Results

Systemic effects of hypercapnic acidosis during LPS infusion

Table 1 shows the effects of hypercapnic acidosis and LPS infusion on systemic circulatory and biochemical parameters versus the sham animals. Hypercapnia group showed a marked hypercapnic acidosis to match the criteria of this group as described in "Materials and methods" versus the normocapnia group. By fluid resuscitation during LPS infusion, mean arterial pressure (MAP) and heart rate (HR) remained constant throughout the study period in both normocapnia and hypercapnia groups, while hypercapnia apparently increased MAP in sham group possibly through the activation of sympathetic system versus normocapnia. The number of circulating WBC in LPS-treated animals was significantly reduced to a similar extent in both study groups versus the baseline, whereas those in the sham groups remained constant throughout the study periods. Lactate dehydrogenase (LDH) activity to reflect the extent of LPS-induced tissue injury was increased in both the study groups, but those in normocapnia group were slightly but significantly higher versus hypercapnia group at 4 h ($P < 0.05$), which was comparable to the sham. Simultaneously, arterial lactate in normocapnia group was significantly elevated versus hypercapnia group, indicating that tissue hypoxia caused by LPS infusion was reduced by hypercapnic acidosis.

Splanchnic effects of hypercapnic acidosis during LPS infusion

Figure 2 illustrates the changes of pHi, PCO_2 gap and portal blood flow at baseline and at 0–4 h of LPS infusion. The pHi values of both normocapnia and hypercapnia groups were progressively depressed, but the extent of the latter group was significantly greater versus the former. PCO_2 gap in hypercapnia group was significantly greater at 2 and 4-h study periods versus normocapnia group. On the other hand, portal blood flows in both normocapnia and hypercapnia groups increased at 2 and 4-h study periods compared to the baseline while the latter was increased significantly greater at 4 h versus the former.

Table 1 Effects of hypercapnic acidosis and lipopolysaccharide (LPS) infusion on systemic circulatory and biochemical parameters

		Group	Baseline	0 h	2 h	4 h
Mean arterial pressure (mmHg)	LPS	Normocapnia	55 ± 9	54 ± 4	53 ± 5	58 ± 11
		Hypercapnia	58 ± 5	58 ± 5	59 ± 12	60 ± 10
	Sham	Normocapnia	64 ± 1	60 ± 13	64 ± 12	67 ± 13
		Hypercapnia	67 ± 12	71 ± 10	70 ± 19	75 ± 25
Heart rate (beats/min)	LPS	Normocapnia	283 ± 24	273 ± 35	267 ± 21	268 ± 30
		Hypercapnia	275 ± 26	254 ± 27	259 ± 30	258 ± 25
	Sham	Normocapnia	272 ± 12	280 ± 24	262 ± 9	270 ± 24
		Hypercapnia	285 ± 12	287 ± 33	272 ± 22	272 ± 37
Arterial pH	LPS	Normocapnia	7.42 ± 0.06	7.43 ± 0.07	7.40 ± 0.05	7.38 ± 0.04
		Hypercapnia	7.25 ± 0.05**	7.27 ± 0.02**	7.25 ± 0.03**	7.24 ± 0.04**
	Sham	Normocapnia	7.40 ± 0.02	7.41 ± 0.01	7.46 ± 0.03	7.45 ± 0.02
		Hypercapnia	7.22 ± 0.07	7.26 ± 0.02	7.27 ± 0.03	7.27 ± 0.04
$PaCO_2$ (mmHg)	LPS	Normocapnia	39 ± 4	37 ± 3	38 ± 3	40 ± 3
		Hypercapnia	68 ± 6**	70 ± 5**	68 ± 5**	71 ± 5**
	Sham	Normocapnia	42 ± 3	40 ± 2	39 ± 3	39 ± 3
		Hypercapnia	74 ± 5	73 ± 5	72 ± 7	70 ± 7
White blood cell count (/mm^3)	LPS	Normocapnia	5,440 ± 830	3,330 ± 1,420†	1,560 ± 430‡	1,870 ± 620‡
		Hypercapnia	5,530 ± 1,470	3,300 ± 1,560†	1,680 ± 930‡	2,020 ± 1,380‡
	Sham	Normocapnia	5,450 ± 500	5,460 ± 1,027	5,280 ± 1,800	5,360 ± 700
		Hypercapnia	5,330 ± 2590	5,470 ± 1,350	6,180 ± 1,500	5,660 ± 1,400
Lactate dehydrogenase (IU/L)	LPS	Normocapnia	120 ± 36	133 ± 41	174 ± 70	184 ± 94†
		Hypercapnia	135 ± 31	135 ± 31	145 ± 20	148 ± 22*
	Sham	Normocapnia	135 ± 21	145 ± 30	139 ± 12	141 ± 19
		Hypercapnia	124 ± 11	135 ± 7	127 ± 29	132 ± 38
Arterial lactate (mmol/L)	LPS	Normocapnia	2.9 ± 1.0	2.9 ± 1.6	3.4 ± 1.1	3.7 ± 1.4
		Hypercapnia	1.9 ± 0.8	1.8 ± 0.9	1.9 ± 0.6*	2.2 ± 0.7*
	Sham	Normocapnia	2.1 ± 0.5	2.1 ± 1.5	2.5 ± 0.8	2.2 ± 1.0
		Hypercapnia	1.9 ± 0.6	1.1 ± 0.3	1.2 ± 0.9	1.7 ± 1.2

Baseline = 45 min after preparatory surgery; 0, 2 and 4 h = study period during lipopolysaccharide infusion
* $P < 0.05$, ** $P < 0.01$ versus Normocapnia
† $P < 0.05$, ‡ $P < 0.01$ versus Baseline
Data are expressed as mean ± SD. No statistical analyses were performed between LPS and Sham

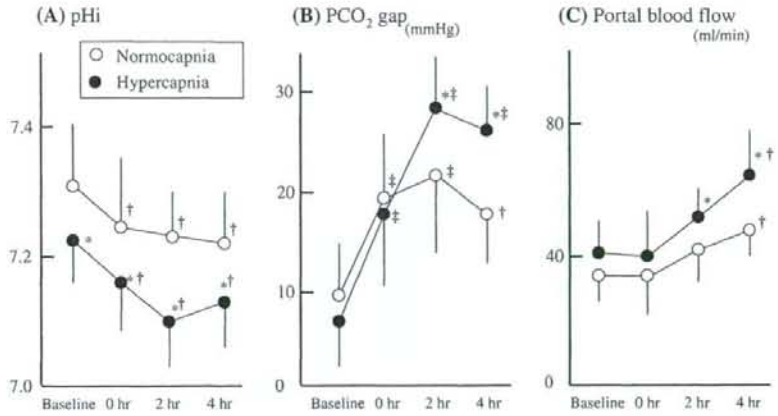

Fig. 2 Changes of intramucosal pH (pHi), PCO_2 gap and portal blood flow during 4-h study periods. Data are expressed as mean ± SD. Significance: * $P < 0.05$ versus normocapnia group. † $P < 0.05$, ‡ $P < 0.01$ versus baseline in each group

Figure 3 illustrates the changes of plasma FD4 concentration, wet/dry weight ratio of gut and ileal MPO activity. Plasma FD4 concentration in hypercapnia group, which was comparable with those in two sham groups was significantly less versus normocapnia group. Simultaneously, the wet/dry weight ratio of terminal ileum in hypercapnia group was significantly lower versus normocapnia group. However, ileal MPO activity to reflect neutrophil accumulation in the intestinal wall was similar between the study groups, both of which appeared to be augmented versus the sham animals.

