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Respiratory Compensation After Epidural Acute Spinal Paralysis

by

Neil Skjodt, M.D.

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Abstract

The mechanisms of respiratory compensation and compromise following acute spinal paralysis remain poorly described. To overcome previous limitations of clinical observation and animal experimentation an injury free model of spinal paralysis using reversible epidural anesthesia was developed. The utility of the model was enhanced by novel fluoroscopically guided catheter insertion, repositioning to prevent asymmetrical onset of anesthesia, and the use of chronic subjects. Diaphragm sparing ascending spinal paralysis produced bradypnea, decreased minute ventilation, increased end tidal capnometer values, and decreased average inspiratory flows with preserved tidal volumes. Diaphragm, but not parasternal intercostal, muscle activity and shortening increased with ascending paralysis. With ascending paralysis greater diaphragm activation was required to maintain peak inspiratory flow, and this recruitment was sustained into expiration. Respiratory compromise secondary to an abnormal ventilatory response, lack of parasternal intercostal recruitment, and mechanically disadvantaged diaphragm recruitment were observed in this model of acute diaphragm sparing ascending spinal paralysis.

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Chapter One: Introduction

The Clinical Problem

Respiratory compromise following spinal paralysis

Respiratory failure remains the commonest cause of death following acute spinal cord injury (1). Death from respiratory failure once usually occurred in the first 24 hours following spinal injury despite mechanical ventilation (2). The incidence of non-lethal respiratory complications and their cause-specific mortality varies given differences in patient sampling and observational techniques. In a review of five clinical series from 1973 to 1990 respiratory complications occurred in 36 to 83% of spinal injury patients, and respiratory complications have been implicated in 80% of spinal deaths (1). Half of all spinal cord injury victims are acutely hypoxic (2), and normocarbic hypoxia occurs frequently despite mechanical ventilation (3). The attributable risk of respiratory complications from spinal cord injury is greater than with equivalent bony vertebral injury alone (4). Respiratory care cost a substantial portion of the extra estimated $1.5 billion (1995 American dollars) annually spent on in-hospital complications following spinal cord injury in the United States (4).

Ventilator dependence is expected with near total respiratory paralysis following high cervical cord injury, however, respiratory failure also frequently occurs following lower cervical injuries. Respiratory complications developed in 22 to

24% of patients with phrenic root sparing injuries (1, 4, 5). In another series 39% of patients with such injuries required acute mechanical ventilation (6), and the need for mechanical ventilation better predicted three month survival than the anatomic level of cervical or thoracic spinal cord injury (7). Respiratory complications occurred sooner following thoracic cord injuries than following cervical cord injuries (5).

No efficacious treatment for spinal injury

Although many therapies have been tried, none has been proven to reduce the respiratory morbidity and mortality following acute spinal injury. Rotating beds, vibratory chest percussion, and early (≤ 72 h post-admission) spinal fixation for pulmonary toilet did not decrease respiratory complications (1). Abdominal binding increases tidal volume in the upright position, but whether this reduces morbidity and mortality was not assessed (8). Two trials of intermittent positive-pressure breathing (IPPB) in spinal cord injury patients showed no sustained changes in lung mechanics after IPPB was withdrawn (9, 10). Three clinical trials found no difference in mortality between phrenic pacing and standard mechanical ventilation in quadriplegia (11, 12, 13). Although arguably improving sensorimotor recovery, methylprednisolone did not decrease respiratory complications (14, 15, 16, 17).

Pulmonary function following spinal cord injury

There are few studies of pulmonary function within the first month following spinal injury. In one quadriplegic (level of injury unspecified) paradoxical breathing and reduced vital capacity (VC) only began to improve 27 days after injury (18). With or without diaphragm paralysis, forced vital capacity was reduced to around half of predicted with only partial recovery over the next couple months (19). In the same study lung (C_L) and chest wall compliances both decrease within one month following spinal injury, however, the ratio of C_L to functional residual capacity (FRC) did not differ between spinal injury patients and normal controls. Supine FRC was found to be 49 ± 14% of predicted in spinal injury patients compared to 75 ± 13% of predicted in normal supine controls volumes ($p = 0.017$). Two other series of chronic quadriplegics reported unchanged or minimally reduced (e.g. 85 to 90% predicted) FRC values within the first year of injury (20, 21). The decrease in C_L with preserved C_L:FRC ratio was attributed to terminal airway closure and alterations in surfactant secondary to low lung volumes following spinal paralysis (22).

Upper manubrial sternum level versus lower xiphoidal sternum level rib displacement between maximal inspiration ("active total lung capacity") and relaxation against an obstructed mouthpiece ("passive total lung capacity") was compared between "acute" quadriplegics (<300 d post-injury), chronic quadriplegics, and normal subjects (19). Exaggerated upper rib cage motion in

"acute" quadriplegics was attributed to increased sternocleidomastoid activity. In chronic quadriplegics both upper and lower rib cage motion was exaggerated, and was attributed to improved thoracic coupling. There was no significant difference between FRC in "acute" and chronic quadriplegics (49 ± 14% vrs. 51 ± 8% predicted, $p > 0.05$, Mann-Whitney test). The diaphragm's resting apposition against the chest wall, and its resultant mechanical advantage were judged unchanged (22).

In 14 lucid, euoxic, and hemodynamically stable patients assessed in the emergency room following C_4 to C_8 spinal cord injury, pCO_2, and arterial pH were normal. Adding three further patients who had mild hypoxia corrected with supplemental oxygen, it was noted that VC, maximal inspiratory pressure, and maximal expiratory pressures were reduced (20).

Post paralysis respiratory muscle function

Abdominal paralysis

The inspiratory function of the abdominal muscles during quiet breathing may be to augment rib cage expansion by contracting to less than relaxation length in late expiration allowing greater subsequent rib cage recoil in early inspiration. Abdominal paralysis does impair coughing with resultant atelectasis and subsequent pneumonia (23). In one "acute" quadriplegic (level of injury

unspecified) the abdominal muscles' contribution to vital capacity as measured by digitized contour line photography of the thorax was negligible for the first month following injury (18). Two dog studies of epidural anesthesia producing acute abdominal paralysis reported no statistically significant changes in ventilation, respiratory muscle EMG, or chest wall configuration (24, 25). Both of these studies were however done under pentobarbital anesthesia, and did not allow recovery from acute post-implantation diaphragm inhibition.

Unchanged ventilation following abdominal paralysis would confirm the absence of thoracoabdominal coupling, the interdependence of thoracic and abdominal pressures and displacements (26, 27). Thoracoabdominal coupling has been kinematically demonstrated in humans, but is lost transiently in acute paraplegia (22). In summary, these physiologic studies do not predict the observed respiratory morbidity and mortality in acute paraplegia.

External intercostal paralysis

The contribution of the intercostals to ventilation depends on the complex interaction between the interspace dependent orientation of intercostal muscle fibers, lung volume, pCO_2, and proprioceptive feedback (28, 29, 30, 31, 32). Kinematically, the rib cage did not contribute to V_T, and only increased predicted VC from 15 to 50% of predicted between 27 and 272 days post injury in one "acute" quadriplegic (18). In chronic human quadriplegics the preservation of

external intercostal activity was associated with preserved FRC, preserved FRC transpulmonary pressures, and preserved static C_L (28). In four adults without known lung disease undergoing genitourinary surgery V_E and pCO_2 remained unchanged following conscious T_1 spinal anesthesia (33).

Normal function of the external intercostals depends on the parasternal intercostals in the dog. External intercostal dependent rib cage expansion depends on intact parasternal intercostal activity (29, 30). The parasternal intercostals contribute approximately 80% of the total intercostal contribution to rib cage expansion (30). Dogs hypoventilate despite increased diaphragm EMG activity following acute intercostal paralysis (25). Diaphragm activation following intercostal paralysis may result from secondary hypercarbia (25), the loss of intercostal afferent inhibition as seen in cats (34), or both. In the dog neither vagotomy nor sympatholytic hypotension altered the effects of acute chest wall paralysis on ventilation, diaphragm EMG activity, or transdiaphragmatic pressure suggesting that sympathetic blockade does not mediate respiratory changes in acute chest wall paralysis (25). These animal studies were however performed acutely under general anesthesia. Despite these limitations, the available data suggest acute lower chest wall paralysis only modestly compromises V_T when diaphragm activity is preserved. As with acute paraplegia, the respiratory morbidity and mortality following lower chest wall paralysis in quadriplegia remains poorly explained.

Parasternal intercostal paralysis

Human studies of acute parasternal paralysis are variable. No changes in V_E or pCO_2 were noted with conscious high thoracic (T_1) spinal anesthesia (33). In a C_1 quadriplegic patient normal upper thoracic expansion did not occur during phrenic pacing (35). The dependence of maximal chest expansion on parasternal activity has also been demonstrated in non-phrenically paced spinal cord injury (18, 23, 28, 37, 38, 39, 40, 41), infant sleep (42), and infant thoracic epidural anesthesia (43). In normal humans, three dimensional optical kinematic analysis revealed 30 to 60% of V_T resulted from parasternal dependent upper rib cage displacement (44).

In dogs selective denervation of the parasternal intercostals produced hypercarbia with decreased tidal volume despite increases in external intercostal EMG activity and preserved diaphragm activity (31). The dependence of maximal chest expansion on parasternal activity has also been shown in various other models of selective canine respiratory paralysis (24, 25, 45, 46, 47). Acute parasternal paralysis is usually associated with significant respiratory compromise.

Diaphragm response to abdominal and thoracic paralysis

Although extensive evidence exists to suggest that the costal and crural diaphragms can function as different muscles (48, 49), few differences in costal and crural diaphragm function were noted following isolated parasternal paralysis (45). The costal and crural diaphragms' responses to hypercarbia or loss of inhibitory afferent feedback associated with respiratory paralysis are likely similar.

The enormous morbidity and mortality of respiratory complications following acute spinal cord injury persist without effective interventions or explanations. Further observational or experimental studies are required to understand and treat these complications.

Studying acute spinal injury

Limitations of human data

The literature describing respiratory function in man and dog is substantial, however, respiratory changes immediately following acute paralysis remain poorly described. Experimental traumatic spinal paralysis cannot be inflicted on humans ethically. Only four of the previously described clinical observation studies included small numbers of patients with injuries only hours to days old.

The effects of selection bias, anesthesia, sedation, anxiety, other injuries, and resuscitation were not controlled. Rare case reports of cordotomy patients with undesired descending respiratory motor neuron ablation are similarly limited by confounding pain, anesthesia, underlying disease, and analgesia. These confounders, combined with the practical difficulties of making detailed observations, essentially preclude detailed observations of acute spinal paralysis in humans. Simply stated, the effect of acute spinal paralysis on breathing pattern and respiratory muscle compensation is unknown.

Experimental non-traumatic spinal paralysis in humans has limited experimental potential. Volunteers would have to consent to rare but potentially lethal risks of cardiovascular instability, adverse drug reactions, and inadvertent total respiratory paralysis during high spinal or epidural anesthesia. The utility of non-invasive measurement of respiratory muscle function in humans is limited.

Limitations of non-human data

Animal studies assessing respiratory function in experimental acute spinal paralysis have all been done acutely and under general anesthesia (24, 25). Diaphragm inhibition following intraoperative manipulation cannot resolve before acute measurements are made (52). General anesthesia alone substantially

influences ventilation and respiratory muscle function. Inflicting traumatic spinal injuries in conscious chronic animal preparations is ethically questionable.

