

Tromethamine Buffer Modifies the Depressant Effect of Permissive Hypercapnia on Myocardial Contractility in Patients with Acute Respiratory Distress Syndrome

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In patients with acute respiratory distress syndrome (ARDS), permissive hypercapnia is a strategy to decrease airway pressures to prevent ventilator-induced lung damage by lowering tidal volumes and tolerating higher arterial carbon dioxide tension. However, in experimental studies hypercapnia impairs myocardial contractility and hemodynamic function. We investigated the effect of short-term permissive hypercapnia on myocardial contractility and hemodynamics in patients with ARDS. We hypothesized that the administration of tromethamine (THAM), a buffer which does not increase carbon dioxide production, would modify these changes. In 12 patients with ARDS, permissive hypercapnia was implemented for 2 h with a target Pa_{CO_2} of 80 mm Hg. Patients were randomized to have respiratory acidosis corrected by THAM (pH-corrected group), or not corrected (pH-uncorrected group). Hemodynamic responses were measured, and transesophageal echocardiography (TEE) was used to determine myocardial contractility. Permissive hypercapnia resulted in significant decreases in systemic vascular resistance (SVR) and increases in cardiac output (\dot{Q}). Myocardial contractility decreased in both groups but significantly less in the pH-corrected group (approximately 10%) than in the pH-uncorrected group (approximately 18%, $p < 0.05$). Mean arterial pressure decreased and mean pulmonary arterial pressure increased significantly only in the pH-uncorrected group. All values returned to baseline conditions 1 h after permissive hypercapnia was terminated. Our study demonstrates a reversible depression of myocardial contractility and hemodynamic alterations during rapid permissive hypercapnia which were attenuated by buffering with THAM. This may have applicability to the clinical strategy of permissive hypercapnia and allow the benefit of decreased airway pressures to be realized while minimizing the adverse hemodynamic effects of hypercapnic acidosis.

High ventilatory pressures and the related risk of lung injury are a major problem in patients with acute respiratory distress syndrome (ARDS). To reduce the risk of pulmonary overdistention and lung damage, several investigators have advocated permissive hypercapnia, i.e., ventilation with smaller tidal volumes and tolerance of higher arterial carbon dioxide tension (Pa_{CO_2}) (1, 2). Hickling and coworkers (3) suggested that permissive hypercapnia results in a lower mortality rate than predicted by Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Recently, two controlled studies demonstrated that permissive hypercapnia results in reduction in barotrauma, higher ventilator weaning rates, and lower short-term mortality (4, 5). However, its beneficial impact on long-

term outcome has been questioned by other researchers (6, 7), and remains to be determined.

Although the physiologic effects of permissive hypercapnia appear to be well tolerated and reversible (8) hypercapnia and respiratory acidosis do affect myocardial contractility and hemodynamics. Experimental studies have demonstrated that although cardiac output (\dot{Q}) increases, owing to a decrease in systemic vascular resistance (SVR) (9), myocardial contractility is actually impaired (10). In an isolated heart model, the correction of respiratory acidosis resulting from permissive hypercapnia by administration of buffers that do not generate CO_2 appeared to preserve myocardial contractility (11, 12). In humans the effects of hypercapnia and respiratory acidosis on \dot{Q} and SVR have been confirmed by data from pulmonary artery catheterization (13). However, the influence of permissive hypercapnia and respiratory acidosis on myocardial contractility in humans remains unknown.

Accordingly, we assessed the effect of short-term permissive hypercapnia on myocardial contractility and hemodynamics in patients with ARDS. We hypothesized that correction of the arterial pH during permissive hypercapnia with tromethamine (THAM), a buffer which does not create additional CO_2 , would have a beneficial effect on myocardial contractility and hemodynamics.

METHODS

After approval from the institutional ethics committee and informed written consent of the patients' next-of-kin, 12 patients were enrolled in this study. All patients met the criteria of ARDS according to the definition of the American-European Consensus Conference (sudden onset of respiratory failure, bilateral infiltrates on chest X-ray, ratio of arterial oxygen tension to fraction of inspired oxygen [$\text{Pa}_{\text{O}_2}/\text{F}_{\text{I}_{\text{O}_2}}$] < 200 mm Hg, pulmonary capillary wedge pressure [P_{pcw}] < 18 mm Hg) (14). Exclusion criteria included age above 80 or below 14 yr, elevated intracranial pressure, hemodynamic instability (systolic arterial pressure < 90 mm Hg), arterial oxygen saturation $< 90\%$, severe metabolic acidosis ($\text{pH} < 7.25$), and esophageal disorders.