Pulmonary effects of hypercapnic acidosis during LPS infusion

To verify the effects of hypercapnic acidosis on injured lungs evoked by LPS infusion in this model, we measured

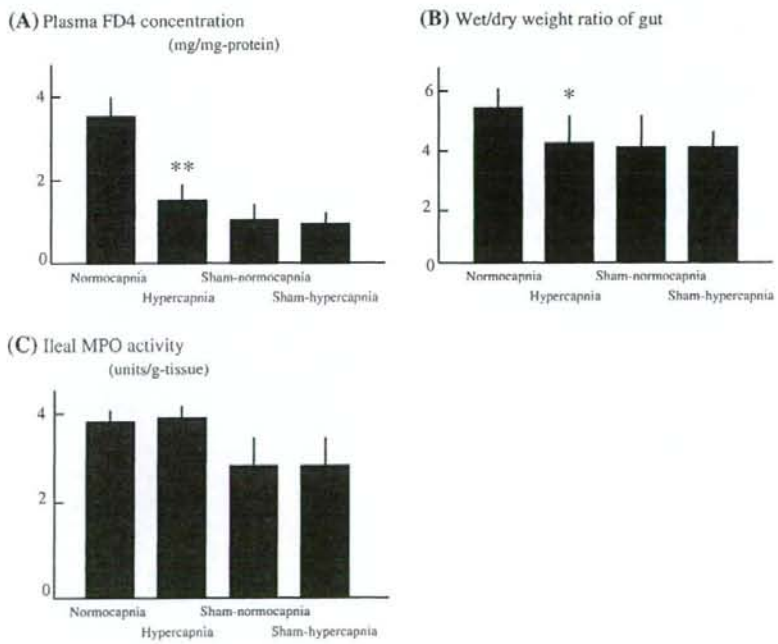

Fig. 3 Changes of plasma FD4 concentrations, wet/dry weight ratio of terminal ileum and ileal myeloperoxidase (MPO) activity. Data are expressed as mean ± SD. Significance: * $P < 0.05$, ** $P < 0.01$ versus normocapnia group

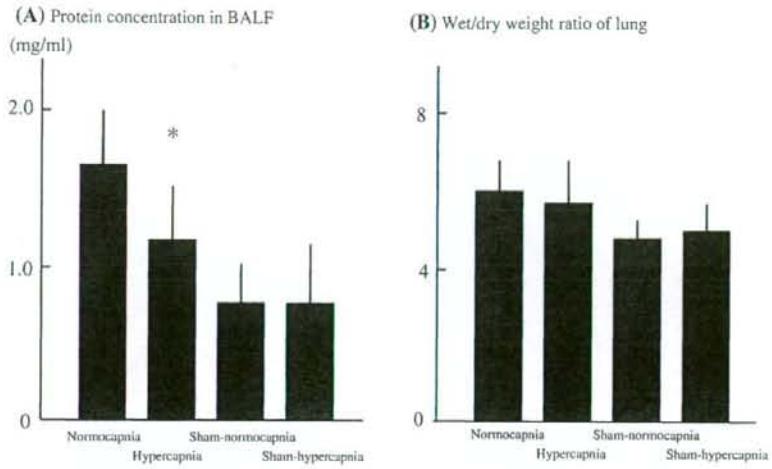

Fig. 4 Changes of protein concentration in bronchoalveolar lavage fluid (BALF) and wet/dry weight ratio of lung. Data are expressed as mean ± SD. Significance: * $P < 0.05$ versus normocapnia group

the changes of protein concentration in BALF and wet/dry weight ratio of lung (Fig. 4). We then found that the protein concentration in BALF was significantly less in hypercapnia versus normocapnia group, whereas wet/dry weight ratio of lung was not significantly different between the groups.

Discussion

The present study indicates that hypercapnic acidosis, approximately at 70 mmHg of $PaCO_2$, ameliorates LPS-induced gut barrier dysfunction associated with the progression of intramucosal acidosis, and that intramucosal acidosis per se is not directly associated with deterioration of mucosal barrier function. In addition, overall tissue and cellular destruction, including the alterations of microvascular and alveolar permeability in endotoxemia, were minimized by short-term application of hypercapnic acidosis. These findings bring up a new hypothesis that lung protective strategy, subsequently inducing hypercapnic acidosis, could be another approach to prevent bacterial translocation from gut in critically ill state like endotoxemia.

To obviate confounding factors such as hypotension but concurrently to elicit gut mucosal injury, we applied low-dose endotoxin infusion model of rabbits with aggressive fluid resuscitation. These animals showed normotensive hyperdynamic circulatory responses as previously reported [16] although it remains unclear why MAP in the LPS-treated animals was kept slightly lower even at baseline period versus the sham (Table 1). Besides, progressive reduction of circulating WBC counts with mild elevation of arterial lactate fit well with the finding in septic patients who were adequately resuscitated [22], suggesting that injected LPS was biologically active for 4-h study periods. Since hypercapnic acidosis ameliorated LPS-induced lung injury as shown in the protein leakage into BALF, our model could be comparable with previous studies, demonstrating protective property of hypercapnic acidosis on several types of injured lung [3, 4, 9]. Protective properties of hypercapnic acidosis on injured organs could be produced by its vasodilating and/or anti-inflammatory mechanisms. Tashkin et al. [23] demonstrated that hypercapnic acidosis caused a significant vasodilator effect, which was not related to arterial pH or β-adrenergic stimulation, on mesenteric arterial beds depending on the extent of hypercapnia. Indeed, we found that hypercapnic acidosis augmented the elevation of portal blood flow evoked by endotoxemia and fluid resuscitation. Such augmentation of blood flow to splanchnic area by hypercapnic acidosis might be able to reduce plasma FD4 concentration and show restoration of gut mucosal permeability by a simple dilution effect. However, portal blood flow was augmented to approximately 20% extent in hypercapnia group, which was unable to account for a marked increase of FD4 concentration, twice as much as higher versus normocapnia. Among inflammatory mediators and cells, tissue accumulation of activated neutrophils is a major contributor to develop gut mucosal injury [14]. Although tissue MPO activity alone may be insufficient to determine the precise involvement of activated neutrophils, the data in the LPS-treated animals showed apparently higher level compared to the sham group as previously reported in lung injury model [24]. However, it should be noted that the effects of hypercapnia on neutrophil function in situ such as phagocytosis and/or bactericidal capacity are not necessarily assessed using MPO activity.

Another important finding of this study was to show that PCO_2 gap progressively increased despite an augmentation of portal blood flow in hypercapnia versus normocapnia group. Paradoxically, arterial lactate in hypercapnia group was slightly but significantly reduced at 4-h study period versus the normocapnia group. As previously documented [25], arterial lactate per se, particularly in sepsis, does not always mirror the severity of tissue hypoxia. Although we did not directly assess the alterations of microvascular blood flow in gut mucosa, this finding suggests that the amelioration of LPS-induced gut barrier dysfunction under hypercapnic acidosis was not caused by the increase of intramucosal blood flow. High PCO_2 produces a rightward shift of the oxygen dissociation curve by increasing P50 value of hemoglobin, resulting in the augmentation of oxygen delivery to tissues as flow-independent mechanism [26]. While the exact mechanisms to enlarge PCO_2 gap remain unclear, hypercapnic acidosis might be able to redistribute blood flow to the others from mucosal layer of intestinal wall, augment intramucosal CO_2 production and/or produce progression of intramucosal hypoxia resulting in anaerobic glycolysis. In addition, the changes of intracellular pH exert a variety of actions on ionic conductance of cellular membranes, thus disturbing electric properties of excitable cells [27]. In gut mucosa, these alterations of membrane potential may be able to make intestinal wall rigid against macromolecules, i.e., hypercapnic acidosis preserves gut mucosal homeostasis possibly through the modulation of membrane potential rather than the amelioration of intramucosal blood flow.

There are several limitations to interpret the data herein. Since the results of this study were obtained during 4 h of acute hypercapnia, prolonged effects remain to be fully determined. The present study clearly showed that gut mucosal barrier dysfunction caused by endotoxin infusion was ameliorated at least within 4 h of moderate hypercapnia. Second, this endotoxemic model may not be clinically relevant to mirror septic patients because hemodynamic parameters such as MAP and heart rate remained constant throughout the study periods. Although we did not measure cardiac output directly, increased portal blood flow up to 30% in normocapnia group suggests that cardiac output in this model was augmented by infusion of endotoxin and aggressive fluid therapy. Finally, since enzyme-linked immunoassay kits for many kinds of inflammatory cytokines are not commercially available for rabbits, we are unable to examine these markers, which might be more convincing to elucidate the mechanisms regarding the modulation of inflammation.

In conclusion, hypercapnic acidosis minimized endotoxin-induced gut barrier dysfunction possibly through neutrophil-independent mechanisms. Lung protective strategy inducing hypercapnic acidosis may serve to protect gut barrier function in critically ill patients.

Acknowledgment Financial support was provided by the departmental source.

