of expiration took place at end-inspiratory lung volume. When the inspiratory muscles relax at the end of inspiration, the previously inspired tidal volume is retained in the lungs, and a positive airway pressure is generated by the elastic recoil of the respiratory system. The airway pressure that develops when the inspiratory muscles relax will be proportional to the tidal volume inspired, and determined by the passive elastic properties of the respiratory system. This passive pressure was estimated from the inspired volume that preceded the occlusion, measured by the optical scan of the chest wall, and the elastic properties measured before the neuromuscular block was reversed. To estimate the active pressure caused by expiratory muscle action, this estimated passive pressure was subtracted from the total pressure measured during expiratory occlusion.

2.9. Statistical analysis

The study was primarily descriptive, and designed as a within subject comparison between the four measurement conditions. For each subject, mean values were calculated for control tidal volume, and active expiratory pressure, during each of the four conditions. Volume data and opioid dosage are summarised as medians with interquartile values, because we could not demonstrate that these values were normally distributed. Other data are summarised as mean (SD). Differences between the four conditions were tested with two way analysis of variance, using factors of drug (levels of Opioid, Naloxone) and carbon dioxide level (levels of no stimulus, stimulus), with subsequent comparisons between conditions using Tukey's test. For assessing changes between conditions, where there was no true "control" measurement, the mean volume from all conditions was used as a baseline value (Sheskin, 2007). To indicate effect size, differences between conditions are expressed as mean and 95% confidence limits.

3. Results

Ten patients gave their informed written consent to participate. Eight were male, and two female. Seven of the surgical procedures were orthopaedic (hand, wrist, or ankle) and three were operations on varicose veins. Mean (SD) age was 46 (18) yr, height 171 (11) cm, weight 70 (14) kg, and BMI 24 (4) m kg^{-2}. During anaesthesia and surgery, a median dose of 425 (quartiles 370, 650) μg of fentanyl was given. During the study, a further 200 (70, 225) μg was given by infusion. The mean study conditions are given in Table 1. After naloxone was given, the dose of isoflurane had to be increased slightly to maintain stable anaesthesia. End-tidal carbon dioxide increased when spontaneous ventilation started, and decreased after giving naloxone. In each period of stimulation with carbon dioxide, the end tidal fraction was increased by about 1%.

3.1. Passive measurements

During mechanical ventilation, changes in the cross-section area of the measured segments were linearly related to static inflation pressure. The median correlation coefficient between segment area change and airway pressure was 1, and 95% of r values were greater than 0.93. As described in Section 2, some scan line positions were common for whole chest wall and rib cage or abdomen scans. This allowed repeated section measurements to be compared. For the same scan line measured during different scans, the difference between two measures of the size/airway pressure relationship was 2.8% of the average value. Because these measurements were very similar, we combined measurements made of the five rib cage lines and the five abdomen lines to give a composite measure of the chest wall, using nine lines. The mean compliance of the respiratory system was 37(6) ml/cm H_2O, and the compliances of the ribcage and abdomen were 18(7) and 19(7) ml/cm H_2O, respectively. The changes in section size were similar in the ribcage and the abdominal segments, although there was some variation between subjects, and the area under the lower abdominal segments showed less change (Fig. 2).

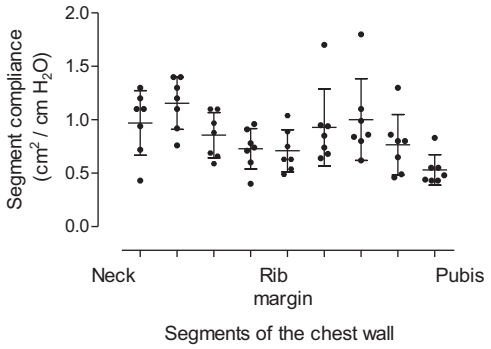

Fig. 2. Mean changes in cross-sectional area of the ribcage and abdomen sections, associated with static inflation of the respiratory system, expressed as a sectional "compliance" (area change/pressure). Values are shown for each subject and each section with mean and SD for each section.