A feasible model

Given these limitations, a feasible model of acute spinal cord injury might use reversible paralysis in an awake higher vertebrate where post-operative respiratory muscle inhibition has resolved. For example, epidural anesthesia could be used to produce ascending step wise spinal paralysis in an awake dog chronically implanted with both respiratory muscle sonomicrometer and EMG wires. Defining the level of sensory block in an awake dog is not practical, but the ascending loss of respiratory EMG activity could be used to follow the level of motor blockade. Abdominal paralysis with chest wall and diaphragm sparing could mimic paraplegia. Lower chest wall paralysis could mimic low quadriplegia while even higher chest wall paralysis would mimic high quadriplegia. Complete respiratory paralysis cannot be inflicted ethically in an awake, non-ventilated animal and corresponds to a ventilator- or phrenic pacer-dependent state in humans.

Response to acute conscious spinal paralysis: Hypotheses

Using experimental methods common to the entire project, the questions, hypotheses, results, and discussion of this thesis follow three themes corresponding to three submitted manuscripts. These manuscripts summarize the feasability of, the mechanisms of ventilatory compromise in, and the respiratory muscle compensation following diaphragm sparing thoracoabdominal epidural anesthesia in awake chronically instrumented dogs.

The feasability of awake epidural anesthesia as a model of acute spinal paralysis

Given the limitations of clinical observation and anesthetized models, can a model of acute respiratory failure in spinal paralysis without spinal injury be developed in an awake subject?

It was hypothesized that step wise thoracoabdominal epidural anesthesia in a chronically instrumented awake dog model will permit the study of acute respiratory compromise associated with spinal paralysis.

Mechanisms of acute respiratory failure in diaphragm sparing spinal injury

Acute respiratory failure following diaphragm sparing spinal cord injury frequently occurs despite the presumed preservation of diaphragm activity. Few such patients remain chronically ventilator dependent. If preserved diaphragm function alone is sufficient to maintain physiologic ventilation, then why does acute respiratory failure so frequently complicate diaphragm sparing spinal cord injuries?

Other head or chest injuries, ventilation suppressing drugs, missed transient respiratory muscle failure, and an altered ventilatory response are all non-exclusive possibilities that cannot be discriminated between by clinical observation alone. Extra-spinal injuries and ventilation suppressing drugs can, however, be excluded by design in experimental models.

Using the epidural anesthesia model to exclude the effects of ventilation suppressing drugs and extra-spinal injuries, does the acute respiratory failure following spinal paralysis result from transient diaphragm failure or from an altered ventilatory response?

It was hypothesized that acute respiratory failure complicating spinal paralysis will be associated with an abnormal ventilatory response.

Respiratory muscle compensation after acute diaphragm sparing paralysis

How do the respiratory muscles respond to abdominal paralysis in a conscious subject? Previous studies of chest wall kinematics in a single acute human quadriplegic studied 27 to 272 days post-paralysis (18) and in anesthetized dogs (24) both demonstrated minimal contribution of the abdominal muscles to inspiratory volume.

It was therefore hypothesized that abdominal paralysis will have minimal effect on tidal volume, and require minimal recruitment of preserved respiratory muscles.

How do the respiratory muscles respond to chest wall paralysis in a conscious subject? In a single human quadriplegic chest wall paralysis did not alter tidal volume (18). In a separate study of anesthetized dogs selective denervation of the parasternal intercostals produced hypercarbia with decreased tidal volume despite increases in external intercostal EMG activity and preserved diaphragm activity (31).

It was hypothesized that following chest wall paralysis in the conscious dog sufficient volitional diaphragm and preserved intercostal recruitment will occur to

preserve tidal volume. Diaphragm recruitment will, however, be characterized by mechanically disadvantaged diaphragm EMG activity to overcome chest wall flaccidity following acute paralysis.

Chapter Two: Methods

Model Selection

The proposed model of acute spinal paralysis involves the application of epidural anesthesia to a previously described chronically instrumented dog model (52). The use of this established dog model offers several technical advantages. First, the use of the pneumotach to measure both air flow and sonomicrometry to correlate changes in EMG activity with general and muscle-specific measures of respiratory muscle function. Second, recognized transient postoperative impairment of respiratory muscles is avoided. Third, the confounding changes in breathing produced by general anesthesia are avoided.

Instrumentation

Sonomicrometer and electromyogram implantation

All protocols have been approved by the University of Calgary's Faculty of Medicine Animal Care Committee. Surplus sled dogs not required for sled pulling were acclimatized to the laboratory, its personnel, the experimental apparatus, and right lateral decubitus positioning. Once acclimatized, transducer

implantation occurred under balanced general anesthesia using 1 $ml \bullet kg^{-1}$ 25% intravenous pentobarbital, 1.0 to 2.0 MAC inhaled halothane, 10 to 20% inhaled nitrous oxide, and supplemental oxygen. Heart rate, rectal temperature, and urine output were monitored intraoperatively. The operative site was prepped with a povoiodine solution and then aseptically draped. During thoracotomies and laparotomies by specialist surgeons, multiple sets of paired custom sonomicrometer transducers with integrated bipolar fine electromyogram (EMG) wires were implanted in the left transversus abdominus along the anterior axillary line, left 3^{rd} to 4^{th} ("high") and 6^{th} to 8^{th} ("low") external intercostals along the midclavicular line, 2^{nd} to 3^{rd} left parasternal, costal diaphragm, and crural diaphragm muscles. The implants were secured to muscle with purse string sutures. Sonomicrometer separation and signal quality were confirmed prior to skin closure. The implanted, insulated wires were further secured internally with adsorbable suture, and tunneled out through separate exit sites.

To demonstrate the simultaneous bilateral onset of epidural blockade additional EMG wires were implanted into contralateral (right) transversus abdominus muscles in the same saggital plane.

Postoperative care

Morphine sulfate 10 mg intramuscularly as required for analgesia, and intramuscular chlorperazine 0.25 mg intramuscularly as required for sedation were given postoperatively for the first 24 hours following surgery. Prophylactic cloxacillin 500 mg daily and chloramphenicol 500 mg daily were also given post-operatively. Starting on the first post-operative day the dogs were normally fed, watered, and exercised.

Epidural catheter insertion

Following recovery from EMG wire implantation, each dog was again given a second general anesthetic. With the unconscious dog held in the flexed right lateral decubitus position, a pediatric anesthetist-veterinarian (Dr. Peter Farran) inserted an epidural catheter aseptically through a Tuohy-Schliff 18 gauge epidural needle placed in an L2 to L5 interspace using a paramedian approach. The needle was also directed caudal given the cephalic orientation of canine thoracolumbar posterior spinous processes. Insertion of the needle into the epidural space was confirmed by needle position on video fluoroscopy, subjective loss of resistance to injected air, absence of cerebral spinal fluid or blood return, and lack of resistance to the injection of radiopaque dye. The catheter tip was then advanced to the thoracolumbar junction, its position

confirmed with further dye injection under fluoroscopy, and the catheter then secured in place through a separate tunneled skin site. Dense radiopaque dye was left in the lumen of the epidural catheter to prevent catheter clogging. The dog was rested overnight prior to physiologic recordings.

Epidural anesthesia

Step wise ascending epidural anesthesia was produced by injecting 1.5 ml doses of 2% (20 mg/mL) plain lidocaine solution (Astra Pharma, Incorporated, Mississauga, Ontario) into the epidural catheter. The first 1.0 ml of each dose was injected with the dog in the right lateral decubitus, and the remaining 0.5 ml of each dose given in the left lateral decubitus position to prevent unequal settling of lidocaine in the epidural space. This 1.5 ml dose was repeated every ten minutes until a desired level of anesthesia was achieved. From preliminary dosing studies if two doses had not extended external to parasternal intercostal level paralysis then subsequent doses were each doubled to total 3.0 ml of lidocaine per dose until parasternal level paralysis was achieved.

Abdominal paralysis was defined as loss of expiratory transversus abdominus EMG activity. The entrainment of 10% CO_2 into the inspiratory limb of the mask apparatus was used to confirm the ablation of intermittently present phasic abdominal EMG activity. CO_2 entrainment had uniformly activated intermittently present phasic abdominal EMG activity in this model. External intercostal

paralysis was defined as loss of inspiratory external intercostal phasic EMG activity. Parasternal intercostal paralysis was defined as loss of inspiratory parasternal intercostal phasic EMG activity.

Data Collection

Sonomicrometry

The awake dogs quietly rested in the right lateral decubitus position. Each pair of sonomicrometer transducers dynamically recorded their physical separation as provided by changes in ultrasound transit time to a sonomicrometer (Model 120, Triton Technology, Incorporated, San Diego, California). Sonomicrometer output was directed through an amplifier (model TA 2000, Gould Electronics, Cleveland, Ohio) to an analog-digital board (Model MC-MIO-16, National Instruments, Austin Texas). The latter was connected to a 80836-processor PC-DOS microcomputer (PS/2 Model 80, International Business Machine Corporation, Boca Raton, Florida) running a proprietary multichannel data recording program (*DataSponge*, BioScience Analysis Software, Calgary, Alberta) to permit real-time display and simultaneous digital recording of all signals to computer disk. Sonomicrometer signals were recorded at 100 Hz, and were calibrated using reference points above and below the measured separation distance between the implanted crystals prior to real-time recording.

Respiratory muscle electromyography

Signals from the implanted EMG wires were preamplified (model 1700 AC amplifier, A-M Systems, Everett, Washington), Bessel band-passed filtered, rectified, moving averaged (model MA-821RSP moving averager, CWE, Incorporated, Ardmore, Pennsylvania), and integrated using an "RC leaky integrator" with a 50 ms time constant before being sampled at 100 Hz to the previously-described analog-digital board and computer data collection system.

Breathing pattern variables

Airflow signals were collected using a snout mask-fitted Fleisch pneumotach (OEM Medical, Incorporated, Richmond, Virginia). Snout mask end tidal capnometer (Model CD-3A CO_2 analyzer, Ametek, Incorporated, Pittsburgh, Pennsylvania) signals were collected using a snugly-fitted snout mask with a Fleisch pneumotach (OEM Medical, Incorporated, Richmond, Virginia). Peripheral pulse oximetry (Biox 3700 pulse-oximeter, Ohmeda, Boulder, Colorado) was recorded from a hind limb. Hind limb electrocardiography, end tidal capnometry, and pulse oximetry signals were each sampled at 100 Hz to the analog-to-digital board before being acquired to the data acquisition program.

Data Analysis

Data review and selection

Digital multi-channel recordings were converted into multi-channel daughter data files using *DataSponge 98* (BioScience Analysis Software Limited, Calgary) file conversion options. The recorded signals for each subject were analyzed using custom software written by Dr. Paul Easton. The flow signal was both evaluated for respiratory timing to generate a master timing file and digitally integrated to produce a corresponding volume signal. The proprietary program generated time values corresponding to beginning of inspiration, the beginning of expiration, and the end of expiration for each breath in the daughter data file. A second proprietary program (mtf2ev98.exe) written by Mr. Harvey Hawes converted these time values to a *DataSponge 98* file for visual review of generated breath events.