References

1. Amato MB, Barbas CS, Mederios DM, Magaldi RB, Schettino GP, Lorenzi-Fihlo G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CRR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
2. ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and acute respiratory distress syndrome. N Engl J Med 342:1301–1308
3. Laffey JG, Tanaka M, Engelberts D, Luo X, Yuan S, Tanswell AK, Post M, Lindsay T, Kavanagh BP (2000) Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med 162:2287–2294
4. Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, McLoughlin P (2004) Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. Am J Respir Crit Care Med 169:46–56
5. Doerr CH, Gajic O, Berrios JC, Caples S, Abdel M, Lymp JF, Hubmayr RD (2005) Hypercapnic acidosis impairs plasma membrane wound resealing in ventilator-injured lungs. Am J Respir Crit Care Med 171:1371–1377
6. Laffey JG, Engelberts D, Kavanagh BP (2000) Buffering hypercapnic acidosis worsens acute lung injury. Am J Respir Crit Care Med 161:141–146
7. Wexeis JC, Myhre ES (1987) Hypocapnia and hypercapnia in the dog: effects on myocardial blood flow and haemodynamics during beta- and combined alpha- and beta-adrenoceptor blockade. Clin Physiol 7:21–33
8. Atkinson JLD, Anderson RE, Sundt TM (1990) The effect of carbon dioxide on the diameter of brain capillaries. Brain Res 517:333–340
9. Takeshita K, Suzuki Y, Nishio K, Takeuchi O, Toda T, Kudo H, Miyao N, Ishii M, Sato N, Naoki K, Aoki T, Suzuki K, Hiraoka R, Yamaguchi K (2003) Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-κB activation. Am J Respir Cell Mol Biol 29:124–132
10. O'Croinin D, Chonghaile MN, Higgins B, Laffey JG (2005) Bench-to-bedside review: permissive hypercapnia. Crit Care 9:51–59
11. Kitakaze M, Weisfeldt ML, Marban E (1988) Acidosis during early reperfusion prevents myocardial stunning in perfused ferret hearts. J Clin Invest 82:920–927
12. Nomura F, Aoki M, Forbess JM, Mayer JE (1994) Effects of hypercapnic acidotic reperfusion on recovery of myocardial function after cardioplegic ischemia in neonatal lambs. Circulation 90:321–327
13. Meakins JL, Marshall JC (1986) The gastrointestinal tract: the motor of multiple organ failure. Arch Surg 121:197–201
14. Kubes P, Hunter JA, Granger DN (1992) Ischemia/reperfusion-induced fenile intestinal dysfunction: importance of granulocyte recruitment. Gastroenterology 103:807–812

15. Ai K, Kotake Y, Satoh T, Serita R, Takeda J, Morisaki H (2001) Epidural anesthesia retards progression of intestinal acidosis and increase of portal endotoxin concentrations during acute hypoxia in rabbits. Anesthesiology 94:263–269
16. Kosugi S, Morisaki H, Satoh T, Ai K, Yamamoto M, Soejima J, Serita R, Kotake Y, Ishizaka A, Takeda J (2005) Epidural analgesia prevents endotoxin-induced gut mucosal injury in rabbits. Anesth Analg 101:265–272
17. Bennett-Guerrero E, Panah MH, Bodian CA, Methikatam BJ, Alfarone JR, DePerio M, Mythen MG (2000) Automated detection of gastric luminal partial pressure of carbon dioxide during cardiovascular surgery using the Tonocap. Anesthesiology 92:38–45
18. Otamiri T, Sjödahl R, Tagesson C (1987) An experimental model of studying reversible intestinal ischemia. Acta Chir Scand 153:51–56
19. Wang W, Smail N, Wang P, Chaudry IH (1998) Increased gut permeability agter hemorrhage is associated with upregulation of local and systemic IL-6. J Surg Res 79:39–46
20. Suzuki K, Ota H, Sagawa T, Sakatani T, Fugikura T (1983) Assay method for myeloperoxidase in human polymorphonuclear leukocytes. Anal Biochem 132:345–352
21. Matute-Bello G, Frevert CW, Kajikawa O, Skerrett SJ, Goodman RB, Park DR, Martin TR (2001) Septic shock and acute lung injury in rabbits with peritonitis. Failure of the neutrophil response to localized infection. Am J Respir Crit Care Med 163:234–243
22. Fink MP, Heard SO (1990) Laboratory models of sepsis and septic shock. J Surg Res 49:186–196
23. Tashkin DP, Goldstein PJ, Simmnons DH (1969) Effect of acute respiratory acidosis on mesenteric circulation of dogs. Am J Physiol 217:1549–1558
24. Laffey JG, Jankov RP, Engelberts D, Tanswell AK, Post M, Lindsay T, Mullen JB, Romaschin A, Stephens D, McKerlle C, Kavanagh BP (2003) Effects of therapeutic hypercapnia on mesenteric ischemia-reperfusion injury. Am J Respir Crit Care Med 168:1383–1390
25. Trzeciak S (2004) Lac-time? Crit Care Med 32:1785–1786
26. Feihl F, Perret C (1994) Permissive hypercapnia: how permissive should we be? Am J Respir Crit Care Med 150:1722–1737
27. Moody W (1984) Effects of intracellular H^+ on the electrical properties of excitable cells. Ann Rev Neurosci 7:257–278

J Anesth (2009) 23:61–66
DOI 10.1007/s00540-008-0706-3

Journal of
Anesthesia

Difference in autologous blood transfusion-induced inflammatory responses between acute normovolemic hemodilution and preoperative donation

Yoshifumi Kotake[1], Michiko Yamamoto[1], Midori Matsumoto[2], Takashige Yamada[1], Hiromasa Nagata[1], Hiroshi Morisaki[1], and Junzo Takeda[1]

[1] Department of Anesthesiology, Keio University, Tokyo, Japan
[2] Department of Anesthesiology, Tachikawa Kyosai Hospital, Tokyo, Japan

Abstract
Purpose. The inflammatory response triggered by transfusion is implicated in the pathophysiology of transfusion-related immunomodulation. The authors hypothesized that two distinctive autotransfusion methods, acute normovolemic hemodilution (ANH) and preoperative donation (PD), have different influences on both inflammatory mediator generation during storage and the inflammatory response after a transfusion. The purpose of this study was to compare the plasma concentrations of neutrophil elastase (NE), interleukin (IL)-6, IL-8, and IL-10 in patients who underwent either of these two autologous transfusion methods.
Methods. With institutional review board approval, the plasma concentrations of the above inflammatory mediators were determined in 23 patients with ANH and 8 patients with PD at the following time points: after anesthetic induction, at the end of the operation, and the morning of postoperative day 1. The concentrations of these inflammatory mediators were also measured in the donated blood obtained by either ANH or PD before retransfusion.
Results. The mean storage durations were 3.7 h and 6.1 days for ANH and PD, respectively. Higher concentrations of NE and IL-10 were detected in the PD blood than in the ANH blood. Long duration of storage and/or low temperature may have been responsible for the increased NE and IL-10 concentrations in the PD blood. However, the difference between the two groups in the extent of increased plasma concentrations of these inflammatory mediators was not statistically significant.
Conclusion. Inflammatory mediators were significantly increased in PD blood during storage compared to the blood obtained by ANH. However, their effects on the inflammatory response elicited in the recipients were not significantly different.

Address correspondence to: Y. Kotake, Department of Anesthesiology, Toho University, 6-11-1 Ohmori-Nishi, Ohta-ku, Tokyo 143-8540, Japan
Received: April 28, 2008 / Accepted: October 10, 2008

Key words Preoperative donation · Acute normovolemic hemodilution · Neutrophil elastase · Interleukin · HES 70/0.5

Introduction

The complications of allogeneic transfusions, such as transfusion-related immunological modulation and the transmission of infectious agents, are widely acknowledged [1–3]. Biological substances released from blood components during storage play important roles in these side effects [4–6]. For example, the cause of the febrile nonhemolytic transfusion reaction was previously attributed to the immune system's reaction against donor leukocytes. However, several studies have implicated inflammatory cytokines generated during storage for this syndrome [7,8]. Furthermore, proteins and lipids released during storage prime neutrophils and may result in transfusion-related acute lung injury [9,10]. In this respect, several studies have compared the generation of inflammatory mediators during storage and the reactions of the recipients of autologous and allogeneic blood transfusions [11–13]. These studies mainly focused on the difference between preoperative donation (PD) and allogeneic blood transfusions and concluded that autologous blood elicited less of an inflammatory response. However, recent reports have demonstrated that even PD blood triggers an inflammatory response in the recipient under certain conditions [14,15]. To clarify the possible effects of autologous transfusion on the inflammatory response, we compared the inflammatory response of PD and acute normovolemic hemodilution (ANH), another method for autologous transfusion.