3.2. Onset of spontaneous ventilation

We compared the end-expiratory cross section area of the chest wall segments during muscle paralysis and mechanical ventilation, with the same areas after the onset of spontaneous ventilation. These were studied with all the body scan line positions. Data from 3 patients were lost because of a software failure before analysis. Data for the remaining 7 patients are shown in Fig. 3. After spontaneous breathing started, the end-expiratory segment areas changed significantly (ANOVA, $P < 0.014$). The end-expiratory areas of the upper rib cage segments increased, and the area of the middle

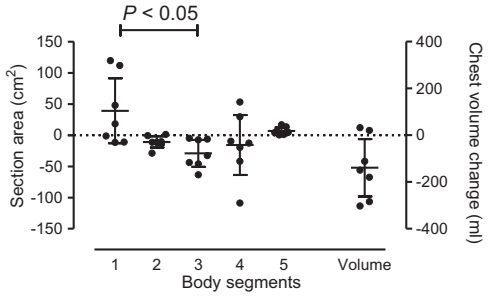

Fig. 3. Plot on the left shows changes in segment cross sectional areas from manubrium to suprapubic positions associated with the reversal of neuromuscular block and onset of spontaneous breathing. Changes are presented relative to the mean value for the two conditions. Lines are median values. The changes in body segment sizes were significant ($P < 0.05$, two way ANOVA). Tukey test showed a significant change between segment 1 (upper rib cage) and 3 (midsection of the body). Plot on the right is end-expiratory volume. This was reduced, by 139 ml (95%CI, 17–272) ($P < 0.05$).

section of the chest wall decreased. The difference between the changes in these two segment areas was significant (Tukey test, mean difference of 68 cm^2, 95%CI, 10–127 cm^2). Overall, the end-expiratory chest wall volume was 139 ml (95%CI, 17–261) less after breathing started, compared with the volume during mechanical ventilation.

3.3. Changes in chest wall volume during the breathing manoeuvres

We assessed end-expiratory chest wall dimensions during the experimental conditions, by comparing the volume in each condition with a mean volume calculated from all four conditions (Fig. 4). The chest wall volumes changed significantly between conditions ($P < 0.05$, repeated measures MANOVA). After naloxone administration, mean chest wall volume increased by 201 ml (95%CI, 122–279) ($P < 0.05$). This increase in volume was the result of increased volume in both the ribcage and the abdomen ($P < 0.05$, ANOVA). Stimulation with carbon dioxide was associated with a significant reduction in both rib cage and abdominal volumes ($P < 0.01$).

3.4. Tidal volumes and volume changes during airway occlusion

Fig. 5 shows volume changes during tidal breathing in the four conditions. As expected, tidal volumes increased when breathing was stimulated by carbon dioxide. Naloxone did not cause a significant change in tidal volume, although respiratory frequency increased significantly ($P < 0.01$). Abdominal compartment volume changes were greater than those of the ribcage ($P < 0.001$). Calculation of the relative contribution of rib cage and abdomen compartments to the tidal volume is difficult to express, because some ribcage volume changes during inspiration were negative. However the median abdomen volume/tidal volume ratio for the four conditions ranged between 67 and 83%. This proportion did not alter when breathing was stimulated by carbon dioxide. When inspiration was occluded, the ribcage volume decreased and the abdominal volume increased by similar amounts, so that the overall chest wall volume change was very small.

3.5. Changes in chest wall shape during breathing

An example of the pattern of regional movement in the four conditions is shown using a composite plot from a representative subject (Fig. 6). The plots show the change in each segment area, relative to the area at the start of inspiration. Although the amplitudes of the changes vary according to the conditions, the overall pattern of the changes was consistent. The changes in shape during occlusion of expiration in the same subject are shown in Fig. 7. The changes are the inverse of those seen during inspiration. Fig. 8 summarises the median changes in shape for the four time conditions. We found no differences in the pattern of chest wall movements between male and female subjects.

To assess the possibility of distortion of the ribcage, we compared the changes of the upper and lower ribcage (i.e. the volume between lines 1–3 was compared with the volume between lines 3–5). In nine subjects, synchronous movements occurred even when airway occlusion was applied.

3.6. Occlusion measurements

Chest wall volume did not remain constant during expiratory occlusion. In some patients, there was a rapid decrease in measured volume of 50–150 ml over approximately 0.5 s, after expiration started. In all patients we noted a progressive volume change during the occlusion of 48(34, 63) ml/s (median (quartiles)).