General Support

At baseline values all patients were mechanically ventilated (Evita II; Draeger, Lübeck, Germany) to maintain a Pa_{CO_2} below 50 mm Hg. Sedatives (midazolam and morphine hydrochloride) were adjusted to keep the patients deeply sedated. Inotropic support with dopamine, dobutamine, norepinephrine and epinephrine was provided as needed to keep mean arterial pressure ($\bar{\text{P}}_{\text{a}}$) above 60 mm Hg. Monitoring included heart rate, pulse oximetry (Component Monitoring System; Hewlett Packard, Andover, MA) invasive blood pressure (PX600; Baxter, Irvine, CA), pulmonary artery pressure and continuous mixed venous oxygen saturation via Swan-Ganz catheter (Edwards Swan-Ganz 171176-1 REF A; Baxter).

Randomization and Preprotocol Interventions

Patients were randomly assigned to two study groups. In the pH-uncorrected group the decreased arterial pH resulting from permis-

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sive hypercapnia was not corrected. In the pH-corrected group, arterial pH values were corrected by continuous intravenous administration of THAM. THAM infusion was started at $1 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 30 min and thereafter adjusted to achieve a $\text{pH} > 7.3$. No changes in fluid administration, inotropic support, hypnotic and analgesic drug administration were made during permissive hypercapnia. If permissive hypercapnia resulted in respiratory efforts, a muscle relaxant (vecuronium) was given.

Respiratory Protocol

The target value for permissive hypercapnia in the pH-corrected group was a PaCO_2 of 80 mm Hg. In the pH-uncorrected group the target value for permissive hypercapnia was either a PaCO_2 of 80 mm Hg or an arterial pH of 7.2. These target values were achieved over 30 to 60 min by decreasing tidal volumes in steps of 100 ml at a time. To prevent changes in preload from altered intrathoracic pressure, mean airway pressure was not allowed to decrease more than 2 cm H_2O from baseline values. If target values were not reached by reductions in tidal volume, respiratory frequency was decreased to not less than 8 breaths/min. Blood gas analysis and ventilator adjustments were performed every 15 min until target values were reached. Permissive hypercapnia was subsequently maintained for 2 h, after which patients were returned to respiratory baseline conditions by increasing tidal volumes, or respiratory frequency, or both, to preprotocol levels. In the pH-corrected group, THAM administration was discontinued at the same time.

Fraction of inspired oxygen (FI_{O_2}) was adjusted to maintain an arterial saturation $> 90\%$ during the study. Patients were withdrawn from the study if permissive hypercapnia resulted in hypoxia (arterial saturation $< 90\%$) at an FI_{O_2} of 1.0, or hemodynamic instability ($\bar{\text{P}}_a < 60 \text{ mm Hg}$) requiring modifications in hemodynamic support.

Hemodynamic Measurements

Baseline measurements were taken before permissive hypercapnia was initiated, followed by measurements 1 and 2 h after implementing permissive hypercapnia and 1 h after return to baseline conditions. The following measurements were performed: arterial and mixed venous blood samples (AVL 995 Hb-Analyzer; Graz, Austria), \dot{Q} , SVR index (SVRI), pulmonary artery vascular resistance index, stroke volume index (Explorer; Baxter, Irvine, CA) and transesophageal echocardiography (TEE) (Sonos 1500; Hewlett-Packard, Andover, MA). \dot{Q} was measured by thermodilution technique as the average of three measurements made during expiration. SVRI, pulmonary artery vascular resistance index, and stroke volume index were calculated by the \dot{Q} monitor.