The purpose of this prospective, observational study was to investigate the production of inflammatory mediators in ANH and PD during storage and the subsequent inflammatory responses in the transfused hosts.

Subjects and methods

The institutional review board of Tachikawa Kyosai Hospital approved the study protocol, and informed consent from each patient was obtained before the study started. Consecutive patients undergoing major abdominal, urological, and orthopedic surgery with 800 ml of ANH or PD at Tachikawa Kyosai Hospital during a 30-month period were prospectively examined. Patients who were transfused with less than 800 ml of autologous blood and those who received concomitant allogeneic blood products were excluded from the analysis. The general anesthesia applied to all the patients was sevoflurane and nitrous oxide.

Autologous transfusion

The inclusion criteria of ANH were as follows: estimated intraoperative blood loss more than 1000 ml and preoperative hemoglobin (Hb) more than 11 $g \cdot dl^{-1}$. After the induction of general anesthesia, 800 ml of autologous blood was drawn into a blood bag containing citrate-phosphate-dextrose (CPD; Terumo, Tokyo, Japan) via an intravenous catheter placed in the right internal jugular vein. After blood collection, 1000 ml of 6% hydroxyethyl starch solution (Saline-Hes HES 70/0.5; Kyorin Pharmaceuticals, Tokyo, Japan) was administered to maintain normovolemia. The autologous blood, stored at room temperature, was retransfused to maintain Hb at more than 8 $g \cdot dl^{-1}$ during surgery. Other anesthetic management, including fluid administration, was at the discretion of the attending anesthesiologist.

In the PD group, orthopedic patients whose estimated intraoperative blood loss exceeded 1000 ml were included. Autologous blood (800 ml) was donated before surgery and was stored in a CPD-containing bag at 4°C. Patients received supplemental $FeSO_4$ and recombinant human erythropoietin (rhEPO; Daiichi Pharmaceuticals, Tokyo, Japan). The same anesthetic management as that in the ANH group was applied, including the trigger for transfusion of autologous blood.

Measurements of neutrophil elastase (NE) and interleukin (IL)-6, IL-8, and IL-10

The sample of donated blood was obtained at the time of retransfusion. Arterial blood was obtained at the following time points: after anesthetic induction, at the end of the operation, and the morning of postoperative day 1 (POD 1). All samples were immediately centrifuged at 4°C and the plasma was stored at –80°C until assay. Plasma concentrations of the following inflammatory mediators were assayed with commercially available enzyme immunoassay systems: NE, with PMN Elastase (Merck, Darmstadt, Germany); and IL-6, IL-8, and IL-10, with Biotrak cytokine human EIA systems (Amersham, Buckinghamshire, UK). All the assays were duplicated and averaged data were used in the subsequent analysis. The clinical presentations of any types of transfusion reactions were recorded.

Statistical methods

The values for demographic and surgical data were expressed as means ± SD. The values for the concentrations of the inflammatory mediators were expressed as medians and 25th–75th percentiles. Friedman's test assessed changes within the groups. If the P value was less than 0.05, post-hoc comparisons were performed for the change from the preoperative value by a two-tailed Wilcoxon test for pair-wise comparisons. Because multiple comparisons were required to evaluate statistically significant change within a group, $P < 0.01$ was used. Comparisons between the ANH and PD groups, were performed with the Mann-Whitney test and differences were considered significant if the P value was less than 0.05.

Results

The patient demographics are summarized in Table 1. There were no significant differences in any parameters between the two groups. The ANH group ($n = 23$) consisted of patients who underwent major gastrointestinal ($n = 10$) and urological ($n = 11$) surgery for malignancy, as well as patients who underwent gynecological and spinal surgery ($n = 1$ each). The PD group ($n = 8$) consisted of patients who underwent orthopedic surgery (spinal or hip replacement surgery).

The mean storage duration of ANH blood and PD blood was 3.7 h and 6.1 days, respectively. All the donated blood was retransfused and there were no clinically relevant transfusion reactions after retransfusion in either of the groups.

The concentrations of the inflammatory mediators in the donated blood at the time of retransfusion are sum-

Table 1. Patient characteristics

	ANH ($n = 23$)	PD ($n = 8$)
Age (years)	52 ± 12	50 ± 13
Sex (M/F)	18/5	5/3
Duration of surgery (min)	327 ± 156	227 ± 88
Blood loss (g)	833 ± 397	780 ± 570
Hb on POD 1 ($g \cdot dl^{-1}$)	11.6 ± 1.5	11.1 ± 1.0
WBC on POD 1 (mm^{-3})	12 160 ± 2770	11 540 ± 1610

Data values are expressed as means ± SD. No significant differences were found in any of the parameters

Table 2. Concentrations of inflammatory mediators in the autologous blood

	ANH ($n = 23$)	PD ($n = 8$)
Neutrophil elastase ($ng \cdot ml^{-1}$)	251 (151–280)	506 (479–633)*
IL-6 ($pg \cdot ml^{-1}$)	4.9 (2.3–4.7)	5.3 (2.0–5.5)
IL-8 ($pg \cdot ml^{-1}$)	10.0 (2.8–11.7)	18.1 (8.2–22.0)
IL-10 ($pg \cdot ml^{-1}$)	11.9 (5.9–18.2)	28.0 (11.4–42.6)*

* $P < 0.05$ vs ANH group
Concentration was determined at the time of retransfusion. Data values are expressed as means (25th–75th percentiles)

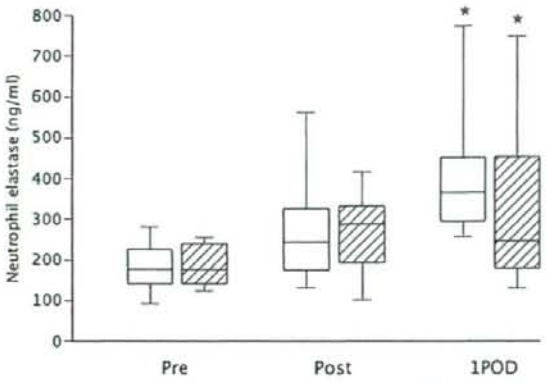

Fig. 1. The plasma concentrations of neutrophil elastase in the acute normovolemic hemodilution (ANH) group ($n = 23$; *open boxes*) and PD group ($n = 8$; *shaded boxes*) are summarized in this box plot. The median values, 25th–75th percentiles, and 10th–90th percentiles are given. *Pre*, after anesthetic induction; *Post*, at the end of operation; *1POD*, the morning after the operation. *$P < 0.01$ vs preoperative value with Wilcoxon rank sum test. No significant differences were noted between the ANH group and the PD group

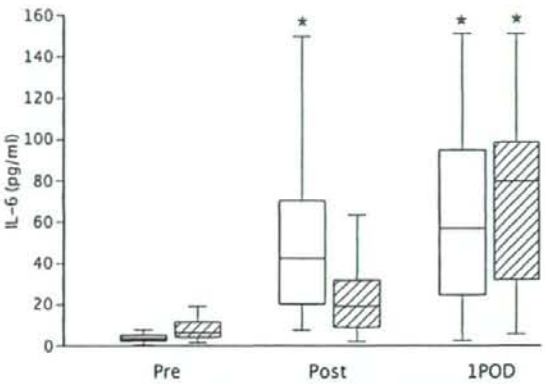

Fig. 2. The plasma concentrations of interleukin-6 (*IL-6*) in the ANH group ($n = 23$; *open boxes*) and PD group ($n = 8$; *shaded boxes*) are summarized in this box plot. The median values, 25th–75th percentiles, and 10th–90th percentiles are given. *Pre*, after anesthetic induction; *Post*, at the end of operation; *1POD*, the morning after the operation. *$P < 0.01$ vs preoperative value with Wilcoxon rank sum test. No significant differences were noted between the ANH group and the PD group

marized in Table 2. The concentrations of NE and IL-10 in the donated blood were significantly higher in the PD group than in the ANH group. However, neither IL-6 nor IL-8 levels in the donated blood differed between the two groups.