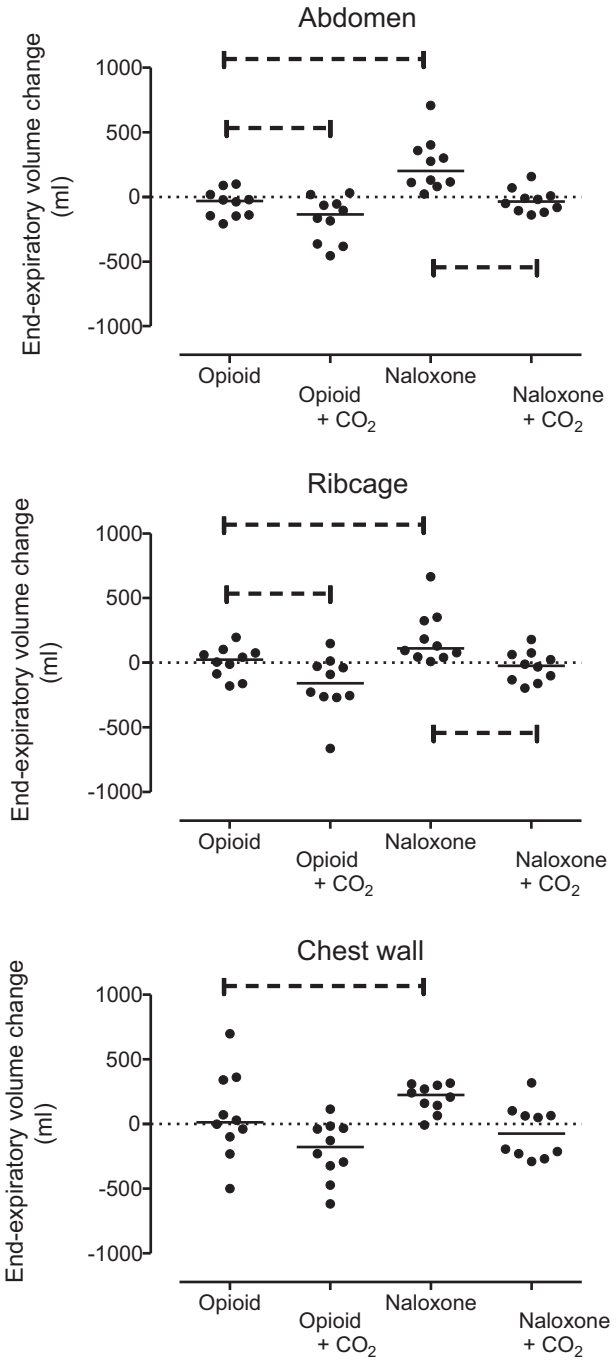

Fig. 4. Changes in end-expiratory volume of the compartments between treatment conditions. Values are expressed relative to a mean for the four conditions. Lines indicate medians and the interrupted bars show significant differences (2 way ANOVA, Tukey multiple comparison). For the complete chest wall, naloxone caused a significant increase ($P < 0.01$) but the effect of stimulus (a reduction) only approached significance, $P = 0.076$. In both rib cage and abdomen, naloxone increased volume, and stimulation with carbon dioxide decreased volume ($P < 0.01$ (or less) for all these comparisons).

The airway pressure values developed during occlusion of inspiration and expiration are given in Table 2. Stimulation with carbon dioxide increased these pressures and also increased the associated control tidal volumes ($P < 0.05$, repeated measures MANOVA). We calculated the passive pressure that would be developed in the occluded respiratory system if the muscles were relaxed. Subtraction of this passive pressure from the total pressure measured during occlusion of expiration indicates the pressure generated by

Table 2
Occlusion pressures during inspiration and expiration, associated tidal volumes, and derived values for active expiratory pressure.

	Opioid	Opioid + CO_2	Naloxone	Naloxone + CO_2
Inspiration (cm H_2O)				
Mean	−16.9	−23.5[a]	−15.6	−25.8[a]
SD	7.4	10.3	4.8	9.3
Expiration (cm H_2O)				
Mean	13.4	17.2	13.6	20.2
SD	5.4	6.9	4.6	10.7
Tidal volume (ml)				
Mean	258	444[a]	292	436[a]
SD	121	236	99	238
Active pressure (cm H_2O)				
Mean	5.8	9.2[b]	6.1	5.0
SD	3.6	6.2	3.8	3.3

[a] Values greater with carbon dioxide ($P < 0.05$, MANOVA).
[b] Active pressure was greater during opioid and carbon dioxide stimulation (Tukey multiple comparison test).

muscle activity during expiration. Active pressure was relatively constant in all the conditions but significantly increased when carbon dioxide was increased in the presence of opioid ($P < 0.05$, repeated measures ANOVA).

