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Effects of mechanical unloading/loading on respiratory loop gain and periodic breathing in man[1]

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Abstract

We investigated the effect of mechanical unloading and loading on Cheyne–Stokes respiration (CSR) in seven intubated patients with preexisting CSR. For mechanical loading patients had to breathe against the resistance of the endotracheal tube. For mechanical unloading patients were supported with a volume-proportional pressure support in the proportional assist ventilation (PAV) mode whilst the flow-dependent (nonlinear) endotracheal tube resistance was continuously compensated for by means of the automatic tube compensation (ATC) mode. Mechanical unloading aggravated CSR as revealed by a prolongation of apnea time and by an increase in the so-called strength index whereas mechanical loading shortened apnea time and decreased strength index. To test whether the observed changes are caused by the effect of mechanical unloading/loading on respiratory loop gain (relationship between minute ventilation and arterial CO_2 tension), the response of respiratory loop gain on mechanical unloading/loading was determined in five healthy subjects (without CSR). In each subject, mechanical unloading increased respiratory loop gain whereas mechanical loading decreased it.

Keywords: Control of breathing, periodic breathing; Mammals, humans; Mechanics of breathing, assisted ventilation, mechanical loading, unloading; Patterns of breathing, Cheynes–Stokes

1. Introduction

Using in tracheally intubated, spontaneously breathing patients the newly introduced automatic tube compensation (ATC) mode (Fabry et al.,

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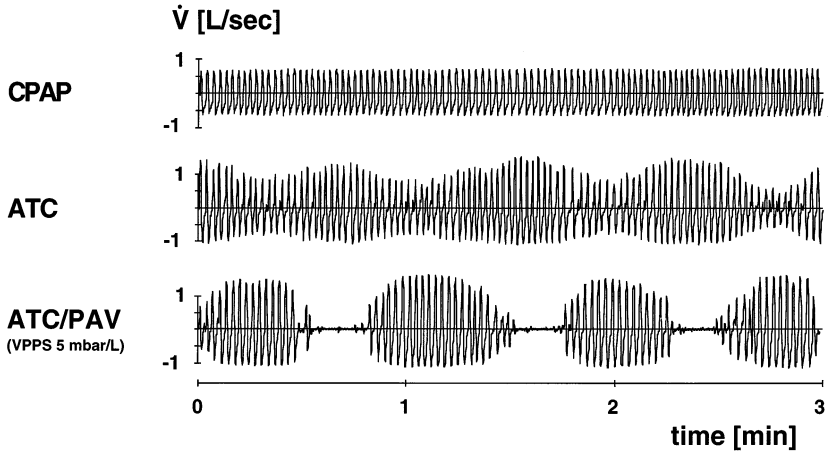

Fig. 1. Flow versus time tracings in a tracheally intubated, spontaneously breathing patient. Whereas the breathing pattern is very regular in the continuous positive airway pressure (CPAP) mode, periodic breathing becomes visible in the automatic tube compensation (ATC) mode. With additional volume proportional pressure support (VPPS) in the proportional assist ventilation (PAV) mode periodic breathing turns to the typical Cheyne–Stokes breathing pattern.

1994), which continuously compensates for the flow-dependent, nonlinear resistive load of the endotracheal tube (ETT) during inspiration and expiration, we observed periodic breathing in 42% and Cheyne–Stokes respiration (CSR; i.e. periodic breathing with apnea) in 18% of patients (Haberthür et al., 1995). Supporting these patients with volume-proportional pressure support (elastic unloading) in the proportional assist ventilation (PAV) mode (Tylor and Grape, 1962; Younes et al., 1987, 1992) in addition to ATC, periodic breathing was aggravated in such a way that apnea phases developed or preexisting apnea phases were prolonged. In contrast, when these patients breathed without any pressure support against the ETT resistance in the continuous positive airway pressure (CPAP) mode (resistive loading), periodic breathing and CSR disappeared or lessened (Fig. 1).

The occurrence of periodic breathing and CSR has been explained by the nature of the respiratory control system as a closed loop system with chemical (and neuronal) feedback loops (Guyton et al., 1956; Milhorn and Guyton, 1965; Longobardo et al., 1966; Grodins et al., 1967; Cherniack et al., 1979; Khoo et al., 1982; Longobardo et al., 1982; Dempsey and Skatrud, 1986; Chapman et al., 1988). Any closed loop system can be characterized by the overall steady state gain which is given by the change in output divided by the change in input. In the chemical respiratory control system, the overall steady state gain (referred to as respiratory loop gain) is defined by changes in minute ventilation in response to changes in arterial carbon dioxide tension (Pa_{CO_2}). Mathematical models of the human respiratory control system (Milhorn and Guyton, 1965; Longobardo et al., 1966; Grodins et al., 1967; Khoo et al., 1982; Longobardo et al., 1982) and studies in experimental animals (Guyton et al., 1956; Cherniack et al., 1979) and humans during sleep (Chapman et al., 1988) have shown that increasing the respiratory loop gain produces oscillations in breathing, i.e. periodic breathing or CSR. Increased respiratory loop gain can be produced either by increasing respiratory controller gain or by increasing controlled system gain (Chapman et al., 1988) whereby respiratory controller gain depicts changes in neuronal output in response to changes in Pa_{CO_2} and controlled system gain represents changes in minute ventilation in response to changes in neuronal output. In this context, controlled system gain is determined by the gain of the ventilatory muscles and thus serves as a measure for the effectiveness of the ventilatory muscles.