Changes in the plasma concentrations of the studied inflammatory mediators during the perioperative period are summarized in Figs. 1 to 4. There was a significant increase in the plasma NE concentration on POD 1 compared to the preoperative value in both groups, but there was no significant difference between the groups (Fig. 1). Plasma IL-6 also steadily increased immediately postoperatively and on POD 1 in the ANH group (Fig. 2). In the PD group, it remained unchanged immediately postoperatively, but was significantly increased on POD 1. Plasma IL-8 was significantly increased immediately postoperatively in the ANH group (Fig. 3) and then decreased significantly on POD 1 and returned to the preoperative level. In the PD group, no significant change in plasma IL-8 was noted during the study period. The plasma IL-10 level did not change during the study period in either of the groups (Fig. 4). Although the changing profiles of these inflammatory mediators in the two groups were somewhat different over time, the plasma concentrations of NE, IL-6, IL-8, and IL-10 at equivalent time points were not significantly different between the two groups.

Discussion

This study demonstrated that NE and IL-10 were significantly higher in PD blood than in ANH blood (Table 2). This finding indicates that the generation of inflammatory mediators is, to some extent, affected by storage conditions. The risks associated with allogeneic blood transfusions have been well recognized, and autologous

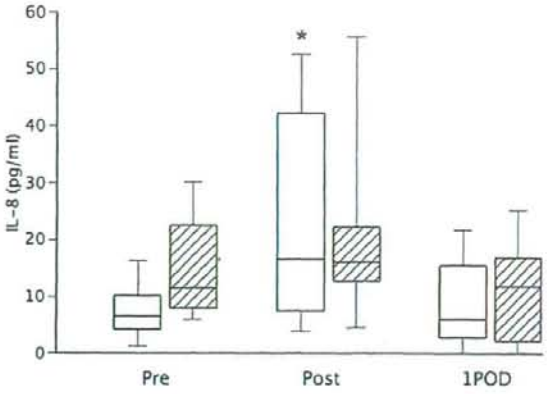

Fig. 3. The plasma concentrations of IL-8 in the ANH group ($n = 23$; *open boxes*) and the PD group ($n = 8$; *shaded boxes*) are summarized in this box plot. The median values, 25th–75th percentiles, and 10th–90th percentiles are given. *Pre*, after anesthetic induction; *Post*, at the end of operation; *1POD*, the morning after the operation. *$P < 0.01$ vs preoperative value with Wilcoxon rank sum test. No significant differences were noted between the ANH group and the PD group

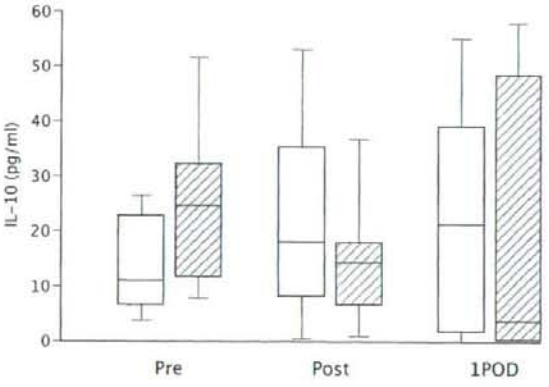

Fig. 4. The plasma concentrations of IL-10 in the ANH group ($n = 23$; *open boxes*) and the PD group ($n = 8$; *shaded boxes*) are summarized in this box plot. The median values, 25th–75th percentiles, and 10th–90th percentiles are given. *Pre*, after anesthetic induction; *Post*, at the end of operation; *1POD*, the morning after the operation. No significant differences were noted between any time points and the preoperative value, nor were any significant differences noted between the ANH group and the PD group

blood transfusion is now widely preferred [16]. One of the major advantages of autologous transfusion is that it causes less of a proinflammatory response when compared to allogeneic blood transfusions.

Recently, much attention has focused on the accumulation of inflammatory mediators during the retrieval and storage of donated blood. Possible relationships between the accumulation of inflammatory mediators and the side effects of blood transfusions, such as nonhemolytic febrile reaction, transfusion-related lung injury, and multiple organ failure after a massive transfusion have been investigated. For example, several studies have reported increased concentrations of NE, IL-1β, IL-6, and IL-8 during storage [17–20]. Additionally, Biedler et al. [13] reported that banked whole blood had an immunosuppressive effect that was largely attributable to storage-dependent factors. Jensen et al. [4] reported an increased IL-6 concentration 3 days after colorectal surgery in patients who underwent allogeneic transfusion, and they noted that the increase was attenuated by leukocyte depletion before storage.

Because these findings suggest that the presence of leukocytes during storage significantly augments the inflammatory response, leukocyte depletion in autologous transfusion may have the potential to attenuate the inflammatory response. Additionally, the storage duration is obviously longer in PD blood than in ANH blood. This storage period may have a significant impact on the transfusion-related inflammatory response. Recent investigations, which have reported that the prolonged storage of allogeneic blood might increase morbidity, may support this possibility [21–23]. The temperature during storage may also affect the inflammatory response. ANH blood is typically stored at room temperature in order to preserve platelet function [24,25]. Based on these possibilities, we hypothesized that the methods of autologous transfusion may affect the perioperative inflammatory response, because different storage durations and conditions may cause a distinct pattern of inflammatory mediator generation.

We found no differences in the IL-6 and IL-8 concentrations in the stored blood between our two groups. These cytokines are, presumably, released from the neutrophils and monocytes contained in the stored blood. Kristiansson et al. [18] reported increased concentrations of these cytokines in red blood cell concentrates during storage. Interestingly, they reported that the increase of IL-6 was independent of the length of storage, but the increase of IL-8 was dependent on the length of storage. In contrast, we found that the IL-10 concentration in the PD blood increased significantly during storage (Table 2). Hodge et al. [26] reported that IL-10 production during storage was decreased at room temperature and increased at 4°C. Our data correspond with their conclusion that temperature plays an important role in IL-10 production during storage.

The plasma concentrations of the investigated cytokines increased at some points of measurement in each study group, as shown in Figs. 1 through 4. However, there were no significant differences in the plasma concentrations of IL-6, IL-8, and IL-10 between the two

groups. Additionally, there was no apparent relationship between the concentration in the stored blood and the plasma sampled from the patients. Avall et al. [12] found that patients who were transfused with PD blood demonstrated higher IL-6 and IL-8 concentrations in plasma than patients who received allogeneic blood transfusion. They concluded that an attenuated cytokine response to allogeneic transfusion was a sign of immunosuppression. Heiss et al. [11] reported a significant increase in plasma IL-10 after an allogeneic transfusion but not after an autologous transfusion in patients undergoing colorectal cancer surgery. Tylman et al. [27] reported that reinfusion of salvaged blood resulted in an increased plasma IL-10 concentration. These results suggest that the difference between PD and ANH had less of an impact on the transfusion-triggered inflammatory response compared to allogeneic transfusion or the reinfusion of salvaged blood.

There are some limitations in the present study. First, the present study population varied in terms of background and surgical procedure. These differences were mainly caused by the fact that the decision to apply autologous transfusion was at the discretion of the surgeons and was based on their clinical preferences. These differences make the interpretation of the data somewhat difficult. The different baseline characteristics of the subjects, especially the presence of malignancy, may have affected the results. Previous investigations have demonstrated that preoperative values of the inflammatory cytokines that we investigated were similar in patients undergoing either surgery for cancer removal or orthopedic reconstructive surgery [4,11,12,27]. However, it is still possible that the transfusion-related inflammatory response was actually less in our ANH group, but the difference may have been undetected due to the influence of a more stressful surgical procedure in the ANH group. Second, the numbers of participants in the two groups were small and unevenly distributed. Because the cytokine concentrations were not normally distributed, formal power analysis was not feasible for our study. However, we do not think that increasing the number of participants would drastically change the results. Third, other medications may also affect the inflammatory response. For example, erythropoietin [28] and $FeSO_4$ [29] were administered to the PD group, while HES 70/0.5 was infused to maintain normovolemia in the ANH group. Thus, the anti-inflammatory properties of the HES solutions may have contributed to the results [30]. However, the preparations used in the present study have characteristics different from those of commonly used HES preparations, such as HES 130/0.4 or 200/0.5, so this possibility remains to be clarified [31]. Despite these limitations, the present study provided previously unknown information about the differences in inflammatory mediator generation during storage and the inflammatory response elicited in the recipients of PD blood and ANH.