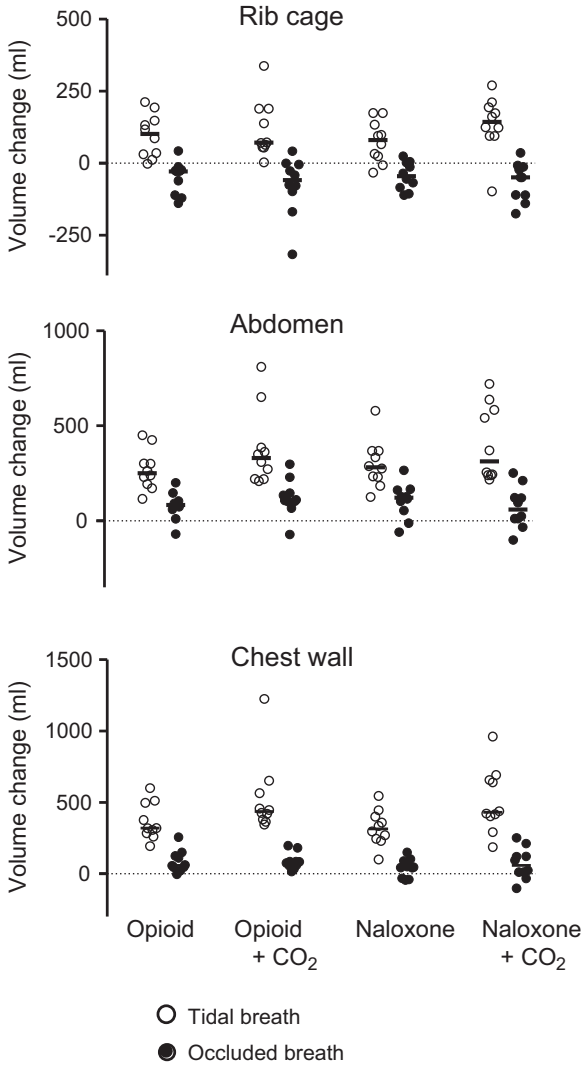

Fig. 5. Tidal volume and volume changes for the entire chest wall, and for ribcage and abdomen, for the four measurement conditions. Lines indicate median values. Open symbols are tidal volumes and the closed symbols are volume changes during occlusion of inspiration.

4. Discussion

4.1. New findings

Our detailed observations of regional chest wall dimensions (both shape and movement) provide several novel findings. First, we noted that the end expiratory position of the chest wall was reduced with the onset of spontaneous activity, and reduced when respiration was stimulated with carbon dioxide, and increased when opioid activity was reversed. Such changes are likely to result from activity of expiratory muscles during opioid activity and respiratory stimulation by hypercapnia. Second, we tracked movements during inspiration and found chest wall movement was predominantly abdominal. Although the amplitude of movements varied, the pattern of movement was very similar, irrespective of the presence or absence of opioid effects and hypercapnia. Finally we noted that when inspiration was occluded, paradoxical movement of the chest wall during occlusion of inspiration was substantial, with a decrease in rib cage volume. With obstruction of expiration, these movements were reversed. These changes suggest that the movements of the abdominal compartment are being driven by two reciprocal muscle systems, the diaphragm during inspiration and the expiratory muscles of the abdomen during expiration (see comments in Section 4.5).

4.2. Consideration of the methods used

The imaging system we used allowed inspection of the shape of the entire chest wall rather than measuring the shape of the lungs and upper 20–30 cm of the thorax (Krayer et al., 1987). The profile of the chest wall cross-section changed shape during the breathing cycle, particularly in the upper abdomen. Distortion of this type reduces accuracy of previous indirect methods of measurement, such as inductance bands (Drummond and Duffy, 2001; Tobin et al., 1987).

Although the method requires care to set up, it is stable, reliable, non-invasive, and does not involve radiation. Precision compares well with methods such as multiple CT (Krayer et al., 1987). If care is taken to avoid "hidden movement" the method is accurate. (Drummond and Duffy, 2001). The supine subject has to be supported on a rigid conforming sub-surface so that chest wall movement causes movement only of the upper, visible, surface, and this is acceptable for studies of anaesthetised subjects who are not otherwise likely to move. The optical system does not calculate the actual volume of the observed body, only changes in the volume lying below the observed surface. A disadvantage is that measurements such as chest wall volume cannot be repeated because the position of the supporting surface cannot be reproduced on a subsequent occasion. Another optical measurement system has similar accuracy, gives consistent measurements in different positions, and can assess absolute chest volume in moving subjects (Aliverti et al., 2001).