Electrocardiographic noise removal

In a preliminary analysis electrocardiographic QRS complexes were found to often be of greater magnitude than low magnitude or ablated respiratory EMG signals from the left-sided implants. To allow uncomplicated analysis of respiratory EMG signals QRS complexes were identified and excised. All edited files were manually reviewed.

Electromyogram baseline offset correction

To avoid the visually confusing overlap of signal tracings rectified, moving averaged EMG signals were instrumented with staggered negative voltage offsets. To facilitate subsequent breath by breath analysis of phasic EMG activity each EMG signal's offset was corrected to between 0 and 0.1 V positive using a dedicated function in *DataSponge 98*.

Breath by breath analysis

All signals were manually reviewed for movement artifacts, transient signal disconnections, transient apneas, and sighs, all of which were deleted from individual mean breath by breath results. Respiratory frequency and tidal volume values were calculated breath by breath using the previously described proprietary programs by Dr. Paul Easton. Using the respiratory timing derived from the flow signal, peak differential and integrated moving averaged EMG values for the costal diaphragm and parasternal intercostal were calculated breath by breath. Peak differential EMG was defined as the difference between maximal and phasic moving averaged EMG activity. Integrated moving averaged EMG was defined as the area under the moving averaged EMG signal during phasic respiration. Again using the respiratory timing derived from the flow signal,

the percentage of positive phasic sonomicrometer shortening from end-expiratory length was calculated breath by breath for the costal diaphragm and parasternal intercostal muscles. End tidal CO_2 and oximetry were also analyzed breath by breath using the proprietary programs and airflow referenced timing files. Individual mean end tidal CO_2 values were converted for altitude to sea level (P_{atm} = 760 mmHg) (50).

The repetitive keyboard strokes required for breath by breath analyses using Dr. Easton's proprietary programs were automated using customizable keystroke macros (*ProKey*, RoseSoft, Inc., Bellevue, Washington). All automated results were manually reviewed.

Intrabreath analysis

Dr. Easton's proprietary programs were also used to define the intrabreath shape of airflow, moving averaged EMG activity, and respiratory muscle sonomicrometer shortening from end-expiratory length. For each breath the peak inspiratory airflow, peak moving averaged EMG voltage, and maximal segmental sonomicrometer shortening from end-expiratory length were noted. The percentage of each maximum was determined after each 5% of the total breath time (T_{TOT}) producing a "bin" analysis of intrabreath signal changes based on T_{TOT}. For each section of analyzed data a profile of mean signal activity

normalized as a percentage of maximal activity was expressed over 20 intrabreath segments each representing consecutive 5% intervals of T_{TOT}. To illustrate the mechanical efficiency of diaphragmatic contraction the intrabreath airflow profile was plotted against the profile of costal diaphragm moving averaged EMG activity before any and after each level of defined paralysis.

Statistical analysis

Individual mean breath to breath values were exported to spreadsheet (*Microsoft Excel97*, Microsoft Corporation, Redmond Washington), graphing (*SigmaPlot,* version 4.01, SPSS, Incorporated, Chicago, Illinois), and statistical (*The SAS System for Windows,* version 6.12, SAS Institute, Cary, North Carolina) software for subsequent analysis. To assess the statistical significance of between-subject to within-subject variance in individual mean breath by breath results before anesthesia, following abdominal paralysis, and following parasternal paralysis one-way repeated measures analyses of variance were performed with exact p values being reported. Not all signals could be collected at all levels of paralysis in all dogs given post-operative EMG wire breakage or sonomicrometer transducer misalignment. Individual and group mean values are shown for muscle signals. No specific p values were selected as an arbitrary threshold of significance. The employed ANOVA method (PROC GLM) accounted for missing variables (51).

Chapter Three: Results

Conscious epidural anesthesia as a model of acute spinal paralysis

To demonstrate the feasability of epidural anesthesia as a model of respiratory compromise in acute spinal paralysis three dogs were studied to confirm that epidural anesthesia could produce symmetrical, step wise, ascending thoracoabdominal spinal paralysis in the awake dog.

Fluoroscopic confirmation of epidural catheter placement

Still images from real time video fluoroscopy recordings are shown during placement of epidural catheters in Figure 1. In the upper window an epidural needle is shown positioned in the epidural space. In the middle and lower windows progressive cephalic migration of radiopaque dye along the thoracic epidural space is marked with arrows. There is no pooling of dye around the tip of the epidural catheter to suggest paradural placement.

Confirmation of symmetrical EMG ablation

To prevent asymmetrical onset of epidural anesthesia we injected part of each dose of epidural lidocaine in the right and the remaining part of each dose in the

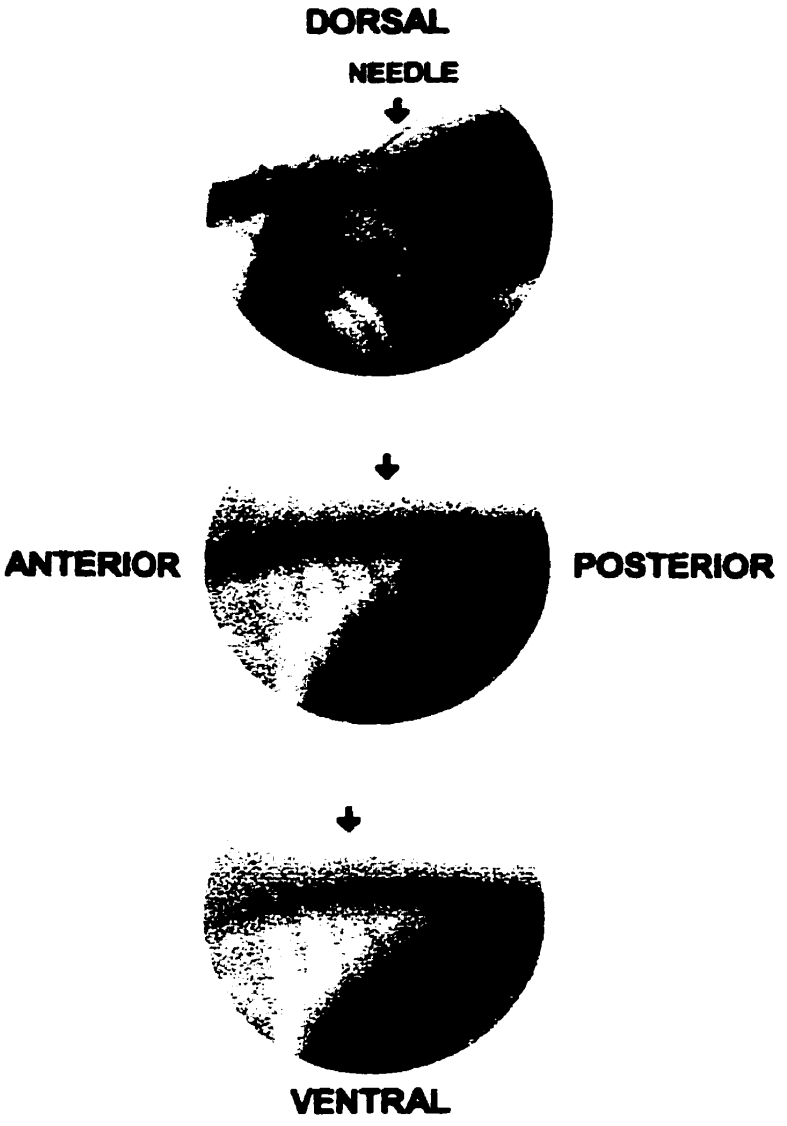

Figure 1: Video fluoroscopy images demonstrating positioning of needle in epidural space (upper window) and progressive cephalic migration of dye through epidural space (arrows, middle and lower windows).

left lateral decubitus position. The simultaneous symmetrical ablation of respiratory muscle EMG activity was confirmed with the bilateral placement of transversus abdominus EMG wires in the same sagittal plane.

In Figure 2 one of the dogs studied was noted to have bilateral continuous phasic abdominal EMG activity which was simultaneously ablated bilaterally by using this repositioning technique during anesthetic injection.

Control of anatomic level of epidural anesthetic motor blockade

We were successful in controlling the anatomic level of epidural motor blockade. In Figure 3 representative airflow and integrated moving-averaged EMG signals from a representative dog is shown. This subject was selected for illustration given continuous phasic abdominal EMG activity before epidural anesthetic was administered. During quiet resting breathing before epidural anesthesia (REST), expiratory phasic abdominal EMG activity and inspiratory phasic external (EXT) intercostal, parasternal intercostal (PARA), and costal diaphragm (COS) EMG activities were noted (Figure 3). Following ablation of expiratory phasic ABD EMG activity (ABDOMINAL level of paralysis), inspiratory phasic EXT, PARA, and COS EMG activities persisted (Figure 3). Following complete ablation of phasic ABD and near complete ablation of phasic EXT EMG activity (EXTERNAL INTERCOSTAL level of paralysis), phasic PARA and COS EMG activities persisted (Figure 3). Following complete ablation of phasic ABD, EXT, and PARA

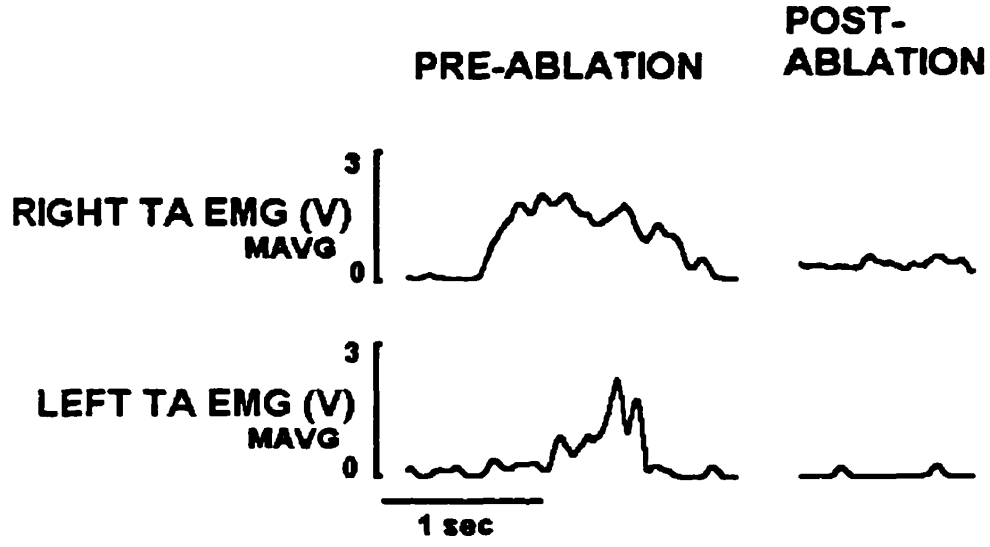

Figure 2: Right and left transversus abdominus (TA) moving averaged electromyograms before (pre-ablation) and after (post-ablation) epidural paralysis demonstrating the simultaneous bilateral onset of spinal paralysis.