Echocardiographic Protocol

TEE was performed using a Sonos 1500 ultrasound system with a flexible multiplane 5-MHz probe. Left ventricular contractility was assessed by calculation of maximal elastance (E_{max}). For calculation of E_{max} we used the peak-systolic-pressure to end-systolic-area rela-

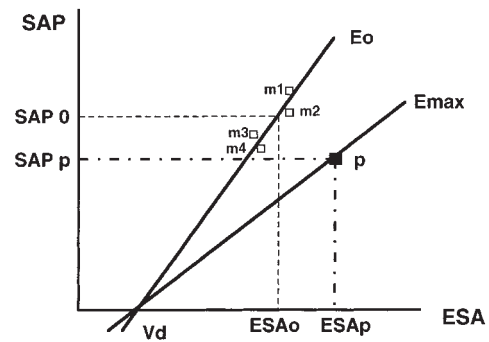


Figure 1. SAP = systolic arterial pressure; ESA = end-systolic left ventricular area; E_o = baseline contractility obtained by linear regression analysis of all pressure-volume points during decrease in preload after injection of 0.1 mg nitroglycerin (m1–m4); V_d = intercept of line E_o with x-axis; p = pressure-volume point during permissive hypercapnia; E_{max} = contractility during permissive hypercapnia defined by pressure-volume point p and V_d .

tionship obtained by the method of Mulier and coworkers (15) from two-dimensional TEE in the transgastric short axis view. Preload was transiently decreased by the intravenous injection of a 0.1-mg nitroglycerin bolus. Subsequently, the change in systolic arterial pressure was observed and end-systolic area was assessed by TEE. Measurements were stopped as soon as heart rate changed, i.e., with the onset of reflex tachycardia. The peak-systolic-pressure to end-systolic-area relationship was calculated as a linear regression line defined by the measured pressure-area points. The slope of this regression line reflects baseline contractility (E_o) (Figure 1). After permissive hypercapnia was implemented, a new pressure-area point (p) was determined. The contractility was again calculated by the slope of a new line E_{max} , drawn through point p and the intercept of line E_o with the x-axis. A change in contractility compared with baseline values was reflected by a change in the slope of line E_{max} compared with E_o .

Echocardiographic data were stored on videotape for off-line calculations. Area measurements for calculation of the peak-systolic-pressure-area relationship were performed independently by two blinded observers.

Statistics

Data analysis was performed by analysis of variance (ANOVA) for repeated measurements to detect changes during permissive hypercapnia. Comparison between the pH-corrected and the pH-uncorrected group during the permissive hypercapnia trial utilized between-group ANOVA for repeated measurements. To test for significant differences in demographic data, the two-tailed *t* test was used. All values are expressed as mean \pm SD. Statistical significance was indicated by $p < 0.05$.

TABLE 1
PATIENT DEMOGRAPHICS

	pH-corrected		pH-uncorrected	
Sex, M:F	4:2		4:2	
Age, yr	57 \pm 4		54 \pm 22	
Weight, kg	90 \pm 23		85 \pm 14	
$\text{PaO}_2/\text{FI}_{\text{O}_2}$	134.6 \pm 32.9		133.2 \pm 35.1	
APACHE II	21 \pm 3		21 \pm 3	
Diagnosis	Pneumonia: 5 Sepsis: 1		Pneumonia: 1 Sepsis: 5	
Inotropic Support	No. of Patients	($\mu\text{g}/\text{kg}/\text{min}$)	No. of Patients	($\mu\text{g}/\text{kg}/\text{min}$)
Dopamine	5	2 \pm 0	6	2 \pm 0
Norepinephrine	4	0.096 \pm 0.13	5	0.104 \pm 0.11
Epinephrine			2	0.08 \pm 0.03
Dobutamine			1	4.1
Outcome (survivor/nonsurvivor)	4:2		4:2	

* No differences between the pH-corrected and pH-uncorrected groups were significant.

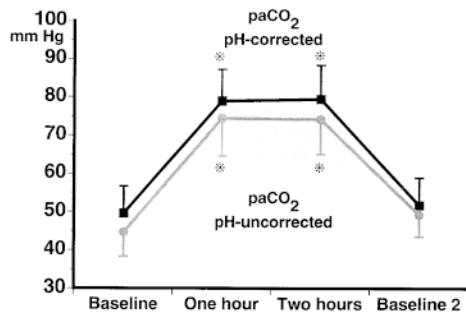


Figure 2. PaCO₂ during rapid permissive hypercapnia. PaCO₂-corrected = PaCO₂ in patients with respiratory acidosis corrected by administration of THAM; PaCO₂ pH-uncorrected = PaCO₂ in patients with uncorrected respiratory acidosis. Baseline 1 = baseline; one hour = 1 h of permissive hypercapnia; two hours = 2 h of permissive hypercapnia; baseline 2 = 1 h after return to baseline. *p < 0.05 compared with baseline.