The optical system does not calculate the actual volume of the observed body, only changes in the volume lying below the observed surface. We measure the volume change of thick "slices" of the chest wall, but cannot attribute the regional changes to specific anatomic components. In particular, movement cannot be attributed to the diaphragm, as can be done with CT measurements, where the exact 3-dimensional structure can be imaged. We did not attempt to delineate the exact positions of the ribcage apposed to the lung volume and the abdomen, as was done by Kenyon et al. (1997) although our middle line would correspond quite closely to the lower rib margin.

Our study plan had some weaknesses. We studied patient volunteers, and the studies had to be conducted after surgery. Our major interest was the effects of opioids on respiratory movements during

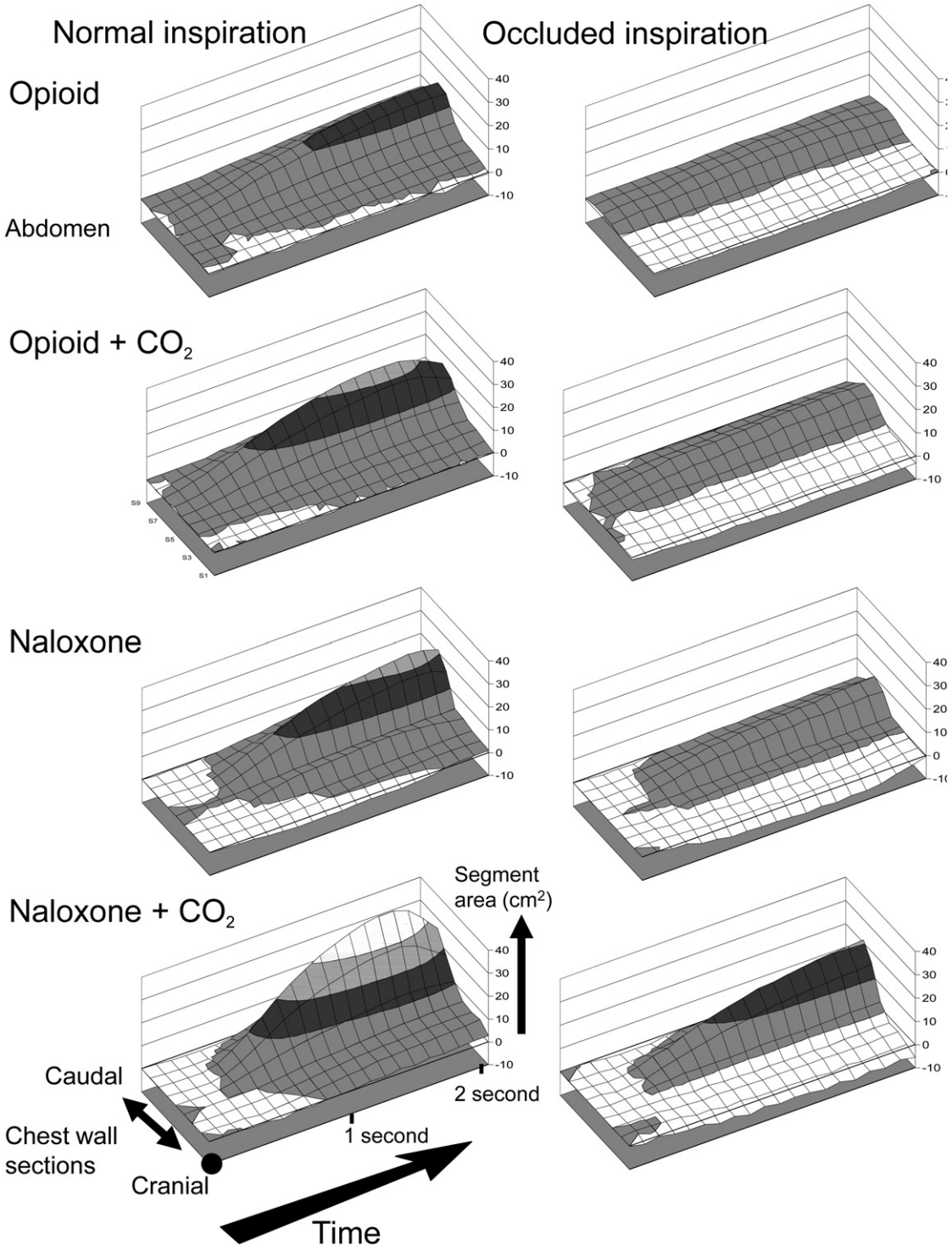

Fig. 6. Pattern of change in each chest wall segment area in a representative subject, during the four measurement conditions. The area change is shown relative to the area at the start of inspiration, during a normal tidal inspiration and an occluded inspiration. Each plot represents the mean of at least 4 breaths. The time markers have units of 0.1 s, and run in the direction of the arrow from the start to the end of inspiration. The plot starts at the black dot.