In conclusion, this study demonstrated higher NE and IL-10 concentration over time in predonated autologous blood than in instantaneous autologous blood obtained by normovolemic hemodilution. This difference may be related to the differences in storage conditions between the two methods. However, the plasma concentrations of these inflammatory mediators were not different between the study groups after retransfusion, indicating that the inflammatory response was not affected by the method of autologous transfusion.

References

1. Landers DF, Hill GE, Wong KC, Fox IJ. Blood transfusion-induced immunomodulation. Anesth Analg. 1996;82:187–204.
2. Blajchman MA. Allogeneic blood transfusions, immunomodulation, and postoperative bacterial infection: do we have the answers yet? Transfusion. 1997;37:121–5.
3. Heiss MM. Risk of allogeneic transfusions. Br J Anaesth. 1998; 81(Suppl 1):16–9.
4. Jensen LS, Hokland M, Nielsen HJ. A randomized controlled study of the effect of bedside leucocyte depletion on the immunosuppressive effect of whole blood transfusion in patients undergoing elective colorectal surgery. Br J Surg. 1996;83:973–7.
5. Innerhofer P, Luz G, Spotl L, Hobisch-Hagen P, Schobersberger W, Fischer M, Nussbaumer W, Lochs A, Irschick E. Immunologic changes after transfusion of autologous or allogeneic buffy coat-poor versus white cell-reduced blood to patients undergoing arthroplasty. I. Proliferative T-cell responses and the balance of helper and suppressor T cells. Transfusion. 1999;39:1089–96.
6. Weisbach V, Wanke C, Zingsem J, Zimmermann R, Eckstein R. Cytokine generation in whole blood, leukocyte-depleted and temporarily warmed red blood cell concentrates. Vox Sang. 1999; 76:100–6.
7. Muylle L, Joos M, Wouters E, De Bock R, Peetermans ME. Increased tumor necrosis factor alpha (TNF alpha), interleukin 1, and interleukin 6 (IL-6) levels in the plasma of stored platelet concentrates: relationship between TNF alpha and IL-6 levels and febrile transfusion reactions. Transfusion. 1993;33: 195–9.
8. Heddle NM, Klama L, Singer J, Richards C, Fedak P, Walker I, Kelton JG. The role of the plasma from platelet concentrates in transfusion reactions. N Engl J Med. 1994;331:625–8.
9. Silliman CC, Voelkel NF, Allard JD, Elzi DJ, Tuder RM, Johnson JL, Ambruso DR. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. J Clin Invest. 1998;101:1458–67.
10. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest. 2004;126:249–58.
11. Heiss MM, Fraunberger P, Delanoff C, Stets R, Allgayer H, Strohlein MA, Tarabichi A, Faist E, Jauch KW, Schildberg FW. Modulation of immune response by blood transfusion: evidence for a differential effect of allogeneic and autologous blood in colorectal cancer surgery. Shock. 1997;8:402–8.
12. Avall A, Hyllner M, Bengtson JP, Carlsson L, Bengtsson A. Postoperative inflammatory response after autologous and allogeneic blood transfusion. Anesthesiology. 1997;87:511–6.
13. Biedler AE, Schneider SO, Seyfert U, Rensing H, Grenner S, Girndt M, Bauer I, Bauer M. Impact of alloantigens and storage-associated factors on stimulated cytokine response in an in vitro model of blood transfusion. Anesthesiology. 2002;97: 1102–9.

14. Domen RE. Adverse reactions associated with autologous blood transfusion: evaluation and incidence at a large academic hospital. Transfusion. 1998;38:296–300.
15. Covin RB, Ambruso DR, England KM, Kelher MR, Mehdizadehkashi Z, Boshkov LK, Masuno T, Moore EE, Kim FJ, Silliman CC. Hypotension and acute pulmonary insufficiency following transfusion of autologous red blood cells during surgery: a case report and review of the literature. Transfus Med. 2004; 14:375–83.
16. Lisander B, Ivarsson I, Jacobsson SA. Intraoperative autotransfusion is associated with modest reduction of allogeneic transfusion in prosthetic hip surgery. Acta Anaesthesiol Scand. 1998;42: 707–12.
17. Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, Denny C, Silliman CC. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. 1999;178:570–2.
18. Kristiansson M, Soop M, Saraste L, Sundqvist KG. Cytokines in stored red blood cell concentrates: promoters of systemic inflammation and simulators of acute transfusion reactions? Acta Anaesthesiol Scand. 1996;40:496–501.
19. Shanwell A, Kristiansson M, Remberger M, Ringden O. Generation of cytokines in red cell concentrates during storage is prevented by prestorage white cell reduction. Transfusion. 1997; 37:678–84.
20. Tolksdorf B, Frietsch T, Quintel M, Kirschfink M, Becker P, Lorentz A. Humoral immune response to autologous blood transfusion in hip surgery: whole blood versus packed red cells and plasma. Vox Sang. 2001;81:180–6.
21. Biffl WL, Moore EE, Offner PJ, Ciesla DJ, Gonzalez RJ, Silliman CC. Plasma from aged stored red blood cells delays neutrophil apoptosis and primes for cytotoxicity: abrogation by poststorage washing but not prestorage leukoreduction. J Trauma. 2001;50: 426–31.
22. Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, Marin-Niebla A, Herruzo-Aviles A, Camacho-Larana P, Loscertales J. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. Anesthesiology. 2003; 98:815–22.
23. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008;358:1229–39.
24. Goodnough LT. Acute normovolemic hemodilution. Vox Sang. 2002;83 (Suppl 1): 211–5.
25. Jamnicki M, Kocian R, van der Linden P, Zaugg M, Spahn DR. Acute normovolemic hemodilution: physiology, limitations, and clinical use. J Cardiothorac Vasc Anesth. 2003;17:747–54.
26. Hodge G, Markus C, Nairn J, Hodge S. Effect of blood storage conditions on leucocyte intracellular cytokine production. Cytokine. 2005;32:7–11.
27. Tylman M, Bengtson JP, Avall A, Hyllner M, Bengtsson A. Release of interleukin-10 by reinfusion of salvaged blood after knee arthroplasty. Intensive Care Med. 2001;27:1379–84.
28. Aguilera A, Selgas R. Effect of recombinant human erythropoietin on inflammatory status in dialysis patients. Nephrol Dial Transplant. 2004;19 (Suppl 5): V46–53.
29. Oldenburg B, van Berge Henegouwen GP, Rennick D, Van Asbeck BS, Koningsberger JC. Iron supplementation affects the production of pro-inflammatory cytokines in IL-10 deficient mice. Eur J Clin Invest. 2000;30:505–10.
30. Lang K, Suttner S, Boldt J, Kumle B, Nagel D. Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. Can J Anaesth. 2003;50:1009–16.
31. Ickx BE, Bepperling F, Melot C, Schulman C, Van der Linden PJ. Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. Br J Anaesth. 2003;91: 196–202.

J Anesth (2009) 23:87–92
DOI 10.1007/s00540-008-0686-3

Journal of
Anesthesia

An individualized recruitment maneuver for mechanically ventilated patients after cardiac surgery

Ryohei Serita[1], Hiroshi Morisaki[2], and Junzo Takeda[2]

[1]Department of Anesthesiology, Tokyo Dental College Ichikawa General Hospital, 5-11-13 Sugano, Ichikawa 272-8513, Japan
[2]Department of Anesthesiology, School of Medicine, Keio University, Tokyo, Japan

Abstract
Purpose. The recruitment maneuver (RM) has been shown to improve oxygenation for post-cardiopulmonary bypass (CPB) patients; however, sustained inflation of the lung gives rise to hypotension. The primary goal of our study was to evaluate the safety and efficacy of our proposed RM, defined on the basis of dynamic lung compliance (Cdyn).
Methods. Twenty-eight patients undergoing elective cardiac surgery with CPB were assigned to two treatment groups: an individualized RM group, in which a pressure equal to 15 ml × real body weight/Cdyn + positive end-expiratory pressure (PEEP) cmH_2O was applied for 15 s; and a control RM group, in which a pressure of 20 cmH_2O was applied for 25 s. Arterial blood pressure, cardiac output, pulmonary artery pressure, and heart rate (HR) were monitored. Tidal volume (Vt), and airway pressure were continuously obtained from an expiratory flow meter and pressure monitor. Blood samples were obtained and analyzed with a blood gas analyzer.
Results. The changes in HR, mean arterial pressure, mean pulmonary artery pressure, and cardiac index at the end of the RM were not significantly different between the two groups. The mean airway pressure of sustained inflation was 28.3 ± 1.3 cmH_2O in the individualized RM group. The individualized RM significantly improved the Cdyn and partial pressure arterial oxygen/inspiratory fraction of oxygen (P/F) ratio compared with values in the control RM group ($P = 0.026$ and $P = 0.012$, respectively).
Conclusion. The present study indicates that the individualized RM resulted in minimum changes of hemodynamics and brought about improvement in oxygenation and lung compliance.