As suggested by animal and human studies (Lourenço et al., 1966; Kelsen et al., 1973; Orth-

ner and Yamamoto, 1974; Altose et al., 1976; Sidney and Poon, 1995), mechanical loading decreases controlled system gain (i.e. the gain of the ventilatory muscles). Although neuronal output increases during mechanical loading the relation between changes in Pa_{CO_2} and neuronal output (i.e. the respiratory controller gain) remains unchanged (Altose et al., 1976). As a net result, respiratory loop gain decreases with mechanical loading.

The effect of mechanical unloading on respiratory loop gain has not been thoroughly investigated yet. We hypothesized that mechanical unloading increases respiratory loop gain by increasing controlled system gain. Furthermore, we hypothesized that the increase in respiratory loop gain is the principal cause for the aggravation of periodic breathing observed during volume-proportional pressure support (elastic unloading) in the PAV mode, whereas the diminution of periodic breathing during CPAP ventilation (resistive loading) is the result of a decreased respiratory loop gain.

Our study was designed (1) to determine the effect of mechanical unloading and mechanical loading on the severity of CSR in patients, and (2) to test in healthy subjects (i.e. without CSR) whether mechanical unloading increases and mechanical loading decreases respiratory loop gain.

2. Methods

The effect of mechanical unloading/loading on respiratory loop gain was studied in five healthy, awake subjects (without CSR). The effect of mechanical unloading/loading on periodic breathing was examined in seven tracheally intubated, spontaneously breathing patients with stable CSR.

2.1. Volunteers and protocol

Five healthy males aged 26–39 years were studied. All subjects were nonsmokers and free of cardiopulmonary diseases. Procedures employed in the study were approved by the Ethics Committee of the University of Basel and written informed consent was obtained from all volunteers.

For elastic unloading a modified Evita 1 ventilator (Fabry et al., 1994) was used to support subjects with a volume-proportional pressure support. The level of volume-proportional pressure support was 6–8 mbar/L. For resistive loading, subjects breathed against the inspiratory and expiratory (nonlinear) resistance of an ETT of 8.0 mm internal diameter (ID) and 31 cm length with a resistance of 6.8 mbar·sec/L at a flow of 1 L/sec (Guttmann et al., 1993).

In order to ensure similar conditions during different levels of mechanical unloading/loading, subjects were connected to the ventilator and the ETT throughout the study. During resistive loading subjects breathed against the ETT resistance without ventilatory support (CPAP mode at zero pressure, ZEEP). During non-loaded breathing (i.e. without mechanical unloading/loading) the ETT resistance was continuously compensated for by means of the ATC mode. Finally, during elastic unloading subjects received the volume-proportional pressure support in addition to ATC (ATC/PAV).

Subjects were seated in the upright position throughout the investigation. They were connected to the ventilator via a mouthpiece, an artificial trachea (Guttmann et al., 1993), the ETT and a heated pneumotachograph. Nasal breathing was prevented by a nose clip. Mechanical loading and unloading was quantified by determining additional and reduced work of breathing (see below). Respiratory loop gain was determined by measuring minute ventilation at three different Pa_{CO_2} levels in each ventilatory mode (i.e. during resistive loading in the CPAP mode, during non-loaded breathing in the ATC mode, and during elastic unloading in the ATC/PAV mode). Different levels of Pa_{CO_2} were achieved by having the subjects breathe three different mixtures of CO_2 (4.0, 5.0, 5.5% CO_2, in 21% O_2, N_2). All measurements were performed during steady state conditions, i.e. after an equilibration period of at least 15 min for each step of investigation.

2.2. Patients and protocol

The quantitative effect of mechanical unloading/loading on periodic breathing was examined

in seven tracheally intubated, spontaneously breathing patients showing regular CSR. The study protocol was approved by the Ethics Committee of the University of Basel and informed consent was obtained from the closest available relative.

Table 1 summarizes the characteristics of the seven patients. All patients were tracheally intubated by the transoral route and were connected to the modified Evita 1 ventilator (Fabry et al., 1994). Prior to the investigation patients breathed spontaneously in the ATC mode and received a positive endexpiratory pressure (PEEP) of 5–10 mbar and supplemental inspiratory oxygen of 30–40% in order to maintain Pa_{O_2} above 10 kPa. As shown in Table 1, all but one patient (patient VA) displayed restricted cardiac function and all showed impaired cerebral function at the time of investigation, either due to neurological disturbances ($n = 2$) or due to sedation ($n = 5$). The overall level of vigilance, as assessed by clinical observation, did not change during the time of investigation.

After assessment of CSR over 5–10 min in the ATC mode, we investigated patients under CPAP and ATC/PAV. Since CSR in the CPAP mode disappeared in three of the seven patients, we used (instead of a level of loading with CPAP) a second level of unloading with ATC/PAV in these patients (ATC, ATC/PAV level 1, ATC/PAV level 2). The extent of the volume-proportional pressure support in the ATC/PAV mode was set at a level as high as possible in order to achieve high levels of mechanical unloading. Dependent on a patient's ventilatory demand and on the ventilator's maximal gas flow delivery of 2 L/sec, the extent of volume-proportional pressure support was 4–5 mbar/L and 6–10 mbar/L for ATC/PAV level 1 and ATC/PAV level 2, respectively. For entry into the study a regular CSR pattern had to be present during each level of mechanical unloading/loading. CSR was defined as regular if apnea time varied by less than 20%.

At each level of unloading/loading, assessment of CSR was started after an equilibration period of about 10 min. CSR was determined over a period between 5 and 10 min. Mechanical unloading and loading was quantified in terms of reduced and additional work of breathing as described below.