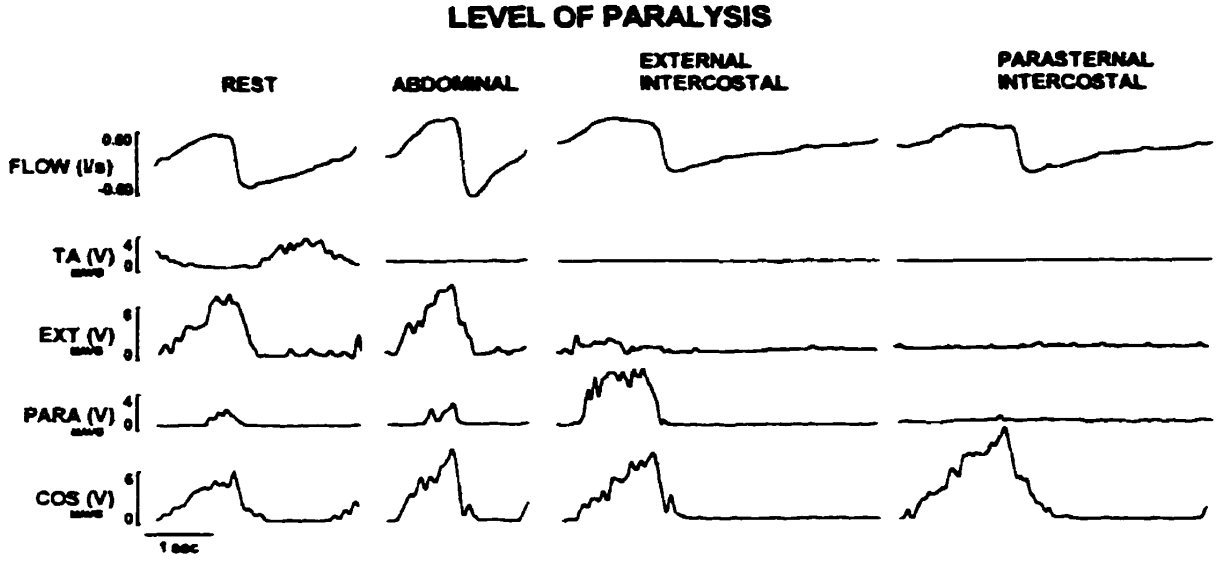

Figure 3: Airflow and selected respiratory muscle moving averaged electromyograms demonstrating step wise ascending epidural anesthesia.

Abbreviations: TA = transversus abdominus, EXT = external intercostal, PARA = parasternal intercostal, COS = costal diaphragm, MAVG = moving averaged

EMG activity (PARASTERNAL INTERCOSTAL level of paralysis), only phasic COS EMG activities persisted (Figure 3).

Clinical signs of spinal paralysis

In all subjects transient hypothermia, shivering, hypotension, rhinorrhea, and scleral vascular engorgement were noted during spinal paralysis. Similar signs of paralysis-induced sympatholysis have been clinically observed in paralyzed humans.

Mechanisms of acute respiratory compromise in spinal paralysis

Following the initial validation of the model, the effects of diaphragm sparing ascending paralysis on breathing pattern were assessed in ten dogs.

Evidence of respiratory compromise

The effect of step wise ascending epidural anesthesia on corresponding group mean (± SE) breath by breath end tidal CO_2 ($ETCO_2$) values is displayed in Figure 4. Between rest and parasternal recordings $ETCO_2$ increased from 30 to 34 mmHg with a corresponding p value of 0.0141. Most of this increase in $ETCO_2$ occurred following the onset of chest wall paralysis, that is following external intercostal levels of paralysis.

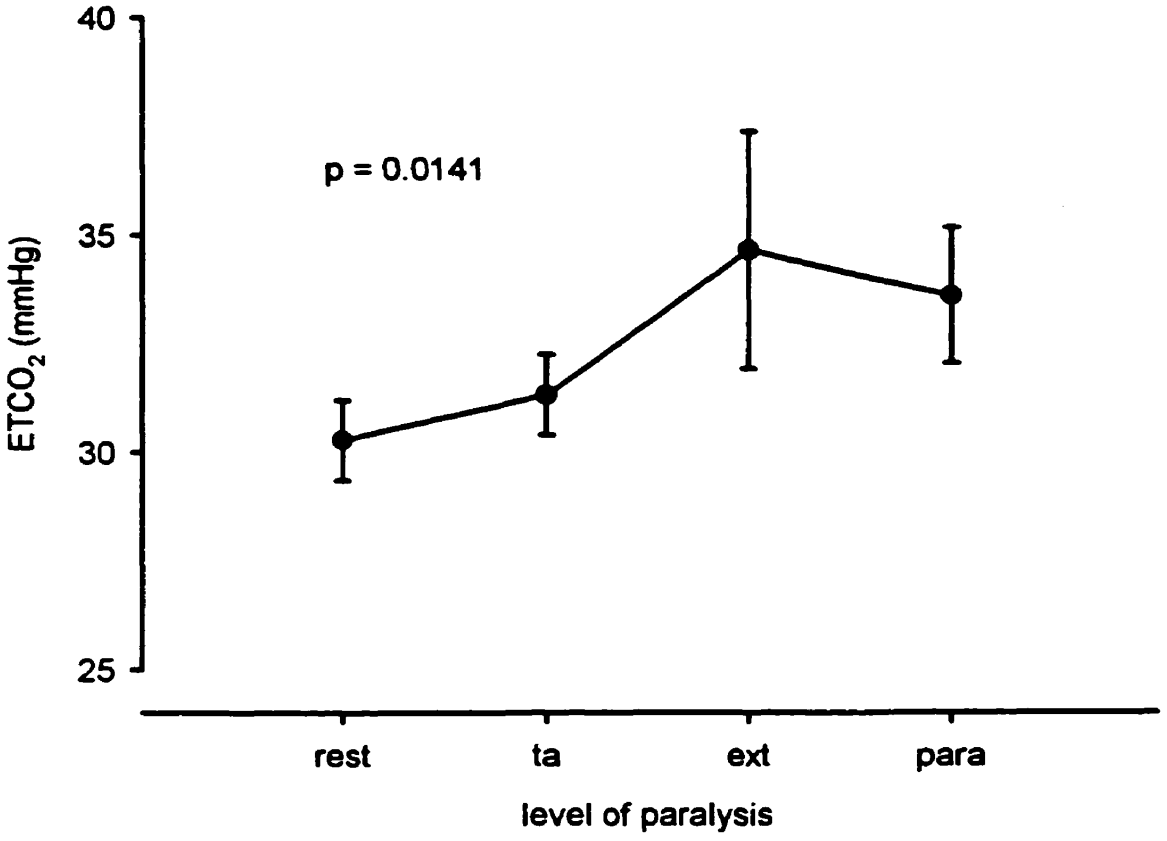

Figure 4: The effect of step wise ascending paralysis of transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on group mean (± SE) breath by breath end-tidal carbon dioxide ($ETCO_2$).

The effect of step wise ascending epidural anesthesia on corresponding group mean (± SE) breath by breath pulse oximetry (SpO_2) values is displayed in Figure 5. Between rest and parasternal recordings SpO_2 modestly decreased from 94 to 92% with a p value of 0.0091. Desaturation principally occurred following the onset of chest wall paralysis, that is following external intercostal levels of paralysis.

Breathing Pattern

The effects of step wise ascending epidural anesthesia on corresponding group mean (± SE) breath by breath respiratory frequency, tidal volume, and minute ventilation values are displayed in Figure 6.

Between rest and parasternal recordings respiratory frequency decreased from 24 to 16 breaths per minute with a corresponding p value of <0.0001. Most of the reduction in respiratory rate occurred following the onset of chest wall paralysis, that is following external intercostal levels of paralysis.

Between rest and parasternal recordings tidal volumes varied between 0.33 and 0.40 L with a corresponding p value of 0.2392. Between rest and parasternal paralysis recordings minute ventilation decreased from 8.4 to 5.8 L/min with a corresponding p value of 0.0012.

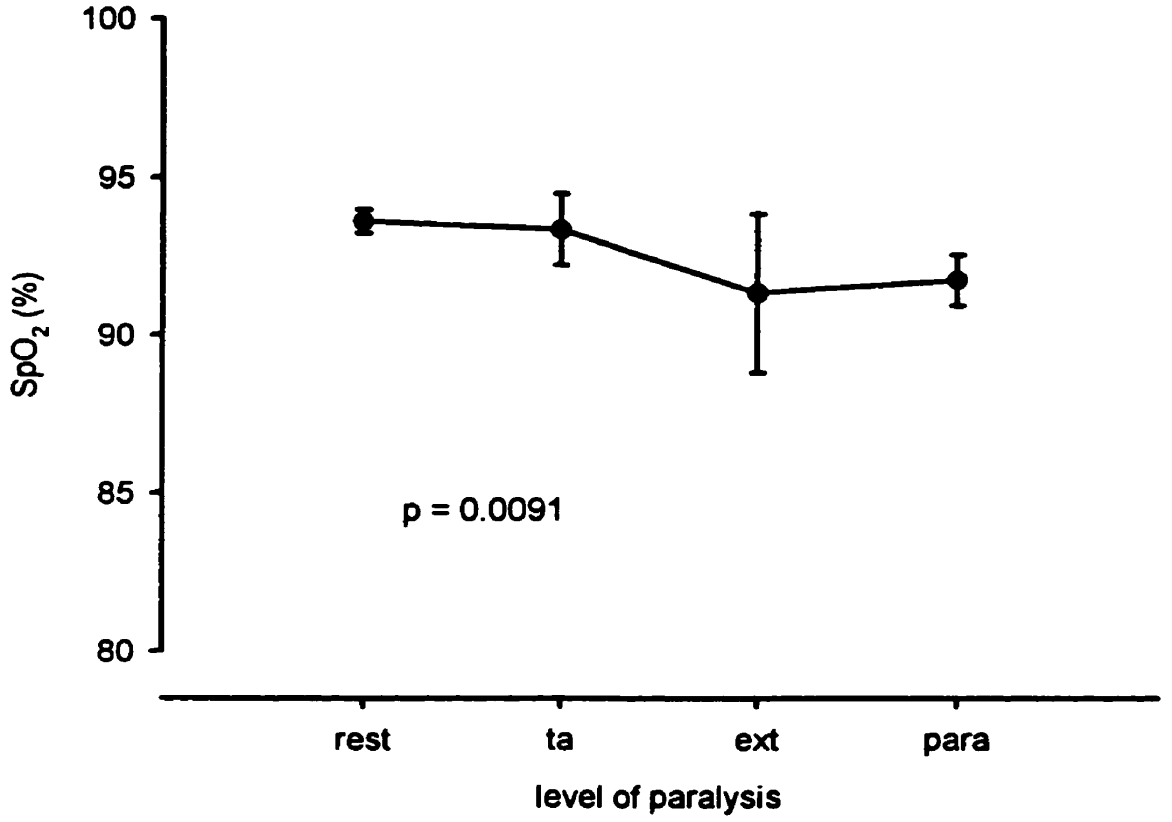

Figure 5: The effect of step wise ascending paralysis of transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on group mean (± SE) breath by breath pulse oximetry (SpO_2).