RESULTS

Twelve patients were enrolled in the study, with six patients randomized into each group. No patient had to be withdrawn because of hypoxia unresponsive to increases in F_IO₂, or hemodynamic instability. Demographic data, inotropic drug support, PaO₂/F_IO₂, and APACHE II score did not differ between the two groups. However, more patients with sepsis were randomized to the pH-uncorrected group, and more patients with pneumonia were randomized to the pH-corrected group (Table 1). Target values for either PaCO₂ or pH were reached in both groups (Figures 2 and 3), with similar decreases in tidal volumes and respiratory rate (Table 2). Mean airway pressure decreased from 20.3 ± 4.2 cm H₂O to 18.7 ± 3.7 cm H₂O (p < 0.01) in the pH-corrected group, and from 17.8 ± 3.4 cm H₂O to 17.0 ± 4.0 cm H₂O in the pH-uncorrected group (p < 0.05). As anticipated, the pH differed significantly between the pH-corrected and the pH-uncorrected group after 2 h of permissive hypercapnia.

Echocardiographic imaging of the transgastric short axis view was obtained without difficulty in all patients. Myocardial contractility at baseline (Eo) and all other hemodynamic parameters were similar in both groups. For the determination of Eo, 7 ± 1 pressure-volume points were obtained per patient. End-systolic area and systolic arterial pressure correlated with an R² of 0.91.

With permissive hypercapnia SVRI decreased and cardiac index increased in both groups (Table 3). Pulmonary vascular resistance index did not change significantly in either group.

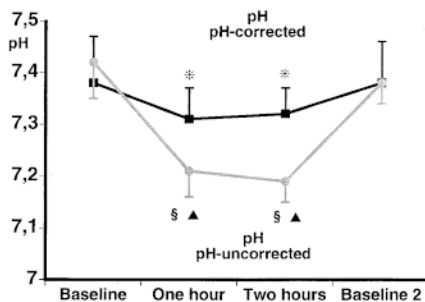


Figure 3. pH during rapid permissive hypercapnia. pH pH-corrected = pH in patients with respiratory acidosis corrected by administration of THAM; pH pH-uncorrected = pH in patients with uncorrected respiratory acidosis. Definitions of baselines and times as in Figure 2 legend. §p < 0.001 compared with baseline; *p < 0.05 compared with baseline. ▲p < 0.05 compared with pH-corrected.

TABLE 2
RESPIRATORY RATE AND TIDAL VOLUMES DURING RAPID PERMISSIVE HYPERCAPNIA*

	Respiratory Rate (breaths/min)		Tidal Volume (ml)	
	pH-uncorrected	pH-corrected	pH-uncorrected	pH-corrected
Baseline 1	21 ± 6	20 ± 5	513 ± 133	570 ± 89
One hour	12 ± 2 [†]	15 ± 4 [†]	390 ± 40 [†]	380 ± 27 [†]
Two hours	12 ± 2 [†]	15 ± 4 [†]	378 ± 32 [†]	378 ± 25 [†]
Baseline 2	21 ± 6	20 ± 5	512 ± 132	562 ± 85

Definition of abbreviations: Baseline 1 = baseline; One hour = 1 h of permissive hypercapnia; Two hours = 2 h of permissive hypercapnia; Baseline 2 = 1 h after return to baseline; pH-corrected = patients with respiratory acidosis corrected by administration of THAM; pH-uncorrected = patients with uncorrected respiratory acidosis.

* Values are expressed as mean ± SD.

[†] p < 0.001 compared with baseline.