2.3. Measurements

In the volunteer study, gas flow was measured using a heated Fleisch No. 2 pneumotachograph which was placed at the outer end of the ETT. Airway pressure (P_{aw}) was measured between the pneumotachograph and the outer end of the ETT. The artificial trachea was placed between the inner end of the ETT and the mouthpiece. The pressure measured in this artificial trachea is referred to as P^*_{trach}. Pressure sensors for measuring P_{aw} and P^*_{trach} (32NA-005D: ICsensor; Milpitas, CA) and a differential sensor for measuring gas flow (CPS 10: Hoffrichter; Schwerin, Germany) were close to the ETT in order to achieve good signal quality and short response time with respect to temporal resolution. Expiratory CO_2 fraction was measured using a mainstream infrared absorption CO_2 analyzer (Siemens 930, Siemens-Elema, Solna, Sweden). Pulse oximetry was used to monitor O_2 saturation (Nellcor N-100, Nellcor Inc., Hayward, CA). Inspiratory and end-tidal CO_2 concentrations were measured using a respiratory mass spectrometer (Centronics 200 MGA, Centronic Medical, Croydon/UK) connected to the airways at the proximal end of the pneumotachograph via a capillary. Transcutaneous CO_2 and O_2 tension were measured to estimate Pa_{CO_2} and Pa_{O_2} (MicroGas 7640, Kontron Instruments, Watford/UK). All signals were digitized with 12 bit resolution and stored at a rate of 100 Hz in a computer for off-line analysis.

In the patient study, the same setup was used with the exception that patients were tracheally intubated and, consequently, there was no need for a mouthpiece and an artificial trachea. P_{trach} was measured by introducing a 1.4 mm ID catheter with multiple side holes and no end hole (K-33: Baxter, Trieste, Italy) into the ETT with its tip 3 cm outside the tip of the ETT (Guttmann et al., 1993). In one patient (patient GU) arterial blood samples were obtained at maximum ventilation and during apnea in the ATC/PAV mode with volume-proportional pressure support of 10 mbar/L.

Table 1
Patient characteristic

Patient	Age (years)	Sex	Relevant diagnosis and cause for intubation	Duration of intubation (h)	Sedative therapy	Ramsay sedation score[a]	Neurologic disorder	Cardiac function	Pa_{O_2}/Fi_{O_2} (kPa/%)	Pa_{CO_2} (kPa)	Lung injury score[b]
RR	70	M	Acute myocardial infarction with lung edema	66	Withdrawn >15 h	5	No	Decreased	30	5.9	1.5
TS	45	M	Coronary bypass grafting	18	Withdrawn >1 h	3	No	Decreased	54	5.7	0.3
GU	62	M	Cardiogenic shock, resuscitation	28	Withdrawn >3 h	4	No	Very decreased	33	4.5	0.3
ST	61	M	Meningococcal meningitis with encephalitis	69	No	4	Yes	Very decreased	62	4.3	0
MA	75	M	Mitral valve replacement due to severe insufficiency	16	Withdrawn >2 h	3	No	Very decreased	49	7.2	0
RE	68	M	Coronary bypass grafting	15	Withdrawn >5 h	4	No	Decreased	40	6.1	0
VA	65	F	Thalamic hemorrhage with rupture into ventricular system	102	No	2	yes	Normal	51	4.3	0

[a] Ramsay et al. (1974).
[b] Murray et al. (1988).

2.4. Off-line analyses

In the patient study, the severity of CSR was determined by both the length of the apnea intervals and the so called strength index, introduced by Waggener et al. (1984). According to this approach, strength index is calculated as follows: strength index = PT/(PT − AT), where PT denotes the total period time and AT the apnea time in seconds. The beginning of a period was defined as the time of transition from the apnea phase to the resumption of ventilation. For each period of CSR, maximal minute ventilation ($V_{E_{max}}$) and mean minute ventilation ($V_{E_{mean}}$) were calculated as $V_{E_{max}}$ = maximal tidal volume · instantaneous respiratory frequency, and $V_{E_{mean}}$ = total ventilation during PT · 60/PT, respectively.

For patients and volunteers, the magnitude of mechanical unloading and loading was expressed in terms of reduced (WOB_{red}) and additional work of breathing (WOB_{add}), respectively. Reduced and additional work of breathing were calculated according to a method developed in our laboratory (Fabry et al., 1997). The concept behind then is the following: at the onset of the patient's inspiration, P_{trach} normally falls below the PEEP level due to the resistance of the tube and the demand-flow characteristics of the ventilator. The fall of P_{trach} below the PEEP level causes additional (or imposed) work of breathing (WOB_{add}) for the patient. Once pressure support has been triggered, P_{trach} increases. When P_{trach} rises above PEEP level, the ventilator reduces the work for the patient and that part is called reduced work of breathing (WOB_{red}). Consequently, WOB_{add} and WOB_{red} can be calculated as follows:

$$WOB_{add} = \int_{P}^{(} EEP\ P_{trach} < PEEP - P_{trach})\ dV$$

$$WOB_{red} = \int_{P}^{(}{}_{trach}\ P_{trach} > PEEP - PEEP)\ dV$$

where V denotes inspired volume above functional residual capacity. In order to obtain a net value for mechanical unloading/loading, the difference between WOB_{red} and WOB_{add} ($WOB_{red} - WOB_{add}$) was calculated breath by breath and averaged for each ventilatory mode.