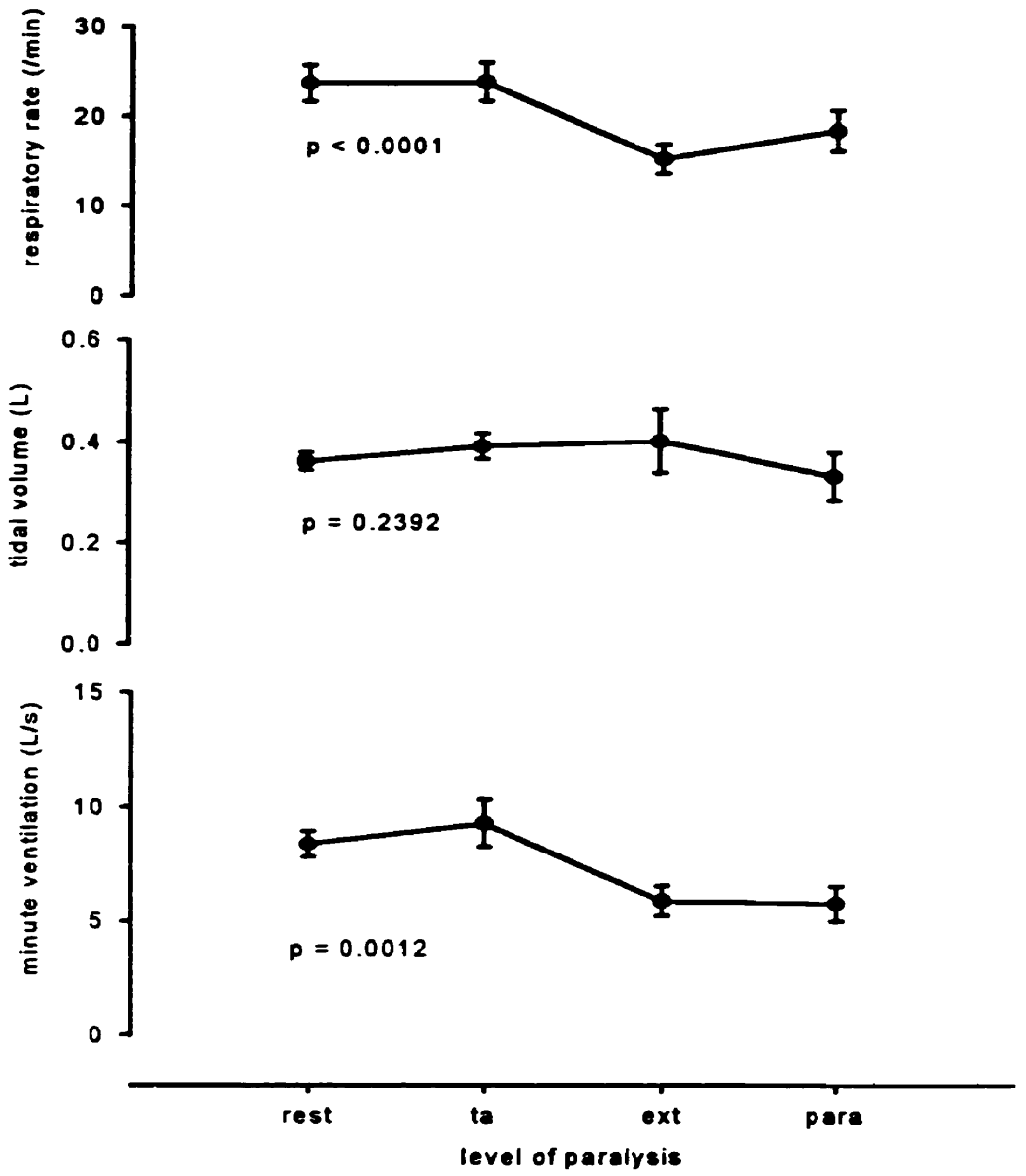

Figure 6: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on group mean (± SE) breath by breath respiratory rate, tidal volume, and minute ventilation.

Most of the decline in minute ventilation occurred following the onset of chest wall paralysis, that is following external intercostal paralysis. Most of the decline in minute ventilation resulted from the decline in respiratory frequency as tidal volume was largely preserved during ascending paralysis.

The effect of step wise ascending epidural anesthesia on corresponding group mean (± SE) breath by breath average inspiratory flow (V_T:T_I) values is displayed in Figure 7. Average inspiratory flow was used as an indirect measure of respiratory drive. Between rest and parasternal paralysis V_T:T_I decreased from 0.33 to 0.24 L/s with a corresponding p value of 0.0015. Most of the decline in average inspiratory flow occurred following the onset of chest wall paralysis, that is following external intercostal paralysis.

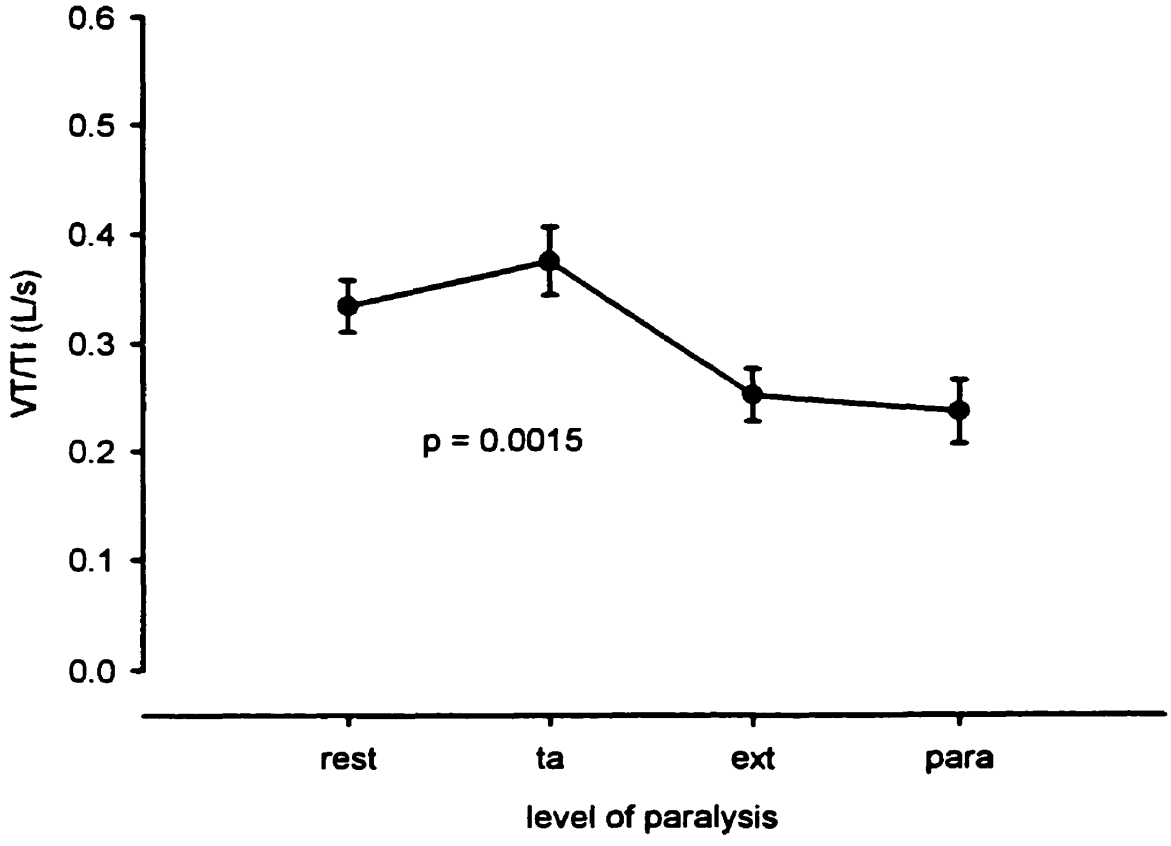

Figure 7: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on group mean (± SE) breath by breath average inspiratory flow (VT/TI).

Respiratory muscle compensation following acute paralysis

The recruitment and mechanical efficiency of preserved respiratory muscles during ascending epidural anesthesia was studied in ten dogs.

Respiratory muscle response to simulated paraplegia (abdominal paralysis)

The effects of ascending paralysis on individual and group mean breath by breath parasternal intercostal integrated moving averaged EMG activity and sonomicrometer shortening are shown in Figures 8 and 9 respectively. The effects of ascending paralysis on individual and group mean breath by breath costal diaphragm integrated moving averaged EMG activity and sonomicrometer shortening are shown in Figures 10 and 11 respectively.

Between pre-anesthetic recordings and abdominal paralysis group mean (± SE) integrated costal diaphragm EMG activity increased from 3.7 ± 0.6 to 4.5 ± 0.8 Vs with corresponding changes in group mean (± SE) shortening from 1.8 ± 0.7 to 3.0 ± 1.3 % (Figures 8 and 9). Between pre-anesthetic recordings and abdominal paralysis group mean (± SE) integrated parasternal intercostal EMG activity remained stable between 3.7 ± 0.4 to 4.0 ± 0.4 Vs with correspondingly small changes in group mean (± SE) shortening from 3.4 ± 0.7 to 3.6 ± 1.3 %

(Figures 10 and 11). Simulated paraplegia mimicked by abdominal epidural blockade resulted in modest diaphragm recruitment and largely unchanged parasternal activity.

Respiratory muscle response to simulated low quadriplegia (external intercostal paralysis)

Following external paralysis parasternal EMG activity did not increase with variable individual parasternal sonomicrometer shortening responses. Usable chest wall signals were fewer than surviving diaphragm signals (Figures 8 and 9). Group mean costal diaphragm EMG activity and sonomicrometer shortening both increased above abdominal paralysis levels (Figures 10 and 11).

Respiratory muscle response to simulated high quadriplegia (parasternal intercostal paralysis)

Following parasternal paralysis parasternal EMG activity and sonomicrometer shortening both substantially decreased (Figures 10 and 11). Group mean (± SE) costal diaphragm EMG activity further increased to 8.0 ± 1.1 Vs with corresponding increases in sonomicrometer shortening to 4.8 ± 1.8 % (Figures 8 and 9). Simulated diaphragm sparing quadriplegia mimicked by extending