Myocardial contractility, as estimated by Emax, decreased significantly from baseline values in both groups (p < 0.001) but significantly less in the pH-corrected group (10.8 ± 6.0%) compared with the pH-uncorrected group (18.5 ± 7.1%, p < 0.05) (Figure 4). Heart rate changed after 2 h of permissive hypercapnia in the pH-uncorrected group and remained unchanged in the pH-corrected group. Pa decreased (Figure 5) and mean pulmonary artery pressure (Ppa) increased significantly from baseline in the pH-uncorrected group but not in the pH-corrected group (Figure 6). The effects of permissive hypercapnia on Emax and hemodynamics returned toward baseline values when the PaCO₂ was normalized at the end of the study.

DISCUSSION

We have confirmed that despite an increase in cardiac index induced by systemic vasodilation, rapid permissive hypercapnia significantly impairs myocardial contractility. This finding is in accordance with animal studies in which elevated PaCO₂ levels resulted in depression of myocardial contractility (10). Several studies have indicated that at the same extracellular pH, hypercapnic acidosis induces more myocardial depression and decrease in intramyocardial pH than metabolic acidosis (16, 17). The explanation probably lies in the greater permeability of the myocardial cell membrane to CO₂ than to metabolic acids. Hypercapnia causes rapid diffusion of CO₂ into myocytes, and the resultant intracellular acidosis impairs myocardial contrac-

TABLE 3
HEMODYNAMIC PARAMETERS DURING RAPID PERMISSIVE HYPERCAPNIA*

	Baseline 1	One Hour	Two Hours	Baseline 2
pH-uncorrected				
HR	89 ± 9	95 ± 9 [†]	95 ± 11 [†]	88 ± 16
CI	3.66 ± 0.52	4.28 ± 0.71	4.28 ± 1.0 [†]	3.7 ± 0.77
SVRI	1,559 ± 399	1,039 ± 270	966 ± 225 [§]	1,599 ± 340
PVRI	343 ± 74	414 ± 164	415 ± 169	358 ± 120
pH-corrected				
HR	89 ± 33	92 ± 28	88 ± 22	85 ± 23
CI	3.57 ± 1.15	4.38 ± 1.1	4.28 ± 1.0 [§]	3.71 ± 0.86
SVRI	1,614 ± 461	1,132 ± 273	1,118 ± 208 [‡]	1,421 ± 442
PVRI	419 ± 138	441 ± 215	399 ± 156	375 ± 90

Definition of abbreviations: CI = cardiac index; HR = heart rate; SVI = stroke volume index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index. Other definitions as in Table 2.

* Values are expressed as mean ± SD.

[†] p < 0.05 compared with baseline.

[‡] p < 0.01 compared with baseline.

[§] p < 0.001 compared with baseline.

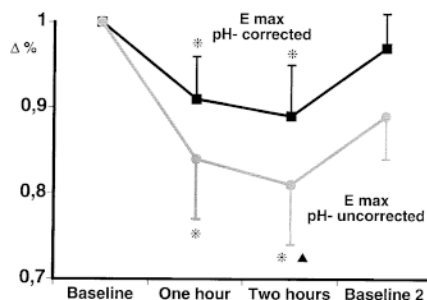


Figure 4. Percent change in measurements of maximal elastance during rapid permissive hypercapnia. E_{max} pH-corrected = maximal elastance in patients with respiratory acidosis corrected by administration of THAM. E_{max} pH-uncorrected = maximal elastance in patients with uncorrected respiratory acidosis. Definitions of baselines and times as in Figure 2 legend. * $p < 0.05$ compared with baseline; $\blacktriangle p < 0.05$ compared with E_{max} pH-corrected.

tility (16) with decreased responsiveness of the myofilaments to calcium (18). This explains why attempts to correct respiratory acidosis with CO_2 -generating buffers such as sodium bicarbonate may simply worsen intramyocardial acidosis.

However, results from studies investigating the use of non- CO_2 -generating buffers such as Carbicarb or THAM are conflicting. The impact of different buffer agents on resuscitability has been examined in animal studies of myocardial acidosis after cardiac arrest. Buffering with Carbicarb did not reverse myocardial acidosis or enhance resuscitability compared with bicarbonate or saline (19–21). However, in these studies, myocardial acidosis was the result of reduced cardiac blood flow, i.e., ischemia. In contrast, permissive hypercapnia in patients with ARDS may be associated with enhanced \dot{Q} and coronary blood flow. Moreover, Tang and coworkers (16) found that in the nonischemic isolated rat heart increases in Pa_{CO_2} markedly decrease myocardial contractility compared with elevated H^+ -levels. They concluded that in this setting buffers that generate CO_2 are theoretically counterproductive by worsening myocardial acidosis. Furthermore, experimental studies found that the administration of Carbicarb (12) or THAM (11) improves the function of isolated acidotic hearts. For this reason we selected THAM as the buffering agent we would investigate.