To link mechanical unloading/loading to the respiratory loop gain in the volunteer study, the relationship between $WOB_{red} - WOB_{add}$ and respiratory loop gain was computed. To link mechanical unloading/loading to the severity of CSR in the patient study, the relationship between $WOB_{red} - WOB_{add}$ and apnea time and strength index, respectively, was calculated. Since these values showed a high interindividual variability, they were normalized to allow direct comparison among patients or volunteers. Normalization was done by setting the values for $WOB_{red} - WOB_{add}$, respiratory loop gain, apnea time, and strength index in the ventilatory mode with the lowest level of unloading (ATC or CPAP, respectively) to zero and calculating the difference to the corresponding values in the other ventilatory modes.

2.5. Statistical analysis

Statistical analyses were performed using SYSTAT, Version 5.2. Differences of parameters of interest were assessed by an analysis of variance for repeated measurements. In the volunteer trial, the dependent variables were the normalized values of the respiratory loop gain and $WOB_{red} - WOB_{add}$ in the CPAP, ATC, and ATC/PAV modes (three within factors, repeated). In the patient study, the dependent variables were the normalized values of apnea time, strength index, and $WOB_{red} - WOB_{add}$ in the CPAP, ATC, and ATC/PAV modes (three within factors, repeated). In both models, overall significance was expressed as the arithmetic mean of Greenhouse–Geisser's and Huynh–Feldt's adjusted P-values. Simple linear regression analysis was used to test the relationship between $WOB_{red} - WOB_{add}$ and respiratory loop gain (volunteer study) and the relationship between $WOB_{red} - WOB_{add}$ and strength index or apnea time (patient study). A two-sided α level of $P < 0.05$ was considered statistically significant. All values are expressed as mean ± 1 SD.

3. Results

3.1. Mechanical unloading/loading and respiratory loop gain (volunteer study)

With increasing levels of inspired CO_2, transcutaneously estimated Pa_{O_2} rose in all volunteers as a result of hypercapnea-related hyperventilation from 117 ± 14 mmHg (ATC; inspired $CO_2 = 4\%$) to 144 ± 17 mmHg (ATC/PAV; inspired $CO_2 = 5.5\%$). Transcutaneously estimated Pa_{CO_2} rose from 52.6 ± 1.8 mmHg (ATC/PAV; inspired $CO_2 = 4\%$) to 63.0 ± 1.4 mmHg (CPAP; inspired $CO_2 = 5.5\%$) whereby transcutaneously estimated Pa_{CO_2} was on average $14 \pm 4\%$ above the endtidal CO_2 concentration. With increasing levels of transcutaneously estimated Pa_{CO_2} minute ventilation rose from 21.8 ± 4.4 L/min (CPAP; inspired $CO_2 = 4\%$) to 47.0 ± 5.7 L/min (ATC/PAV; inspired $CO_2 = 5.5\%$).

Compared to ATC all five subjects uniformly displayed an increase in respiratory loop gain on mechanical unloading under ATC/PAV and a decrease in respiratory loop gain on mechanical loading by breathing against the ETT resistance in the CPAP mode ($F = 19.45$, $P = 0.008$) (Fig. 2). In four of the five volunteers (one excluded due to incomplete data acquisition), the quantitative relationship between mechanical unloading/loading ($WOB_{red} - WOB_{add}$) and respiratory loop gain is characterized by a slope of 0.63 L/(min·mmHg) per J/L ($r^2 = 0.70$; $F = 23.0$; $P < 0.001$) (Fig. 3). During this investigation no subject displayed CSR or periodic breathing, and we were not able to induce periodic breathing or CSR with high levels of PAV in the ATC/PAV mode (data not shown).

3.2. Mechanical unloading/loading and Cheyne–Stokes respiration (patient study)

The flow versus time tracings of Fig. 4 illustrate the effect of elastic unloading on CSR in a representative patient (patient RE): with rising levels of mechanical unloading (increasing levels of PAV) CSR was aggravated as demonstrated by a prolongation of apnea time.

The effect of mechanical unloading/loading on apnea time and on strength index are summarized for each patient in Fig. 5. Averaged for all patients, mechanical unloading (represented by increasing levels of $WOB_{red} - WOB_{add}$) prolonged apnea time ($F = 35.30$; $P < 0.001$) and increased strength index ($F = 37.85$; $P < 0.001$). Consequently, strength index and mechanical unloading are positively correlated with a slope of the corresponding regression line of 0.48 per J/L ($r^2 = 0.75$; $F = 60.49$; $P < 0.001$). Apnea time and mechanical unloading are positively correlated with a slope of 7.01 sec per J/L ($r^2 = 0.64$; $F = 35.02$; $P < 0.001$).

Table 2 depicts the ventilatory modes used for mechanical unloading/loading and the resulting effects on mean minute ventilation and mean endtidal CO_2 concentration as well as on maximal minute ventilation, and maximal and minimal endtidal CO_2 concentration.

O_2 saturation showed the well known paradoxical pattern (see: Tobin and Snyder, 1984; Younes, 1989) with the highest level during apnea and the lowest level during the ventilatory phase of a cycle (data not shown). In patient GU, in whom arterial blood samples were obtained at maximum ventilation and during apnea in the ATC/PAV mode, Pa_{O_2} was highest during the apnea phase (15.4 kPa) and lowest during the phase of increased ventilation (14.1 kPa) whereas Pa_{CO_2} was lowest during apnea (5.3 kPa) and highest during maximum ventilation (5.7 kPa). In the other patients, arterial blood samples were obtained only at study entry. As shown in Table 1, no patient (except patient VA) showed a hypocapnic Pa_{CO_2} level, which can cause exaggeration of CSR (Dempsey and Skatrud, 1986).