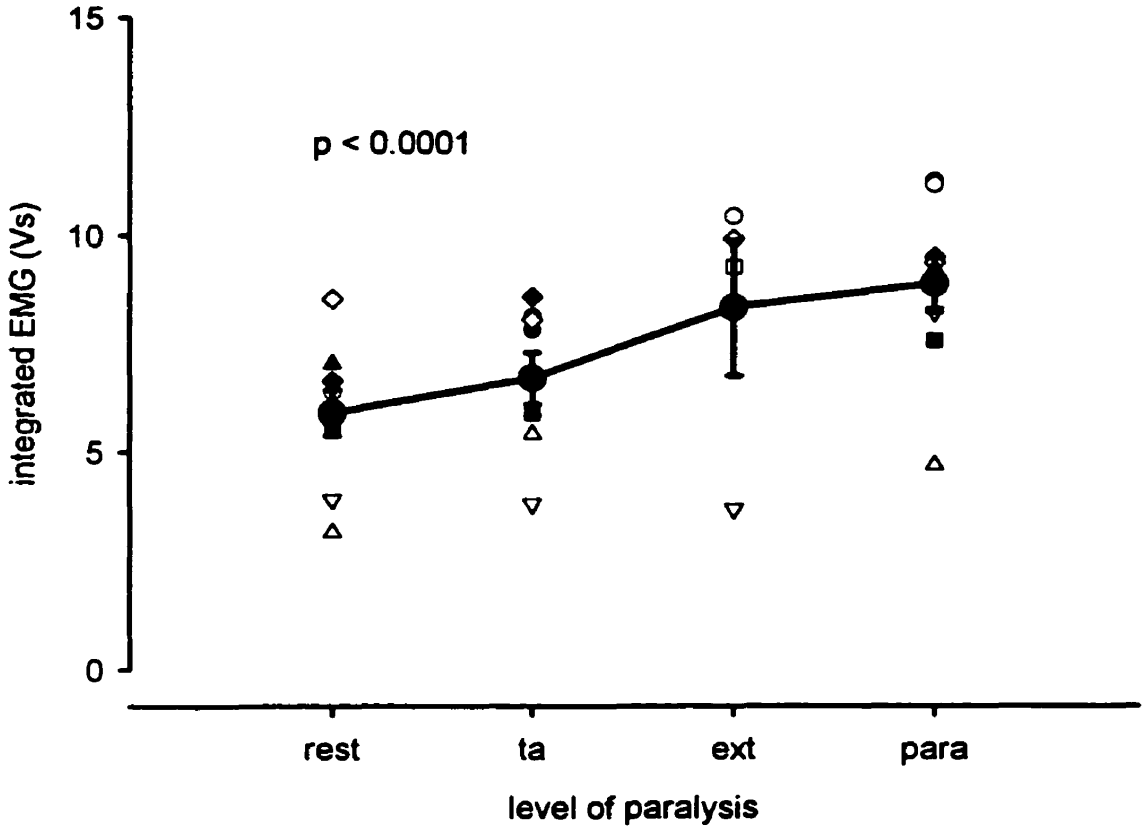

Figure 8: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on individual (small symbols) and group mean (± SE, line) breath by breath integrated moving averaged costal diaphragm EMG.

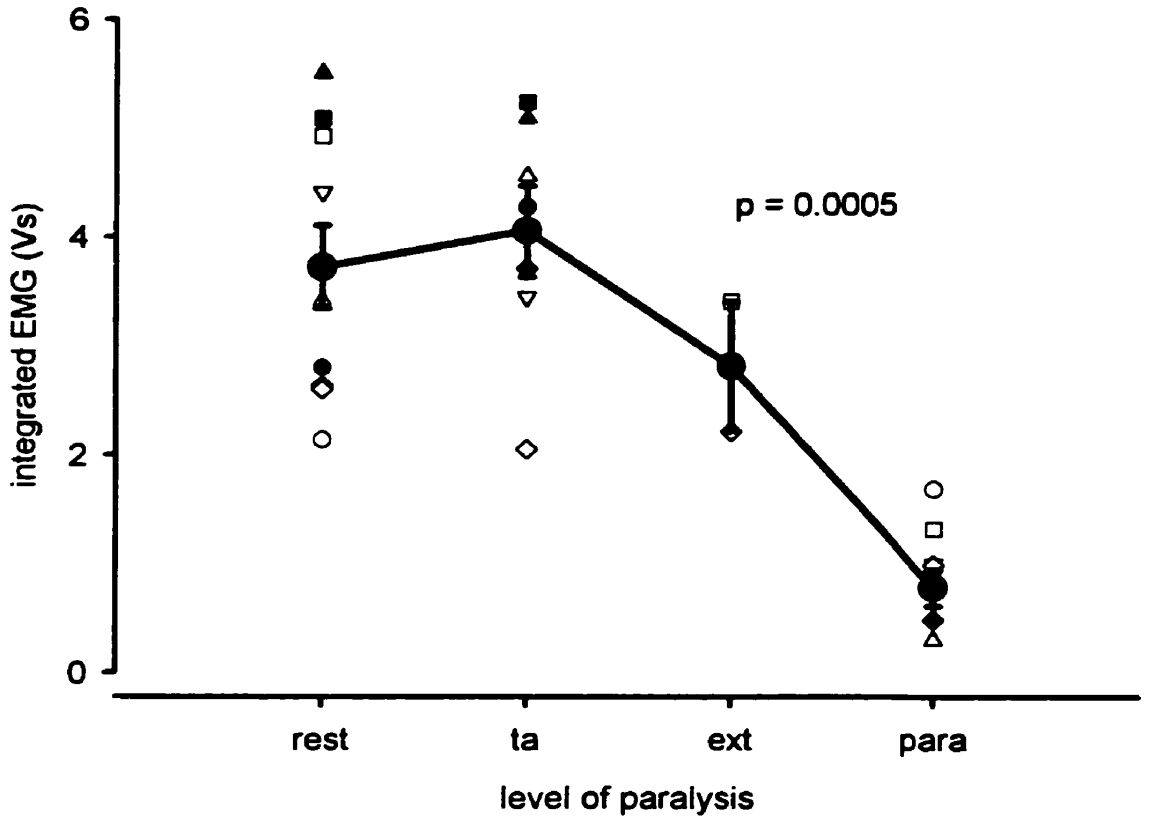

Figure 9: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on individual (small symbols) and group mean (± SE, line) breath by breath integrated moving averaged parasternal intercostal EMG.

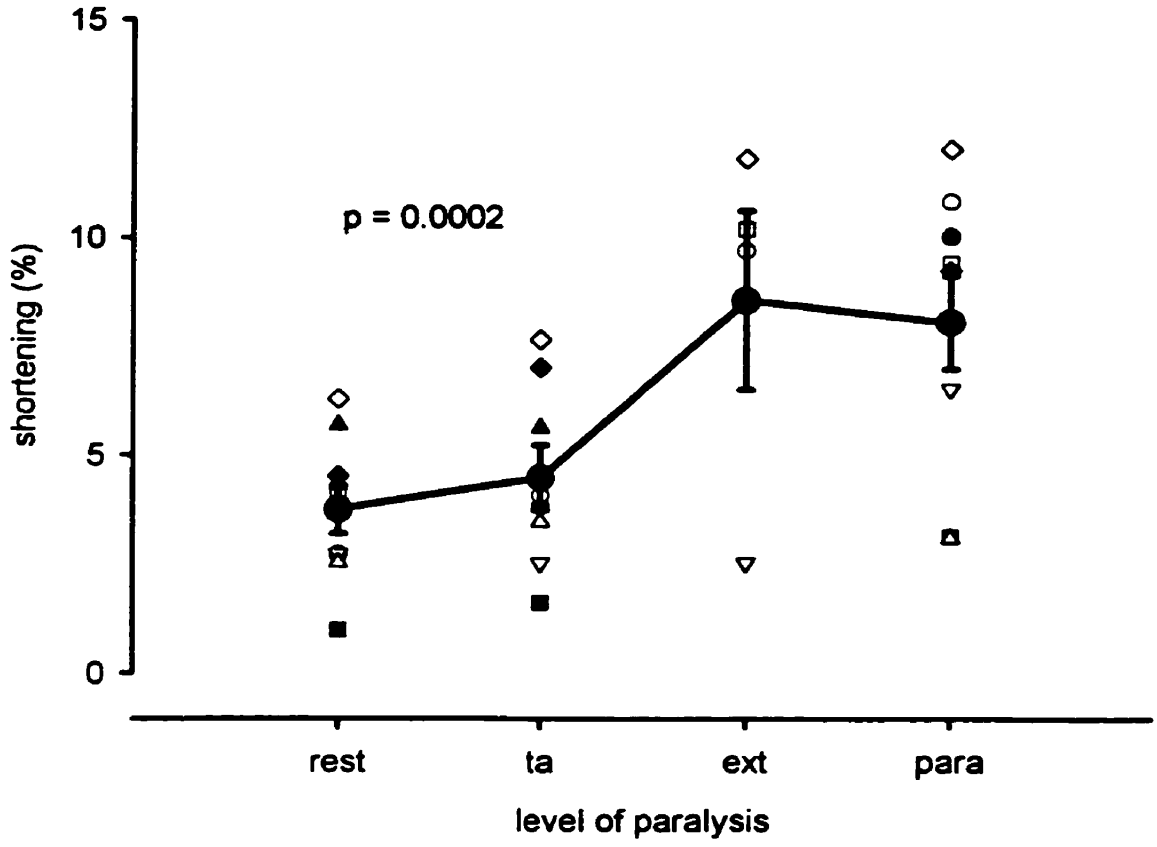

Figure 10: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on individual (small symbols) and group mean (± SE, line) breath by breath costal diaphragm sonomicrometer shortening from resting end-expiratory length.

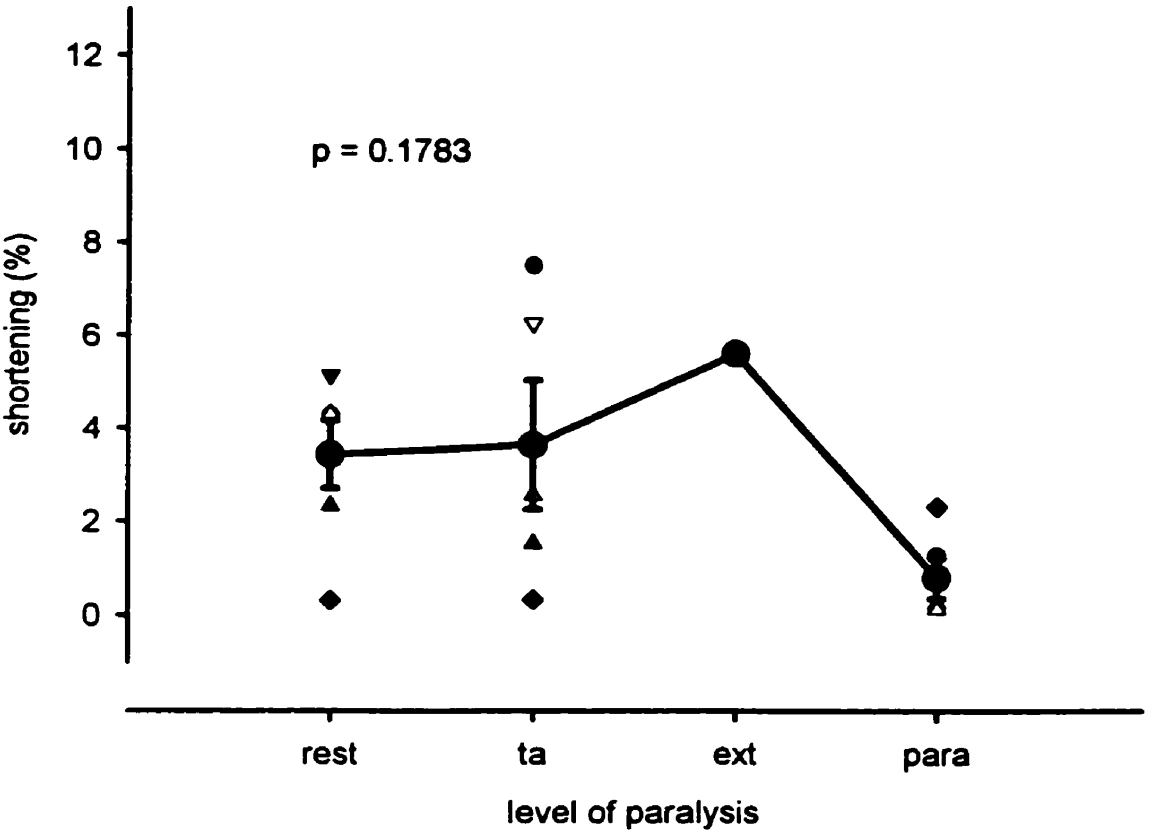

Figure 11: The effect of ascending paralysis of the transversus abdominus (TA), external intercostal (EXT), and parasternal intercostal (PARA) muscles on individual (small symbols) and group mean (± SE, line) breath by breath parasternal intercostal sonomicrometer shortening from resting end-expiratory length.

abdominal to parasternal intercostal epidural blockade resulted in further diaphragm recruitment.