Key words Recruitment maneuver · Dynamic compliance · Cardiopulmonary bypass · Cardiac surgery

Introduction

The recruitment maneuver (RM) has been shown to improve oxygenation for patients with cardiopulmonary bypass (CPB) [1]. However, sustained inflation of the lung often gives rise to a decrease in venous return and cardiac output (CO) in patients ventilated after CPB [2–6]. A previous study demonstrated that the RM using a sustained pressure technique with continuous inspiratory pressure of 40 cmH_2O for 10 s and 20 s reduced CO by more than 50%, reduced left ventricular end-diastolic area by about 45%, and reduced mean arterial pressure (MAP) by 20% in cardiac patients [6]. The hemodynamic effects of positive airway pressure will depend on the degree of lung inflation and holding time [3,4]. Furthermore, the inflation volume of the lung will contribute to lung compliance and chest wall elastance [5]. Although lung compliance varies among mechanically ventilated patients, in previous studies the level of the sustained inflation pressure used in RMs has been the same constant pressure [1,7]. The optimal pressure and duration of inflation have not been documented for RMs, so that the most effective technique for RM remains undetermined, despite many studies of acute respiratory distress syndrome (ARDS) [8].

Individualization of RM to respiratory mechanics may improve oxygenation without causing hemodynamic effects. Traditionally, static pulmonary mechanics has been used to assess lung mechanics [5]. However, recent studies have indicated that the application of dynamic respiratory mechanics in ventilated patients is more appropriate than the use of static lung mechanics [9–11]. Therefore, we have proposed the concept of an individualized RM that was defined on the basis of dynamic compliance (Cdyn), which is easily obtained from the ventilator as a bedside diagnostic tool [9–11].

The purpose of the present study was to assess the safety and efficacy of our individualized RM in patients after cardiac surgery. The primary endpoint of our study was to verify the hemodynamic effects induced by the individualized RM and to evaluate the improvement in oxygenation and Cdyn.

Address correspondence to: R. Serita
Received: December 3, 2007 / Accepted: August 12, 2008

Methods

Patients

With the approval of our institutional ethics committee and informed consent, from the patients, patients who had undergone elective cardiac surgery with CPB and received overnight mechanical ventilation were enrolled in this prospective and randomized study. Patients were admitted to the 14-bed medical and surgical intensive care unit (ICU) at a university hospital. All patients were mechanically ventilated with an 840 Ventilator System (Nellcor Puritan Bennet, Boulder, CO, USA). Patients with chronic obstructive lung disease (percent volume exhaled during the first second of a forced expiratory maneuver ($[FEV_{1.0\%}] < 70\%$), intraoperative pulmonary trauma, and hemodynamic instability (cardiac index [CI] < 2.2 $l \cdot min^{-1} \cdot m^2$ and/or arterial systolic pressure < 80 mmHg) were excluded. Patients with a pacemaker, intraaortic balloon pumping, or percutaneous cardiopulmonary support were also excluded.

Protocol

All patients were ventilated in the pressure-regulated control mode with 5 cmH_2O of positive end-expiratory pressure (PEEP). Other ventilatory parameters were set as follows: inspiratory plateau pressure (≤30 cmH_2O) was set to obtain a tidal volume (VT) of 10–12 $ml \cdot kg^{-1}$, or inspiratory plateau pressure (>30 cmH_2O) was set to obtain a VT of 6–8 $ml \cdot kg^{-1}$; respiratory rate (RR) and inspiratory fraction of oxygen ($F_{I_{O_2}}$) were set to obtain a Pa_{CO_2} of 38–42 mmHg and a Pa_{O_2} of 150–180 mmHg; inspiratory time was set at 1.0 s. A standard-size tracheal tube was used, with a 7.5-mm inner diameter (ID) for women and an 8.5-mm ID for men. A standard ventilator tubing set (Universal Ventilator Tubing Set; Hudson Respiratory Care, Durham, NC, USA) was used for the respiratory circuit. The patients were well-sedated with a continuous infusion of propofol (50–100 $mg \cdot h^{-1}$), and were observed for 3 to 4 h after intensive care unit (ICU) admission so as to ascertain hemodynamic stability, which was defined as less than 15% variation of hemodynamic parameters with no clinically relevant bleeding (<100 $ml \cdot h^{-1}$).

The VT, RR, and airway pressure were obtained from the eligible patients, and the Cdyn in each patient was calculated as VT/(end-inspiratory pressure—PEEP), breath-by-breath. Then the eligible patients were randomly assigned to two treatment groups: an individualized RM group and a control RM group. In the individualized RM group, an inflation pressure (cmH_2O) equal to 15 × real body weight/Cdyn + PEEP (previously used) was applied for 15 s. We allowed a maximum inflation pressure of up to 45 cmH_2O. In the control RM group, an inflation pressure of 20 cmH_2O was applied for 25 s; this has been reported to have minimal effects on CO and arterial pressure in cardiac surgery patients [2,4]. A table of random numbers, generated by computer software, was utilized for patients' randomization into the two groups (Fig. 1).

The baseline variables of hemodynamics and respiration were obtained before the initiation of RM, and then hemodynamic variables were measured at the end of RM. Respiratory measurements were repeated at 15, 60, and 180 min after RM. The percent change (Δ%) in the variables was calculated [(variables post-RM–the variables at baseline) × 100/ variables at baseline].

Measurements and calculations

Arterial blood pressure was monitored through a radial artery catheter (20-G Arterial Line Kit; Argon Medical, Athens, TX, USA). Cardiac output (CO) and pulmonary arterial pressure (PAP) were measured by the thermodilution method, using a continuous CO catheter (Swan-Ganz CCO mbo; Edwards Life Sciences, Irvine, CA, USA). Heart rate (HR) was monitored by an electrocardiogram.

The VT, RR, and airway pressure were continuously obtained from the expiratory flowmeter and pressure monitor of the ventilator system. Calibrations of the flowmeter and oxymeter, and correction of the respiratory circuit, were performed daily by a biomedical engineer. Respiratory variables, which were obtained from

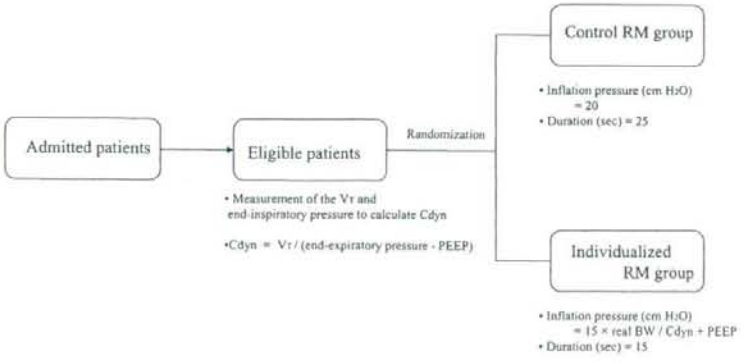

Fig. 1. Protocol for the setting of the recruitment maneuver (RM). *VT*, Tidal volume; *Cdyn*, dynamic compliance; *real BW*, real body weight; *PEEP*, positive end-expiratory pressure

the flowmeter and pressure monitor, were calculated by an average of five breaths. Arterial blood samples were analyzed with a blood gas analyzer (ABL 700; Radiometer, Copenhagen, Denmark). Dynamic compliance was calculated on a breath-by-breath basis.

Statistical analyses

All data values are expressed as means ± SEM unless otherwise described. Before starting the present study, we determined the number of subjects based on a power calculation; this showed that 28 subjects would be needed to achieve an 80% power to detect a difference of 10% in the Pa_{O_2}/FI_{O_2} (P/F) ratio, with $\alpha = 0.05$. The patient characteristics were analyzed using Student's *t*-test, the Mann-Whitney *U*-test, and the Kruskal-Wallis test for differences between the groups. The data were analyzed by two-way repeated-measures analysis-of-variance for differences between the groups, followed by the Mann-Whitney *U*-test. $P < 0.05$ was considered to be statistically significant.