4. Discussion

The first aim of our study was to investigate in tracheally intubated patients with preexisting CSR the effect of mechanical unloading/loading on the severity of CSR. The results show that mechanical unloading using ATC/PAV aggravates CSR whereas mechanical loading in the CPAP mode lessens it. Preexisting CSR might have originated from prolonged circulation time caused by a de-

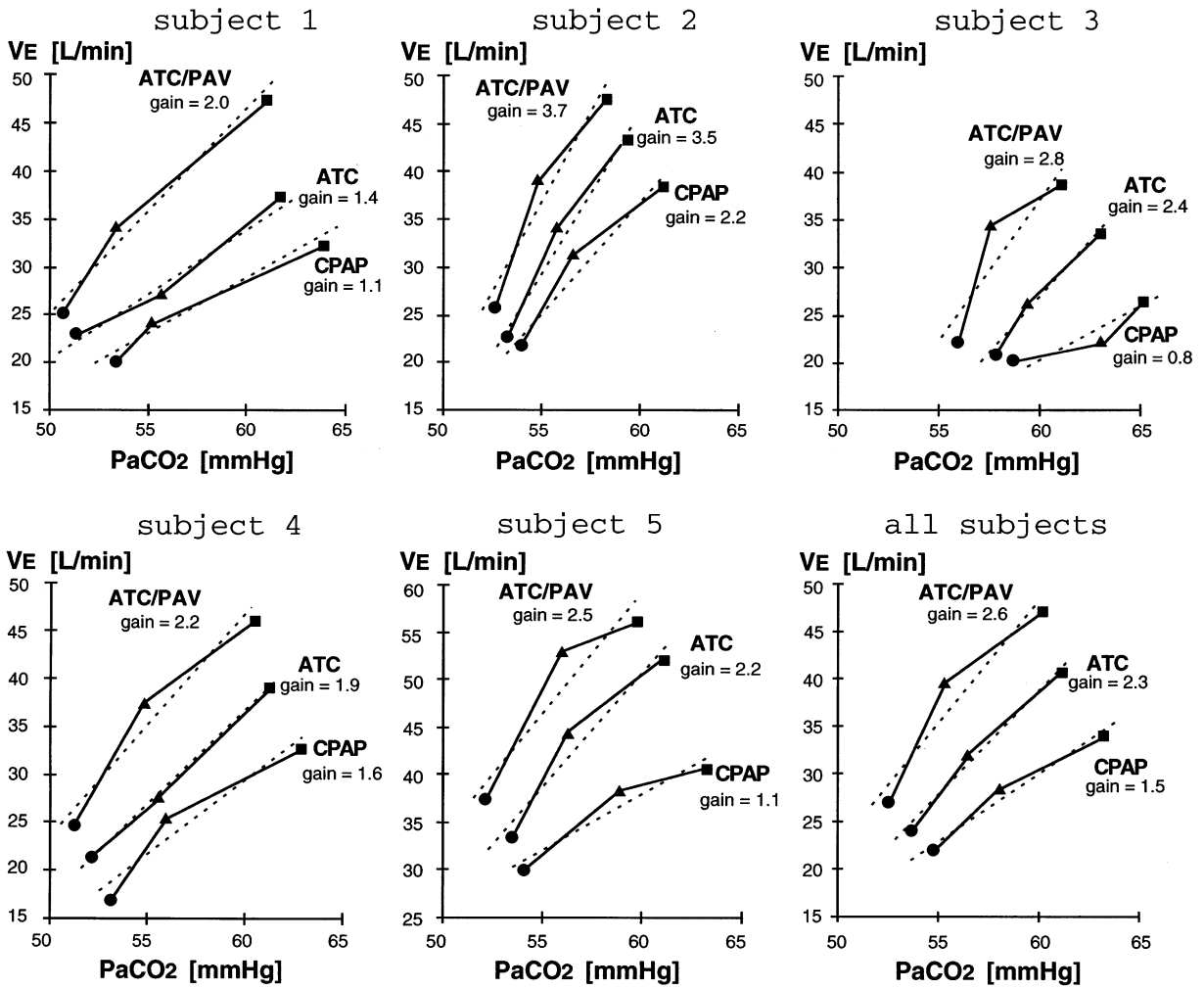

Fig. 2. Respiratory loop gain without mechanical unloading/loading (ATC), during mechanical loading (CPAP) and during mechanical unloading (ATC/PAV) in 5 healthy subjects. Respiratory loop gain corresponds to the slope of the regression line between minute ventilation (VE) and transcutaneously estimated Pa_{CO_2} at different inspiratory CO_2 concentrations (● = 4%; ▲ = 5%; n = 5.5%). Each subject showed an increase in respiratory loop gain under mechanical unloading (ATC/PAV) and a decrease in respiratory loop gain under mechanical loading (CPAP).

pressed cardiac function (Guyton et al., 1956) and from impaired cerebral function as a result of either the sedation therapy or the underlying neurologic disorder (see: Tobin and Snyder, 1984; Dempsey and Skatrud, 1986; Chapman et al., 1988; Younes, 1989). The finding that PAV aggravates the already preexisting periodic breathing pattern is of clinical importance, since periodic breathing, in particular CSR, can be associated with serious side effects, such as considerable fluctuations in oxygen saturation and marked blood pressure changes (see: Tobin and Snyder, 1984). The clinical importance is further strengthened by our observation that these side effects were worsened by increasing the level of PAV. Taking into account that periodic breathing has been observed in 42% and the typical CSR pattern in 18% of tracheally intubated, spontaneously breathing patients (Haberthür et al., 1995), further studies are needed to clarify the applicability of ATC/PAV in these patients. In our experience with more than 80 patients it is not possible to

induce periodic breathing by increasing the level of PAV, if periodic breathing is not present in the ATC mode (unpublished observations). This holds true for the five awake volunteers investigated in this study.