Contraction properties of the diaphragm with ascending paralysis

The percentage of maximal air flow after each 5% of the total breath time (T_{TOT}) was plotted against the percentage of maximal costal EMG activity after each 5% of T_{TOT} in a representative subject (Figure 12). In this subject recordings were made before any epidural blockade (rest), following abdominal epidural blockade (abd), and following parasternal intercostal epidural blockade (para). For each set of airflow and costal EMG profiles the origin of inspiration (IO), the point of peak inspiratory flow (I_{MAX}), and the origin of expiration (EO) were identified.

The first point for each profile represents the mean of the first 5% of the breath cycle IO values are greater than zero for each pair of profiles (Figure 12). For similar IO air flow values the corresponding costal EMG value was much greater at the parasternal level of paralysis than at either before any paralysis or following abdominal paralysis (Figure 12).

The first point for each profile represents the mean of the first 5% of the breath cycle IO values are greater than zero for each pair of profiles (Figure 12). For similar IO air flow values the corresponding costal EMG value was much greater

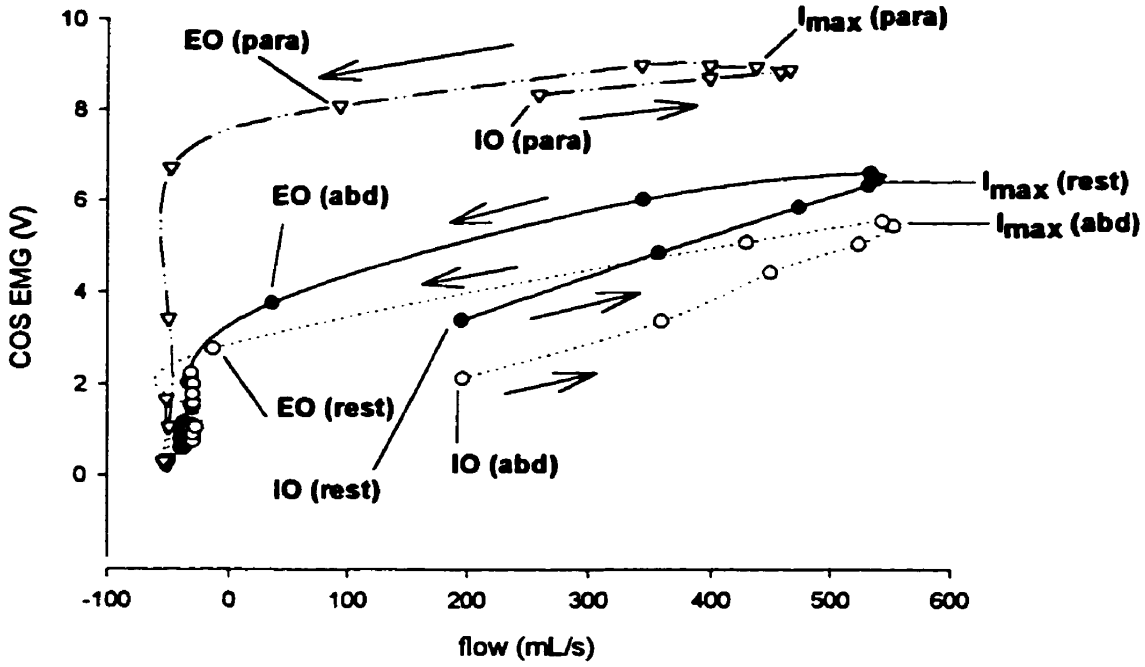

Figure 12: Illustrative intrabreath contraction properties of peak differential moving averaged diaphragm EMG referenced to airflow at rest, following abdominal paralysis (abd), and following parasternal intercostal (para) paralysis in a representative subject.

Abbreviations: IO = onset of inspiration, I_{MAX} = point of peak inspiratory flow, EO = expiratory origin, rest = anesthesia free quiet breathing, abd = following ascending transversus abdominus paralysis, and para = following ascending parasternal intercostal paralysis.

at the parasternal level of paralysis than at either before any paralysis or following abdominal paralysis (Figure 12).

There was increased costal EMG activity at the onset of inspiration (IO) following chest wall paralysis. Peak inspiratory flow (I_{MAX}) was less following parasternal paralysis than before any or after abdominal paralysis (Figure 12). Simultaneously, costal EMG activity at I_{MAX} was greater following parasternal paralysis than before any or after abdominal paralysis (Figure 12). Peak inspiratory flow was reduced despite increased diaphragm EMG activity following chest wall paralysis. Airflow approached zero during the 5% interval of the breath cycle that included the origin of expiration (EO) (Figure 12). Simultaneously, costal EMG activity between I_{MAX} and EO was much greater following parasternal intercostal paralysis than before any or after abdominal paralysis (Figure 12). Between peak inspiratory flow (I_{MAX}) and the origin of expiration (EO) there was increased and sustained diaphragm EMG activity following chest wall paralysis.

Diaphragm recruitment was characterized by increased early inspiratory, enhanced peak inspiratory, and prolonged post-peak inspiratory diaphragm contraction.

Chapter Four: Discussion

Conscious epidural anesthesia as a model of acute spinal paralysis

Summary of results

A method of step wise ascending diaphragm sparing epidural anesthesia in an awake dog instrumented with both respiratory muscle EMG wires and sonomicrometers was developed. This method can be used to model the effects of diaphragm sparing spinal cord injury. Ablation of the abdominal muscles with preservation of the chest wall mimics acute paraplegia. Ablation of the abdominal and chest wall muscles with diaphragm preservation mimics acute high thoracic to low cervical quadriplegia. Ablation of the abdominal, chest wall, and diaphragm muscles cannot ethically be performed in conscious subjects since distress and dyspnea from respiratory failure would likely ensue.

The use of video fluoroscopy greatly aided positioning of the epidural catheter, and provided objective evidence of its final position within the epidural space (Figure 1). The injection of part of each anesthetic dose in the right lateral decubitus position and the subsequent injection of the remaining dose in the contralateral left decubitus position prevented asymmetrical onset of epidural

anesthesia (Figure 2). With serial injections controlled step wise ablation of tranversus abdominus, external intercostal, and parasternal anesthesia were achieved (Figure 3).

Prior acute studies of epidural anesthesia

Two other groups have also used epidural anesthesia to study respiratory muscle function. Warner, *et al.* (24) studied six intubated dogs under pentobarbital anesthesia instrumented with percutaneously-placed epidural catheters ending at the L4 to L5 interface, balloon esophageal and gastric manometers, and EMG wires (parasternal intercostal, triangularis sterni, scalene, and transversus abdominus). After resting recordings were made, etidocaine hydrochloride was injected until two sequential goals were achieved. First, the ablation of phasic transversus abdominus activity, and then, following a second set of recordings, ablation of all rib cage muscles with preservation of diaphragm activity. Diaphragm and rib cage displacements were derived from high speed three dimensional computed tomography measurements of thoracic volumes. The authors' main conclusions were that rib cage muscles were mechanically the most active during quiet expiration, and that breathing with only the diaphragm caused minimal rib cage displacement in this model. They also noted imprecision in the level of motor blockade, whose definition depended on the anatomic

separation of EMG wires, and asymmetrical motor blockade in two of the six dogs studied.

Brichant, *et al.* (25) studied 35 intubated mongrel canines with percutaneously-placed epidural catheters ending at the L1 to L2 interface. Balloon esophageal and gastric manometers were also placed. Multiple bilateral intercostal, tranversus abdominus, and diaphragm EMG wires were inserted. The latter were placed using a special introducer needle to minimize previously recognized inhibition of the diaphragm with surgical manipulation. Following resting recordings sequential boluses of lidocaine were injected into the epidural catheter until all tranversus, but not parasternal EMG activity was ablated. Following a second set of recordings further aliquots of lidocaine were injected into the epidural catheter until parasternal EMG activity was ablated. Initially asymmetric parasternal ablation was frequently observed, but this was subsequently corrected by tilting the dog toward the side of lesser motor blockade until the blockade became symmetrical. The effects of equal doses of intramuscular lidocaine after spontaneous reversal of epidural anesthesia, bilateral vagotomy, and CO_2 stimulated breathing were also studied in selected canines.

The authors' main conclusions were that paralysis of the abdominal muscles had no effect on tidal volume or diaphragm activity. Second, rib cage paralysis

resulted in diminished tidal volumes, increases in P_aCO_2, and increases in diaphragm EMG with unchanged swings in transdiaphragmatic pressures (ΔP_{di}). The authors also noted that sympathetic blockade from epidural anesthesia produced hypotension which could alter control of breathing.

Utility of the chronic model

Both of these acute experiments advanced the understanding of the relative contribution of respiratory muscles to ventilation under spinal paralysis. Both, however, studied acutely instrumented, intubated dogs under general anesthesia. Neither experiment can, therefore, control for the potentially confounding effects of general anesthesia or endotracheal intubation on ventilation. Conscious mammals can volitionally change their respiratory rate and tidal volume in response to changes in their respiratory systems and environments. Intubation may interfere with upper airway sensation and tone, both of which can affect ventilation. Neither experiment could confirm that acute instrumentation had not altered diaphragm function. Using a chronic, awake model with documented post implantation recovery of diaphragm function avoided these limitations in our protocol. The use of a chronic model also allows for serial inductions of epidural anesthesia in the same subject on different days.

In both acute experiments ΔP_{di} measurements were used to generally correlate changes in individual respiratory muscle EMG activity with an overall measure of respiratory system performance. In our protocol we are capable of measuring both individual respiratory muscle EMG activity and corresponding length changes as measured by sonomicrometry.

Utility of fluoroscopy

In neither acute experiment were measures to confirm the position of the epidural catheter within the epidural space documented. Although neuroradiologists use fluoroscopy to guide epidural steroid injections in patients with low back pain (53), a MEDLINE database search from 1966 to 1999 inclusive did not reveal a single report of fluoroscopy being used to guide epidural anesthesia catheter placement. With video fluoroscopy we found difficulties inserting the epidural catheter given the smaller canine intervertebral space and the cephalic orientation of canine thoracolumbar posterior spinal processes were minimized. Observing the characteristic tracking of dye through epidural space (Figure 1) also minimized the risks of paradural injection. Where precision in the level of epidural anesthesia is desired, fluoroscopy also allowed precise documentation of the catheter tip's position within the epidural space.

Utility of repositioning during anesthetic injection

In the first acute experiment assymetrical levels of motor blockade were noted, but not corrected. In the second acute experiment assymetrical levels of motor blockade were corrected only after they had occurred. We found that symmetrical anesthesia could be achieved by switching the dog's position between the right and left lateral decubitus positions during injection of the anesthetic agent into the epidural catheter (Figure 3).