anaesthesia, so we did not study the subjects while awake, which would have involved re-positioning the patients. Measurement of oesophageal and gastric pressures would have been of interest although oesophageal pressure may not be an accurate measure of pleural pressure in supine anaesthetised subjects (Drummond and Wright, 1983). Accurate placement of catheters in the oesophagus and stomach is difficult in mechanically ventilated subjects. We attempted measurements in some patients, but were unable to acquire sufficient reliable data. However our measurements of occlusion pressure, which were made in inspiration or expiration, provide a useful index of muscle neural activation, although isometric conditions may not be achieved (Easton et al., 1987).

We studied a single opioid, fentanyl, which is a very commonly used agent during anaesthesia and has typical μ opioid agonist effects, representative of μ opioid agonists generally. The degree of opioid action present may not have been equivalent between

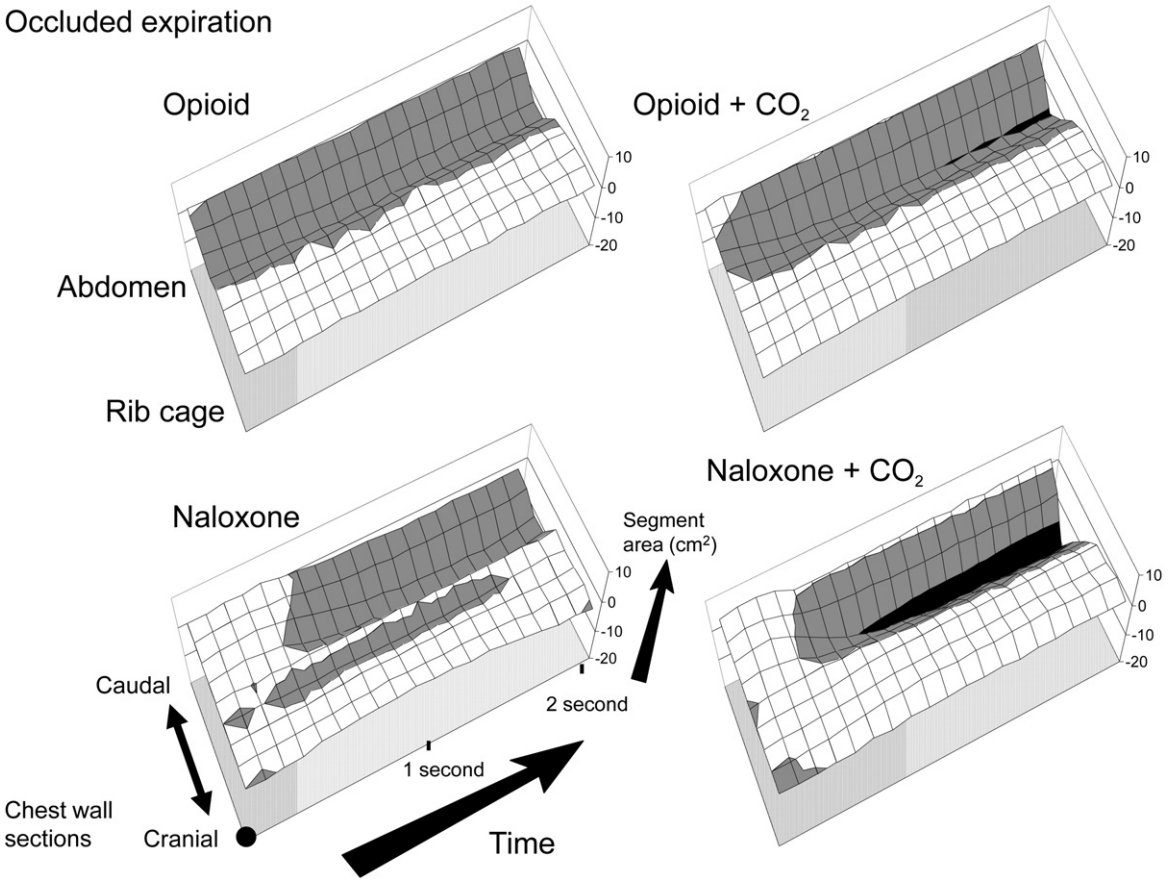

Fig. 7. Pattern of changes in chest wall segment area, relative to the area at the end of inspiration, in a representative subject, during an occluded expiration, for the four time conditions. The time lines on the surfaces have units of 0.1 s, and run in the direction of the arrow from the start to the end of inspiration.