In our study permissive hypercapnia caused impairment of myocardial contractility, as assessed by E_{max} , in both the pH-corrected and the pH-uncorrected group. However, buffering with THAM significantly attenuated the effect of hypercapnia. This finding may appear incongruous with the statement

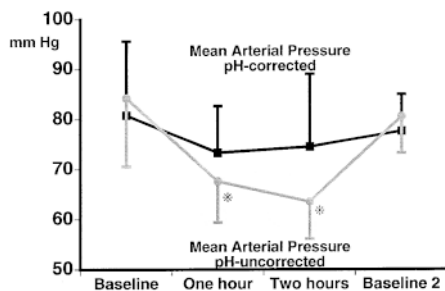


Figure 5. \bar{P}_a during rapid permissive hypercapnia. Mean arterial pressure pH-corrected = \bar{P}_a in patients with respiratory acidosis corrected by administration of THAM; mean arterial pressure pH-uncorrected = \bar{P}_a in patients with uncorrected respiratory acidosis. Definitions of baselines and times as in Figure 2 legend. * $p < 0.02$ compared with baseline.

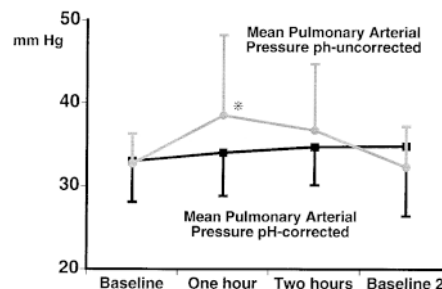


Figure 6. \bar{P}_{pa} during rapid permissive hypercapnia. Mean pulmonary artery pressure pH-corrected = \bar{P}_{pa} in patients with respiratory acidosis corrected by administration of THAM; mean pulmonary artery pressure pH-uncorrected = \bar{P}_{pa} in patients with uncorrected respiratory acidosis. Definitions of baselines and times as in Figure 2 legend. * $p < 0.02$ compared with baseline.

that hypercapnia, rather than elevated extracellular H^+ -ion concentration, impairs myocardial contractility. However, THAM is an effective intracellular buffer and does counteract the effects of CO_2 accumulation (11). Thus, buffering with THAM may decrease myocardial acidosis by decreasing intracellular CO_2 content.

Several studies have investigated the effects of correction of respiratory acidosis on hemodynamics. Nishikawa (22) demonstrated in instrumented dogs that administration of sodium bicarbonate during respiratory acidosis resulted in more profound hemodynamic depression than its administration during metabolic acidosis. In contrast, Cardenas and coworkers (9) found that sodium bicarbonate attenuated the increase in \dot{Q} and organ blood flow induced by rapid permissive hypercapnia.

Permissive hypercapnia resulted in a decrease in SVRI and an increase in cardiac index in both study groups. Buffering with THAM attenuated the intragroup decrease in \bar{P}_a and increase in \bar{P}_{pa} induced by hypercapnia, although the intergroup differences were not significant. These results are in accordance with the findings of Thorens and coworkers (13) who investigated the effects of rapid permissive hypercapnia on hemodynamics in patients with ARDS. A high percentage of ARDS patients have increased P_{pa} and decreased \bar{P}_a . Exacerbation of these changes by permissive hypercapnia could result in severe hemodynamic instability and right heart failure and should therefore be avoided. Although intergroup differences between the pH-corrected, and the pH-uncorrected group were not significant, intragroup changes in hemodynamics during permissive hypercapnia were markedly attenuated. Therefore, a beneficial effect of THAM administration during permissive hypercapnia on hemodynamics is suggested by our findings.