Mechanisms of acute respiratory compromise in spinal paralysis

Summary of results

With step wise ascending epidural paralysis of abdominal, external intercostal, and parasternal intercostal muscles progressive increases in end tidal CO_2 (Figure 4) with modest oximetry desaturation (Figure 5) occurred. Most of these changes followed the onset of thoracic (external intercostal) paralysis. The observed rise in end tidal CO_2 has been previously shown capable of evoking a respiratory response in this dog model without spinal paralysis (54). Despite this elevation in end tidal CO_2, tidal volume was only preserved and significant bradypnea followed, again predominantly following paralysis of the chest wall (Figure 6). Corresponding decreases in minute ventilation followed decreases in respiratory rate (Figure 6). Average inspiratory flow, an indirect marker of

respiratory drive, decreased with ascending spinal paralysis (Figure 7). In response to acute paralysis there was an altered ventilatory response from the respiratory system.

Mechanisms of respiratory compromise in diaphragm sparing spinal paralysis

Bradypnea and decreased average inspiratory flow, an indirect marker of respiratory drive, both occurred despite increases in end tidal CO_2 and partial respiratory paralysis. All dogs were conscious and responsive during ascending epidural paralysis. All dogs should have also been capable of tachypnea to augment respiratory compensation, but instead bradypnea was noted. To further corroborate an abnormal ventilatory response progressive decreases in average inspiratory flow also occurred. In this model, appropriate mechanical and altered ventilatory responses followed thoracoabdominal paralysis.

Bradypnea in spinal paralysis

The functional purpose of the paradoxical decrease in respiratory rate with prolonged inspiratory and expiratory times following chest wall paralysis is elusive. Tidal volume is at best only maintained following chest wall paralysis, and the observed decrease in respiratory rate resulted in a failure to maintain minute ventilation. Bradypnea following acute thoracic spinal paralysis has also been observed in sedated children undergoing thoracic epidural anesthesia (55) and in a murine model of spinal shock (56). In the murine model bradypnea was

associated with increased levels of endogenous opioids and reversed with naloxone, an opioid antagonist. Bradypnea has also been induced by the epidural administration of lidocaine or xylazine, an α-adrenergic antagonsist, in llamas (57).

The exact mechanism of bradypnea in acute spinal paralysis requires further explanation. The bradypnea could be caused by loss of afferent, efferent, sympathetic, or other miscellaneous function with epidural anesthesia. Since most respiratory changes occurred only after chest wall paralysis in this model bilateral intercostal blockade could be used to isolate the effects of peripheral compared to spinal level blockade. Theoretically if dorsal and ventral blockade could be separately achieved then the respective effects of sensory and motor blockade could be tested. Giving an epidural adrenergic agent or a sympathetic agent could test the association of sympatholysis with bradypnea. Alternatively, peripheral cardiorespiratory parasympathetic blockade with topical airway anesthesia and vagotomy could be performed. The latter techniques would better distinguish the effects of loss of sympathetic tone from unopposed parasympathetic activity. Giving a narcotic antagonist to the paralyzed subject could test the association of endogenous opioids with bradypnea. Giving volumes of sterile isosmotic buffered saline equal to but in place of the volume of lidocaine used to achieve parasternal intercostal level paralysis could assess the effect of introducing volume into the epidural space. Administration of nasal

decongestants to relieve secondary rhinorrhea prior to epidural anesthesia could be used to study the effects of nasal obstruction on respiratory rate. Repeated epidural paralysis with general anesthesia could discern the effects of any conscious response to spinal paralysis on breathing pattern. Previous investigators (25) have administered intramuscular lidocaine of equal amount to that previously epidurally administered to achieve parasternal intercostal level of spinal paralysis. No change in respiratory pattern was noted following intramuscular lidocaine.

Clinical implications

Our model provides insight into potential mechanisms of acute respiratory failure in diaphragm sparing spinal cord injuries. Controlling for the effects of drugs and extra-spinal injuries an altered ventilatory response was noted. Unless appropriate monitoring and ventilatory support are provided, respiratory compromise can quickly occur without invoking other injuries or drugs following acute diaphragm sparing spinal paralysis. In patients with concomitant brain injury occult hypercarbia could aggravate neurological impairment. The detrimental respiratory effects of traumatic coma, sedation, pharmacological paralysis, and respiratory muscle impairment could aggravate any altered ventilatory response from acute spinal paralysis. Close observation, serial blood gases, supplemental oxygen, and the prescription of an appropriate mandatory minute ventilation would obviate the risks of an altered ventilatory response.

Inadequate ventilator alarm settings and an over reliance on traditional bedside spirometry could be hazardous where an occult altered ventilatory response exsists. By anticipating an altered ventilatory response appropriate management can be preemptively instituted.

Respiratory muscle compensation after acute diaphragm sparing paralysis

Summary of results

Using step wise ascending epidural anesthesia we mimicked acute paraplegia with abdominal blockade and acute quadriplegia by extending abdominal to parasternal blockade in an awake, chronically implanted dog model. Following abdominal blockade only modest diaphragm and parasternal intercostal recruitment occurred (Figures 8 to 11). Following external intercostal paralysis costal diaphragm, but not parasternal intercostal recruitment was observed. Following parasternal intercostal further diaphragm recruitment occurred. Diaphragm recruitment referenced to airflow was characterized by increased early inspiratory, enhanced peak inspiratory, and prolonged post-peak inspiratory diaphragm contraction (Figure 12).

Effect of abdominal paralysis on preserved respiratory muscles

Acute paraplegia mimicked by abdominal epidural blockade produced only modest diaphragm and parasternal intercostal recruitment. Kinematic observations of an acute human quadriplegic (18) and epidural abdominal blockade in anesthetized dogs (24) had also previously noted only minimal abdominal contributions to the maintenance of tidal volume. At rest observed diaphragm recruitment was modest compared to that observed with subsequent chest wall paralysis, and may have resulted from some lower chest wall impairment with abdominal blockade.

During resting breathing the abdominal muscles do not substantially contribute to the maintenance of ventilation. This is logical given the abdominal muscle is typically only intermittently active during during expiration in the dog. This model was unable to assess the effects of the loss of active expiration, especially cough, following abdominal paralysis. An impaired cough would prevent the expulsion of respiratory secretions and could worsen respiratory compromise following spinal injury by increasing physiologic dead space and ventilation-perfusion mismatch. Mechanical ventilation strategies that distend open airways and the suctioning of airway secretions fouling proximal airways may be required following the loss of active expiration. Active expiration could potentially also

shorten the expiratory time needed to restore lung volume to functional residual capacity. For a given respiratory rate, a shortened expiratory time would allow a longer inspiratory time to permit more effective ventilation. The bradypnea observed in this model was characterized by a relatively preserved inspiratory:expiratory time ratio (at rest 0.737 and following parasternal intercostal paralysis 0.657). Prolonging inspiratory time was not used to offset acute respiratory compromise at rest. Abdominal paralysis and the associated impairment of active expiration did not impair ventilation in the model at rest, but the period of observation was insufficient to assess the affect of impaired cough.

Effect of chest wall paralysis on preserved respiratory muscles

Acute quadriplegia mimicked by extending abdominal to external then to parasternal intercostal epidural blockade resulted in only slight, if any, changes in tidal volume. Diaphragm recruitment, when compared to prior abdominal recordings, was characterized by large increases in EMG activity at the beginning of inspiration, at peak inspiration, and following peak inspiration. The increases in early and peak inspiratory diaphragm activity may overcome changes in diaphragm shape with abdominal wall flaccidity and the added mechanical disadvantage imparted by the loss of paralyzed accessory inspiratory intercostal muscles. These observed substantial increases in post-peak inspiratory diaphragm activity may be needed to preserve functional residual capacity given progressive rib cage flaccidity. The observed magnitude of

diaphragm recruitment corresponds to similar values observed during extreme isocapnic hypoxic or hypercarbic breathing (54).

The lack of parasternal intercostal recruitment following caudal external intercostal paralysis is difficult to explain. The implants were only separated by a single interspace so partial parasternal intercostal level sensory, motor, or sympathetic anesthetic block may have occurred with external intercostal level paralysis. Given the small physical separation of the external and parasternal transducers afferent chest wall information provided by each may not be distinguished by the respiratory system in its subsequent efferent output to the parasternal intercostal muscle. The anterior chest wall may function as an integrated unit such that impairment of some of its muscles impairs the remaining muscles as well. There may also be ordered recruitment of inspiratory muscles. The ventilatory gains of increasing diaphragm recruitment may exceed those of recruiting the anterior chest wall. Anterior chest wall recruitment might be deferred until the maximum physiologically effective diaphragm recruitment has occurred. Given increased thoracic compliance and possible deformity of the chest wall with partial thoracic paralysis there may also be an unappreciated ineffectiveness of residual chest wall recruitment in maintaining ventilation. The failure of parasternal intercostal recruitment in response to partial chest wall paralysis remains unexplained.

In contrast to abdominal paralysis, ascending paralysis involving the chest wall significantly compromises ventilation. Bradypnea, but not the loss of tidal volume, was the principal cause of hypoventilation. The upper chest wall intercostal muscles did not appear to recruit in response to paralysis of more caudal muscles. Diaphragm recruitment was characterized by mechanically disadvantaged more rapid, more sustained, and more prolonged contraction to maintain peak inspiratory flow and tidal volume. These three insults paradoxically produced respiratory compromise in a conscious mammal able to sense changes in lung volume, sense changes in arterial carbon dioxide tension, and recruit preserved inspiratory muscles whose reserve would likely be sufficient to maintain ventilation. The respiratory compromise observed in this model could result from the loss of afferent thoracoabdominal feedback, otherwise altered central control of ventilation, or both.

The effects of mechanically disadvantaged diaphragm contraction on the kinematics of the thoracic cavity, muscle structure, and muscle biochemistry may be significant. Diaphragm distortion may reduce inspiratory capacity. Serial rapid, strong, and sustained contractions of the diaphragm could shear myofibrils and generate secondary inflammation thereby progressively compromising diaphragm function. Oxygen delivery to the diaphragm may over time be insufficient to maintain aerobic metabolism with the exaggerated diaphragm contraction observed following chest wall paralysis. If aerobic metabolism fails

the diaphragm's energy requirements would be met by anaerobic metabolism. The resulting lactic acidosis would aggravate the systemic acidosis already generated by respiratory compromise, could not be corrected given pre-exsisting respiratory impairment, and would shift oxygen-hemoglobin desaturation. Bradypnea and disadvantaged diaphragm function following chest wall paralysis would also be aggravated by the impairment of cough and ability to actively alter expiratory time with concomitant abdominal paralysis. Following thoracoabdominal paralysis there is a high multifactorial risk of respiratory failure.

Limitations of protocol

At each level of paralysis only 15 to 30 minutes were available to make all recordings before the achieved level of motor blockade began to recover or further anesthetic was needed to maintain and extend the epidural block. This limited study of the temporal evolution of respiratory compensation at each level of paralysis.

Further studies

Work is presently ongoing with this model to further characterize the respiratory compensation following spinal paralysis to mechanically loaded, CO_2 stimulated, and isocapnic hypoxic breathing. During such experiments opioid antagonists and α-adrenergics could be administered to further clarify the mechanism of paradoxical bradypnea following spinal paralysis.

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