It may be argued that in susceptible patients ATC/PAV can only unmask periodic breathing otherwise masked by more controlled modes of ventilatory support but not intensify periodic breathing. This might be supported by the fact that ATC and ATC/PAV can unmask periodic breathing and CSR not being present in the pressure support ventilation (PSV) mode (Haberthür et al., 1995). However, some patients with periodic breathing or the CSR pattern (including the patient, whose tracings are shown in Fig. 1) displayed exactly the same pattern of periodic breathing after extubation as they did when intubated and under the ATC mode. They did not, however, show the pattern of aggravated periodic breathing after extubation as when intubated and under the ATC/PAV mode (Haberthür et al., 1996). It therefore appears that in tracheally intubated, spontaneously breathing patients with already present periodic breathing, either suppressed or masked, the true nature of periodic breathing becomes obvious with ATC and is intensified by PAV (i.e. by ATC/PAV). In contrast, periodic breathing is lessened or suppressed when the patient breathes against the resistance of the ETT in the CPAP mode.

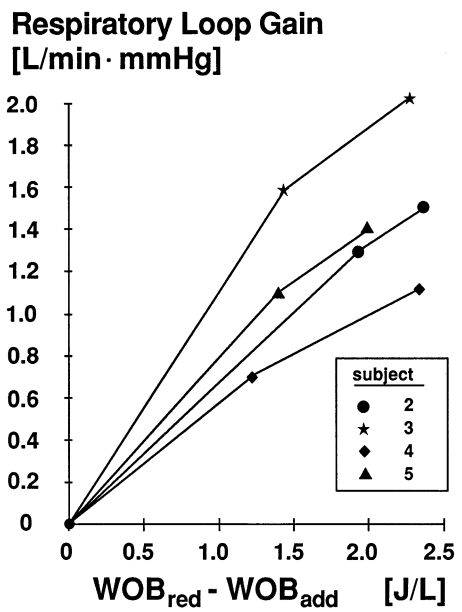

Fig. 3. Relationship between normalized values of mechanical unloading/loading (expressed in terms of $WOB_{add} - WOB_{red}$) and normalized values of respiratory loop gain in four healthy subjects. Increasing mechanical unloading (increase in $WOB_{add} - WOB_{red}$) is related with an increase in respiratory loop gain and vice versa. Averaged for all subjects the slope in this relation equals 0.63 L/(min·mmHg) per J/L ($r^2 = 0.70$; $F = 23.0$; $P < 0.001$).

The question then arises by which mechanism PAV aggravates and CPAP lessens periodic breathing. As mentioned earlier, in the closed loop system of chemical respiratory control any increase in respiratory controller gain or in controlled system gain produce instability in the system with oscillations in output. Since PAV unloads a patient from imposed mechanical load of his or her respiratory system by proportionally augmenting his or her muscular effort (Younes et al., 1992), PAV increases the gain of the ventilatory muscles and, consequently, PAV increases controlled system gain and, thus, respiratory loop gain.

To test this hypothesis, the effect of ATC/PAV and of CPAP on respiratory loop gain was investigated in five healthy subjects. The results of this study clearly show that respiratory loop gain increases by mechanical unloading in the ATC/PAV mode and decreases by mechanical loading in the CPAP mode. This result, however, substantially differs from that reported from Georgopoulos and coworkers (Georgopoulos et al., 1997) who did not found any significant effect of mechanical unloading on respiratory loop gain in healthy subjects. Several technical differences between the two studies could have accounted for the discrepant results: 1) The maximal amount of elastic unloading was 4 cmH_2O/L (assist 2) in the study of Georgopoulos whereas it was 6 to 8 cmH_2O/L in our study. 2) In the study of Georgopoulos the response time of the ventilator reported was 0.1 sec (which is roughly identical with the response time of our ventilator), but the response time of the entire setup (i.e. ventilator and rebreathing bag in box) would be longer. As a consequence, gas flow delivery to the subjects might be delayed,