subjects, and exact equivalence is difficult to define precisely, since the dose-effect relationship may vary between subjects. However the opioid effects we observed were similar: respiratory rates were consistent when spontaneous breathing started, typical of patients given opioids during anaesthesia, and we observed substantial changes within subjects when naloxone was given. We are confident that the conditions can be considered representative of "with and without" opioid. Similarly, the stimulation of ventilation by a combination of increased inspired carbon dioxide and rebreathing was not necessarily the same in all subjects although it was adjusted to approximately double minute ventilation. Other factors would be active whose magnitude was uncertain, such as individual responses to both carbon dioxide and to the opioid. However the primary purpose of stimulation was not to assess ventilatory responses, but to assess any possible changes in the pattern of respiratory movements when ventilation was increased. Thus the four conditions chosen should be considered "categorical" rather than "quantitative" and this is reflected by the statistical analysis, which concentrated on within subject comparisons. Our statistical analysis was restricted to comparisons between conditions. Analysis of variance assumes that values are normally distributed and of equal variance, but tolerates some deviation from normality and a twofold variation in SD between groups (Moore and McCabe, 1993).

4.3. Comments on results

We found passive movements of the chest wall that resembled those reported in previous studies (Grimby et al., 1975; Hedenstierna et al., 1981). Ribcage and abdominal movements were equivalent, and the mean compliance of the compartments was indistinguishable. Inspection of the 9 chest wall sections showed only one patient in whom the abdominal movement was consistently greater than the ribcage. Such movements reflect the coupling of the chest wall to the passive changes in intrapleural and abdominal pressure swings. However previous measurements of chest wall movements have been limited to the circumference or diameter of the ribcage and abdomen. Our more detailed measurements showed that the central region of the chest wall, at the rib margin, moved consistently less than the other segments. We suggest that this represents a tethering effect of the rib margin and the costal diaphragm, and note that this segment also shows little motion during occlusion manoeuvres.

We did not find substantial differences in the phase of the ribcage and chest wall movements during un-stimulated breathing, in contrast to studies using inductance bands (Brown et al., 1992; Tusiewicz et al., 1977). However we did find that during stimulation with carbon dioxide, ribcage dimension continued to increase at the end of inspiration, when the abdominal volume had started to decrease, supporting observations previously made by Warner and Warner (1995) using inductance bands. These workers suggested that the paradoxical movements were confined to the upper part of the ribcage, but we found no distortion, and movement of the whole rib cage followed this pattern.

4.4. Changes in end-expiratory lung volume

The changes in end expiratory lung volume, on resumption of spontaneous breathing, were similar to those found by Warner who studied volunteers first awake and then anaesthetised with halothane (Warner et al., 1995). The decrease in size of the