Myocardial contractility is difficult to monitor at the bedside, as most measured hemodynamic parameters are dependent on the loading conditions of the heart. Echocardiographic measurement of E_{max} is a largely load-independent index of myocardial contractility. It is defined as the slope of the end-systolic pressure to end-systolic volume relationship and was first described by Suga and Sagawa in 1973 (23). However end-systolic pressure requires measurement of left ventricular or aortic pressure. Substitution of peak systolic pressure facilitates the use of this index in the clinical setting and does not alter the pressure–volume relationship (24). Studies using this approach for assessment of myocardial contractility have demonstrated its feasibility in clinical practice (15, 25).

A disadvantage of E_{max} is the requirement for off-line calculations from videotaped recordings, where the image quality

can be less satisfying compared with the cine-loop technique. The use of on-line pressure-volume recordings (26) could overcome this problem and facilitate bedside assessment of myocardial contractility. A further limitation is the need to alter preload to obtain a baseline estimation of myocardial contractility, which precludes the determination of Emax in hemodynamically unstable patients.

Our study has a number of limitations. Its power was insufficient to define an intergroup difference in the modification of the hemodynamic response to hypercapnia by THAM. Only the short-term effects of permissive hypercapnia were investigated. In contrast to the gradual permission of hypercapnia in the clinical setting, hypercapnia was rapidly induced in our study. Compensatory mechanisms to respiratory acidosis require a few hours for full activation. Therefore, the long-term effects of gradual permissive hypercapnia on myocardial contractility in patients with ARDS may be different from those observed in our study. The two groups differed with respect to the primary underlying disease. However, their APACHE II scores were not different, suggesting that the severity of illness was comparable between the pH-corrected and pH-uncorrected groups. Furthermore, Emax and all other hemodynamic parameters at baseline conditions did not differ between the groups, suggesting similar cardiac performance. A further limitation might be that the mean airway pressures decreased, but although this decrease was statistically significant, it remained within the predefined range (< 2 cm H₂O) and thereby probably had no impact on the data measured.

In summary, we have demonstrated that although rapid permissive hypercapnia is associated with decreased SVR and increased \dot{Q} , myocardial contractility is significantly depressed. Administration of a non-CO₂ producing buffer, THAM, significantly attenuates the effects of hypercapnia on myocardial contractility and, to a lesser extent, on \bar{P}_a and \bar{P}_{pa} . We conclude that buffering respiratory acidosis with THAM might be beneficial for preservation of myocardial contractility and hemodynamic stability during rapid permissive hypercapnia. Further studies are required to determine the long-term effects of permissive hypercapnia on myocardial contractility and hemodynamics.