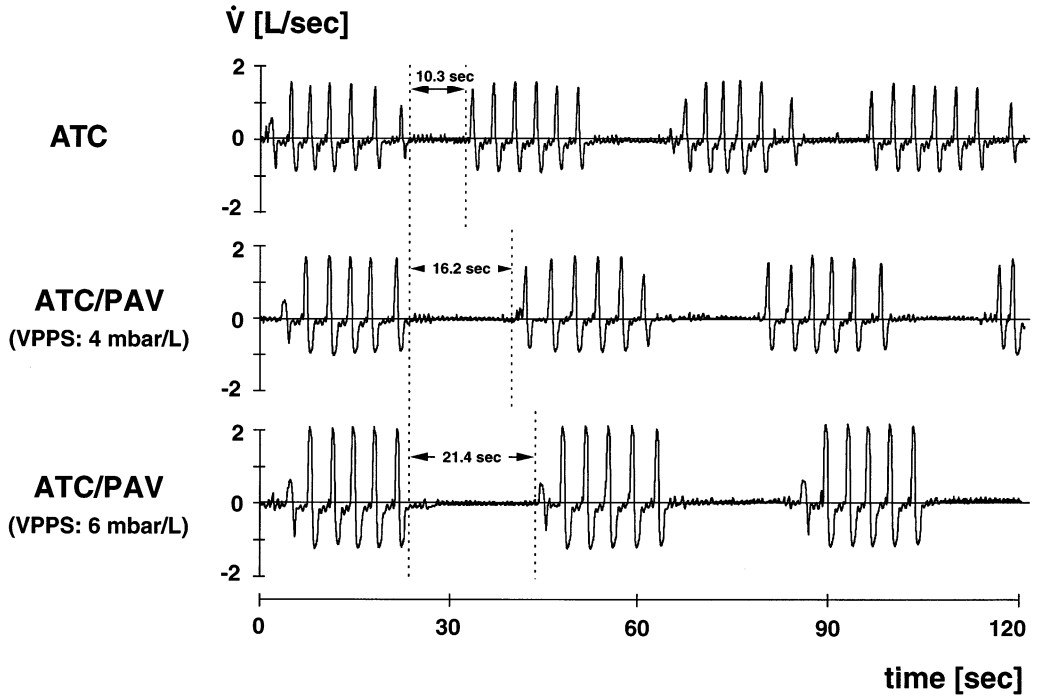

Fig. 4. Flow versus time tracings of a tracheally intubated, spontaneously breathing patient with Cheyne–Stokes respiration. With increasing levels of volume-proportional pressure support (VPPS) in the ATC/PAV mode Cheyne–Stokes respiration is aggravated as revealed by a prolongation of apnea time. Note that with increasing levels of VPPS inspiratory peak flow increases whereas the number of breathes during the ventilatory phases of Cheyne–Stokes respiration decreases.

especially during high gas flow demand at increased blood CO_2 concentrations. Delayed gas flow delivery in turn can decrease ventilation and, thus, prevent the otherwise resulting increase of the respiratory loop gain during mechanical unloading. And chief among these 3) the Read rebreathing method used by Georgopoulos and coworkers substantially differs from our method which becomes visible in the different duration of the protocol, i.e. 3 to 4 min for each level of unloading with the rebreathing technique in the Georgopoulos study compared to ≈ 15 min for each level of unloading with our method. This may explain (at least in part) the discrepant results between the two studies as demonstrated by Sidney and Poon (Sidney and Poon, 1995). Additionally, from a theoretical point of view there is no physiological reason why respiratory loop gain should be decreased by mechanical loading (as has been demonstrated by many investigators) whereas, vice versa, it should not be increased by mechanical unloading.

Due to ethical considerations, or death, or transfer to another hospital of two patients each, we were, unfortunately, not able to determine the effect of mechanical unloading on the respiratory loop gain in our patients with CSR. Nevertheless, our data suggest that the aggravation of periodic breathing or CSR by ATC/PAV is related to the effect of mechanical unloading on respiratory loop gain and that the attenuation of periodic breathing and CSR by the CPAP mode is related to the effect of mechanical loading on respiratory loop gain.

It can not be fully ruled out, however, that concomitant changes in CO_2 concentration brought by mechanical unloading/loading might have facilitate, at least in part, the observed changes in the severity of CSR. As shown in Table 2, mean ventilation increased and mean endtidal CO_2 concentration decreased with rising level of mechanical unloading in four of seven

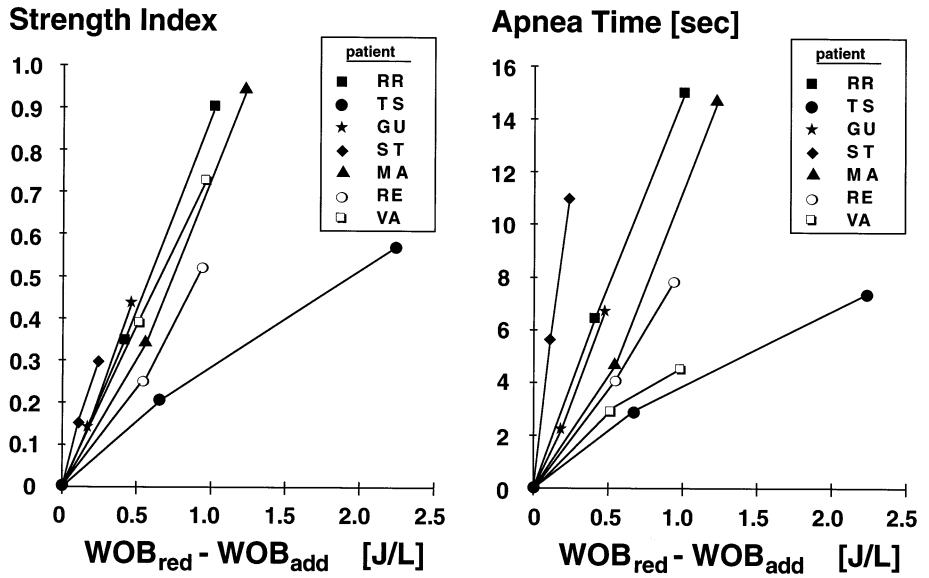

Fig. 5. Relationship between normalized values of mechanical unloading/loading (expressed in terms of $WOB_{add} - WOB_{red}$) and normalized values of strength index (left) and of apnea time (right) in 7 tracheally intubated, spontaneously breathing patients. Increasing mechanical unloading (increase in $WOB_{add} - WOB_{red}$) goes together with an increase of both strength index and apnea time of Cheyne–Stokes respiration. Averaged for all patients mechanical unloading and strength index are positively correlated with a slope of 0.48 per J/L ($r^2 = 0.75$; $F = 60.5$; $P < 0.001$) and mechanical unloading and apnea time with a slope of 7.01 sec per J/L ($r^2 = 0.64$; $F = 35.4$; $P < 0.001$).