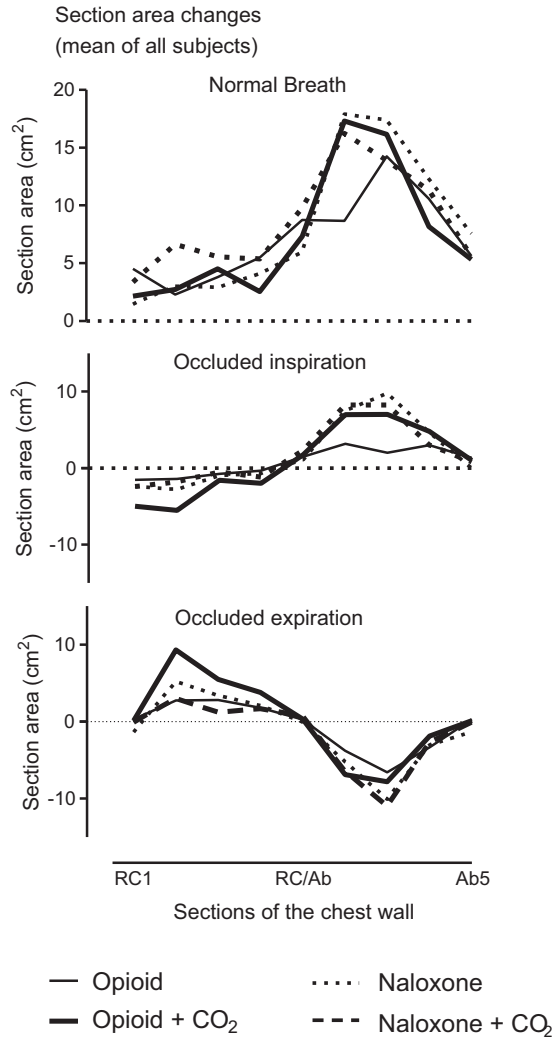

Fig. 8. Upper panel: normal breath: plot of mean values of increase in section areas with inspiration, for the four measurement conditions. Middle panel: occlusion of inspiration: plot of mean values of change in section areas during inspiratory attempt, for the four measurement conditions (note altered scale). Lower panel: occlusion of expiration: plot of mean values of change in section areas during expiration (relative to end-inspiratory area), for the four measurement conditions (note altered scale).

central body segment that we noted is consistent with the onset of expiratory muscle activity in the lower intercostal and upper abdominal muscles. Stimulation with carbon dioxide caused a further reduction in end-expiratory position, also presumably related to expiratory muscle activation (Yasuma et al., 1993). Our findings support Warner and co-workers' conclusion that "expiratory muscle activity significantly constricts the rib cage" (Warner et al., 1996).

Our findings, and those of Warner, differ considerably from the recent report of Aliverti et al. (2011) who studied patients anaesthetised with propofol. They describe a very different pattern of ribcage movement, with outward movement of the upper rib cage before the lower ribcage and abdomen. They attribute this movement to intercostal muscle action, but their reported changes in cavity pressures cannot exclude expiratory muscle activity. These differences may be related to the agent used in their study, which was propofol.

In a study with a very similar design, we showed that abdominal muscle activity is present and augmented by stimulation with carbon dioxide. Opioids reduce lung volume (Chawla and Drummond, 2008; Kallos et al., 1973), and increase intra-abdominal pressure (Drummond and Duncan, 2002). In the present study we found that when expiration was occluded, expiratory muscle action moved the abdomen inwards and ribcage outwards. Since we know that abdominal muscle activity is not affected by occlusion (Drummond et al., 2011) we assume that these actions also occur in the process of a normal, un-occluded expiration. Abdominal muscle action augments expiration, reducing lung volume to less than FRC. The subsequent tidal volume will be augmented by the return of chest wall volume to FRC as the expiratory effect ceases with the onset of the next inspiration. In addition, the reduction of lung volume will augment the force of contraction of the diaphragm (Eldridge and Vaughn, 1977; Mier et al., 1990).

4.5. Inspiratory and expiratory muscles have similar effects on chest wall movements

We observed a consistent pattern of chest wall movement, despite substantial changes in factors affecting the control of breathing such as opioid action and carbon dioxide levels. This may be explained by predominant muscle action on the abdominal compartment of the chest wall. In an unobstructed breath, chest wall expansion was substantially abdominal, and ribcage contribution was small (see Figs. 5 and 8) The rib cage movement was probably generated by abdominal pressure acting on the lower ribcage via the zone of apposition (Mead and Loring, 1982). When inspiration was occluded, abdominal expansion was not prevented, and there was paradoxical inwards movement of the ribcage, suggesting that the inspiratory force of the ribcage was weak or absent. A reciprocal pattern of movement was found when expiration was prevented (Fig. 8). In all conditions studied, there was evidence of active expiration (Table 2). Predominant diaphragm action during inspiration, and abdominal action during expiration, will both generate volume changes in the abdominal compartment, with the amplitude depending on the level of stimulus present. Our findings are comparable to increased ventilation noted during exercise by incursion on the expiratory reserve volume (Sanna et al., 1999).

In the awake subject, inspiration is active and involves coordination of both ribcage and diaphragm agonists. During anaesthesia with volatile agents, this pattern is replaced by reciprocal activity of inspiratory and expiratory agonists acting on the abdomen.

Central respiratory rhythm is generated by a predominantly reciprocal process in brain stem centres (Smith et al., 2007). A major source of expiratory neurons are found in the Bötzinger complex, and become more active when expiration is augmented (Fortuna et al., 2008). Abdominal muscle input from the respiratory centre appears to be resistant to opioids (Janczewski et al., 2002), whereas inspiratory intercostal activity is suppressed by volatile anaesthetic agents (Jones et al., 1979; Warner et al., 1995). We have described a pattern of respiratory movement that is consistent with both the diaphragm and abdominal activity displacing the abdominal wall, in the inspiratory and expiratory phases of the respiratory cycle, respectively.

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