References

- Lewandowski, K. 1996. Permissive hypercapnia in ARDS: just do it? [editorial; comment]. *Intensive Care Med.* 22:179-181.
- Slutsky, A. S. 1994. Consensus conference on mechanical ventilation—January 28-30, 1993 at Northbrook, Illinois, USA. Part I. European Society of Intensive Care Medicine, the ACCP and the SCCM. *Intensive Care Med.* 20:64-79.
- Hickling, K. G., J. Walsh, S. Henderson, and R. Jackson. 1994. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit. Care Med.* 22:1568-1578.
- Amato, M. B., C. S. Barbas, D. M. Medeiros, G. d. P. Schettino, G. Lorenzi-Filho, R. A. Kairalla, D. Deheinzelin, C. Morais, E. d. O. Fernandes, T. Y. Takagaki, and C. R. R. Carvalho. 1995. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. *Am. J. Respir. Crit. Care Med.* 152:1835-1846.
- Amato, M., C. Barbas, D. Medeiros, R. Magaldi, G. Schettino, G. Lorenzi-Filho, R. Kairalla, D. Deheinzelin, C. Munoz, R. Oliveira, T. Takagaki, and C. Carvalho. 1998. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N. Engl. J. Med.* 338:347-354.
- Stewart, T. E., M. O. Meade, D. J. Cook, J. T. Granton, R. V. Hodder, S. E. Lapinsky, C. D. Mazer, R. F. McLean, T. S. Rogovein, B. D. Schouten, T. R. Todd, and A. S. Slutsky. 1998. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome: Pressure- and Volume-Limited Ventilation Strategy Group. *N. Engl. J. Med.* 338:355-361.
- Weg, J. G., A. Anzueto, R. A. Balk, H. P. Wiedemann, E. N. Pattishall, M. A. Schork, and L. A. Wagner. 1998. The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. *N. Engl. J. Med.* 338:341-346.
- Feihl, F., and C. Perret. 1994. Permissive hypercapnia: how permissive should we be? *Am. J. Respir. Crit. Care Med.* 150:1722-1737.
- Cardenas, V. J., Jr., J. B. Zwischenberger, W. Tao, P. D. Nguyen, T. Schroeder, L. D. Traber, D. L. Traber, and A. Bidani. 1996. Correction of blood pH attenuates changes in hemodynamics and organ blood flow during permissive hypercapnia. *Crit. Care Med.* 24:827-834.
- Walley, K. R., T. H. Lewis, and L. D. Wood. 1990. Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output in dogs. *Circ. Res.* 67:628-635.
- Sirieux, D., S. Delayance, M. Paris, S. Massonnet Castel, A. Carpentier, and J. F. Baron. 1997. Tris-hydroxymethyl aminomethane and sodium bicarbonate to buffer metabolic acidosis in an isolated heart model. *Am. J. Respir. Crit. Care Med.* 155:957-963.
- Shapiro, J. I. 1990. Functional and metabolic responses of isolated hearts to acidosis: effects of sodium bicarbonate and Carbicarb. *Am. J. Physiol.* 258:1835-1839.
- Thorens, J. B., P. Jolliet, M. Ritz, and J. C. Chevrolat. 1996. Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. *Intensive Care Med.* 22:182-191.
- Bernard, G. R., A. Artigas, K. L. Brigham, J. Carlet, K. Falke, L. Hudson, M. Lamy, J. R. Legall, A. Morris, and R. Spragg. 1994. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am. J. Respir. Crit. Care Med.* 149:818-824.
- Mulier, J. P., P. F. Wouters, H. Van Aken, G. Vermaut, and E. Vandermeersch. 1991. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach [see Comments]. *Anesth. Analg.* 72:28-35.
- Tang, W. C., M. H. Weil, R. J. Gazmuri, J. Bisera, and E. C. Rackow. 1991. Reversible impairment of myocardial contractility due to hypercarbic acidosis in the isolated perfused rat heart. *Crit. Care Med.* 19:218-224.
- Steenbergen, C., G. Deleuw, T. Rich, and J. R. Williamson. 1977. Effects of acidosis and ischemia on contractility and intracellular pH of rat heart. *Circ. Res.* 41:849-858.
- Orchard, C. H., and J. C. Kentish. 1990. Effects of changes of pH on the contractile function of cardiac muscle. *Am. J. Physiol.* 258:967-981.
- Kette, F., M. H. Weil, M. von Planta, R. J. Gazmuri, and E. C. Rackow. 1990. Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. *Circulation* 81:1660-1666.
- Kette, F., M. H. Weil, and R. J. Gazmuri. 1991. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. *J.A.M.A.* 266:2121-2126.
- Blecic, S., D. De Backer, M. Deleuze, J. L. Vachieri, and J. L. Vincent. 1991. Correction of metabolic acidosis in experimental CPR: a comparative study of sodium bicarbonate, bicarb, and dextrose. *Ann. Emerg. Med.* 20:235-238.
- Nishikawa, T. 1993. Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis. *Br. J. Anaesth.* 70:196-200.
- Suga, H., K. Sagawa, and A. A. Shoukas. 1973. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ. Res.* 32:314-322.
- Grossman, W., E. Braunwald, T. Mann, L. P. McLaurin, and L. H. Green. 1977. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. *Circulation* 56:845-852.
- Goertz, A. W., W. Seeling, H. Heinrich, K. H. Lindner, and U. Schirmer. 1993. Influence of high thoracic epidural anesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship. *Acta Anaesthesiol. Scand.* 37:38-44.
- Gorcsan, J., III, A. Deneault, T. A. Gasior, W. A. Mandarino, M. J. Kancel, L. G. Deneault, B. G. Hattler, and M. R. Pinsky. 1994. Rapid estimation of left ventricular contractility from end-systolic relations by echocardiographic automated border detection and femoral arterial pressure. *Anesthesiology* 81:553-562.