patients (patients TS, ST, MA, RE). This might indicate that the observed changes in the CSR pattern were promoted by the concomitant changes in CO_2 concentration (see for example Steens et al., 1994), although mean endtidal CO_2 concentrations were still above hypocapnic levels. In the remaining 3 patients (patients RR, GU, VA), however, the level of mechanical unloading/loading and changes in mean ventilation and mean endtidal CO_2 concentration, respectively, are not matched indicating that the unloading/loading-related changes in CO_2 concentrations can not be the cause for the observed alterations in the severity of CSR. Other causes for both induction and amplification of periodic breathing and CSR (such as changes in vigilance or circulation time, etc.; see Younes, 1989) were not present throughout the study.

Pressure support for mechanical unloading can be applied not only in proportion to a patient's muscular effort (as given with PAV) but also with any form of pressure support (e.g. with a constant pressure support as in the PSV mode). According to our hypothesis, periodic breathing and CSR might as well be aggravated by increasing the level of pressure support in the PSV mode. In our experience, this was, however, the case in only a minority of intubated patients having periodic breathing or CSR in the ATC mode although they showed an amplification of periodic breathing and CSR using ATC/PAV. This apparent inconsistency can be explained by the nature of the ETT resistance which is not a constant but a nonlinear, flow-dependent resistive load. This means that the adequate pressure support for its compensation will vary with flow rate (Guttmann et al., 1993). Having highly variable flow rates in spontaneously breathing patients (from zero flow just before the beginning of inspiration to peak flow within and to zero flow at the end of inspiration) the ETT resistance can not be adequately compensated for with a constant pressure support as provided by the PSV mode (Fabry et al., 1997). Consequently, dependent on the preset level of the constant pressure support in the PSV mode and on the flow-dependent pressure drop across the

Table 2
Effect of mechanical unloading on ventilation and endtidal CO_2 concentration

Patient	Ventilatory mode	Minute ventilation (L/min)		ET_{CO_2} (%)		
		Mean	Maximal	Mean	Minimal	Maximal
RR	ATC/PAV 5	6.72	12.5	5.8	4.9	6.3
	ATC	6.80	11.0	5.7	5.2	6.8
	CPAP	6.54	9.1	6.0	5.3	6.9
TS	ATC/PAV 4	7.59	22.5	5.4	4.9	6.3
	ATC	6.29	20.0	5.7	5.1	6.5
	CPAP	5.98	19.1	5.8	5.3	6.7
GU	ATC/PAV 10	7.51	17.5	5.1	4.2	6.2
	ATC/PAV 5	6.63	15.5	5.6	4.4	6.2
	ATC	7.11	14.2	5.2	4.7	6.5
ST	ATC/PAV 6	9.44	18.4	3.9	3.7	4.1
	ATC/PAV 4	9.03	15.9	4.1	3.9	4.3
	ATC	8.56	13.4	4.3	4.1	4.4
MA	ATC/PAV 5	8.15	17.6	6.8	5.6	7.6
	ATC	8.11	16.4	6.9	5.9	7.9
	CPAP	7.54	11.6	7.4	6.2	8.2
RE	ATC/PAV 6	7.51	17.1	6.3	4.9	7.9
	ATC/PAV 4	7.46	14.2	6.6	6.0	8.0
	ATC	7.38	10.5	6.8	6.4	7.4
VA	ATC/PAV 5	6.89	14.9	4.0	3.6	4.3
	ATC	6.92	14.2	3.9	3.6	4.4
	CPAP	7.02	13.7	3.9	3.8	4.3

Definition of abbreviations: ATC, automatic tube compensation; PAV, proportional assist ventilation (the number indicates the level of volume proportional pressure support in mbar/L); CPAP, continuous positive airway pressure; ET_{CO_2}, endtidal CO_2 concentration.

ETT, the ETT resistance will be overcompensated at low flow rates and will be undercompensated at high flow rates (Guttmann et al., 1997). Undercompensation of the ETT resistance is nothing else but resistive loading whereas overcompensation represents mechanical unloading. In periodic breathing and CSR with the typical pattern of waxing and waning, tidal volume and peak flow rate increase during waxing and decrease during waning. Consequently, in the middle of ventilatory phases of CSR (or during phases of maximal ventilation in periodic breathing), when flow rate is highest, the ETT resistance behaves as a resistive load counteracting the effectiveness of ventilatory muscles (thus decreasing controlled system gain). In contrast, at both ends of the ventilatory phases of CSR (or during phases of minimal ventilation in periodic breathing) when flow rate is lower, the ETT resistance might be overcompensated by the constant pressure support (depending on its preset level) having the effect that pressure support really leads to mechanical unloading and, thus, increases controlled system gain. Increasing controlled system gain at both ends of the ventilatory phases of periodic breathing or CSR, when the patient's effort is at a lower level, and decreasing controlled system gain at maximum ventilation, when the patient's effort is highest, counteract the waxing and waning and, thus, suppress periodic breathing and CSR. With ATC, the flow-dependent pressure drop across the ETT is continuously compensated for (not only during inspiration but also during expiration) eliminating the resistive load of the ETT resistance in intubated patients at any flow rate. With ATC, mechanical unloading imposed by additional PAV is not disturbed by the variable degree of resistive load imposed by the ETT.

In summary, our results suggest that mechanical unloading using PAV intensifies periodic

breathing and CSR by increasing the respiratory loop gain.

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