Results

Thirty-nine post-CPB patients were admitted our ICU, and 11 patients were excluded (1 patient with chronic obstructive lung disease, 3 patients with intraoperative pulmonary trauma, 3 patients with hemodynamic instability, 2 patients with a pacemaker, and 2 patients with intraaortic balloon pumping). In total, 28 patients were randomly allocated to the individualized RM group ($n = 14$) or the control RM group ($n = 14$).

The patients' characteristics, including the duration of CPB, were not significantly different between the groups (Table 1). Both hemodynamic and respiratory parameters in the two groups had similar values at baseline and there were no significant differences (Table 2). No patient was ventilated with an inspiratory plateau pressure of more than 30 cmH_2O in either group. The P/F ratio in 4 of the 14 patients in the RM control group and in 6 of the 14 patients in the individualized RM group ranged between 200 and 300. There was no patient with a P/F ratio of less than 200 in either group.

Table 3 shows the percent changes in HR, MAP, mean pulmonary arterial pressure (MPAP), and cardiac index (CI) at the end of the RM. There were no significant differences between the groups. During the RM, no patient in either group was observed with hypotension (MAP < 50 mmHg), arrhythmia, or a low CI ($<2.2\ l \cdot min^{-1} \cdot m^2$). There were significant improvements in the Δ Cdyn and the Δ P/F in the individualized RM group, compared with values in the control RM group ($P = 0.026$ and $P = 0.012$, respectively; Fig. 2). The mean airway pressure of sustained inflation was 28.3 ± 1.3 (21.4–33.8) cmH_2O in the individualized RM group. In the six patients with a P/F ratio ranging between 200 and 300, this pressure was 28.6 ± 1.8 cmH_2O range, 24.2–32.9 cmH_2O. Two of the 14 patients in the control RM group were ventilated with a noninvasive positive-pressure ventilator within 24 h of extubation due to hypoxemia, whereas none of the patients in the individualized RM group needed such ventilation.

There was no correlation between the inflation pressure and the changes in hemodynamic parameters, involving the HR, MAP, MPAP, and CI, in the individualized RM group ($P > 0.1$; linear regression analysis). Also the inflation pressure was not correlated with the improvement of the P/F ratio (Fig. 3; $r^2 = 0.07$, $P = 0.18$, linear regression analysis).

Discussion

The present study indicates that the individualized RM, defined on the basis of dynamic compliance, improved pulmonary oxygenation and slightly increased lung compliance in post-CPB patients. In addition, there was no difference in hemodynamic stability between the two groups, and both groups were stable and safe. These findings suggest that our individualized RM, which is optimized for each patient's dynamic compliance, is appropriate for post-CPB patients without hemodynamic instability.

Table 1. Patients' characteristics

	Control RM group ($n = 14$)	Individualized RM group ($n = 14$)	*P* value
Age (years)	64.6 ± 3.4	66.7 ± 3.4	0.67
Height (cm)	161.8 ± 1.9	158.5 ± 2.9	0.36
Weight (kg)	62.8 ± 2.4	59.6 ± 2.6	0.38
Sex (M/F)	10/4	10/4	1
Surgery			
CABG	7	6	0.56
AVR	3	3	
MVR	1	3	
Ao graft	3	2	
Duration of CPB (min)	111.1 ± 9.4	111.1 ± 12.6	1

Values are means ± SEM
CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; Ao graft, aortic graft surgery; CPB, cardiopulmonary bypass

Table 2. Baseline hemodynamic and respiratory parameters

Parameter	Control RM group ($n = 14$)	Individualized RM group ($n = 14$)	P value
Heart rate (bpm)	81.1 ± 3.0	87.6 ± 3.5	0.18
Mean arterial pressure (mmHg)	73.3 ± 2.9	75.0 ± 3.1	0.70
Mean pulmonary pressure (mmHg)	15.6 ± 1.1	15.6 ± 1.6	0.98
Cardiac index ($l \cdot min^{-1} \cdot m^2$)	3.1 ± 0.2	3.5 ± 0.2	0.20
$F_{I_{O_2}}$	0.51 ± 0.02	0.50 ± 0.02	0.78
Pressure (cmH_2O)	20.7 ± 1.0	20.7 ± 1.7	1.00
Respiratory rate (bpm)	11.6 ± 0.6	12.1 ± 0.9	0.64
Tidal volume (ml)	650.4 ± 32.7	610.1 ± 28.3	0.36
Dynamic compliance ($ml \cdot cmH_2O^{-1}$)	41.5 ± 2.3	39.2 ± 2.1	0.46
Pa_{O_2} (mmHg)	163.3 ± 6.4	157.0 ± 9.3	0.58
Pa_{CO_2} (mmHg)	38.3 ± 1.9	39.9 ± 1.2	0.45
$Pa_{O_2}/F_{I_{O_2}}$	326.8 ± 18.4	313.7 ± 19.5	0.63

Values are means ± SEM
$F_{I_{O_2}}$, inspiratory fraction of oxygen; Pa_{O_2}, partial pressure of arterial oxygen; Pa_{CO_2}, partial pressure of arterial carbon dioxide

Table 3. Hemodynamic changes at the end of the RMs

Percent change in parameter	Control RM group ($n = 14$)	Individualized RM group ($n = 14$)	P value
Heart rate (%)	7.9 ± 4.8	1.8 ± 1.2	0.25
Mean arterial pressure (%)	0.3 ± 1.8	−2.7 ± 6.3	0.64
Mean pulmonary artery pressure (%)	17.3 ± 7.8	28.2 ± 13.5	0.49
Cardiac index (%)	−1.0 ± 0.7	1.0 ± 1.2	0.14

Values are means ± SEM

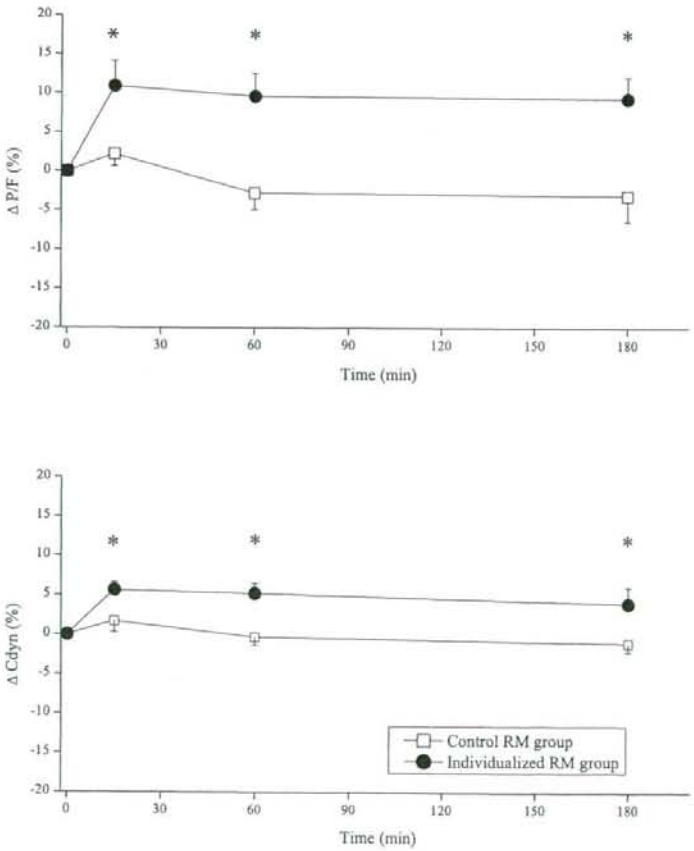

Fig. 2. Effects of control *vs* individualized recruitment maneuver (*RM*) on the percent change in partial pressure arterial oxygen/inspiratory fraction of oxygen (*P/F*) and dynamic compliance (*Cdyn*). Changes in both parameters decreased beyond 15 min after the control RM, whereas significant improvements were found in the individualized RM group immediately after RM, and these were preserved for 3 h. There were significant improvements in the percent changes in P/F and Cdyn in the individualized RM group compared with values in the control RM group ($P = 0.026$ and $P = 0.012$, respectively). $^*P < 0.05$ vs control group, at each time point

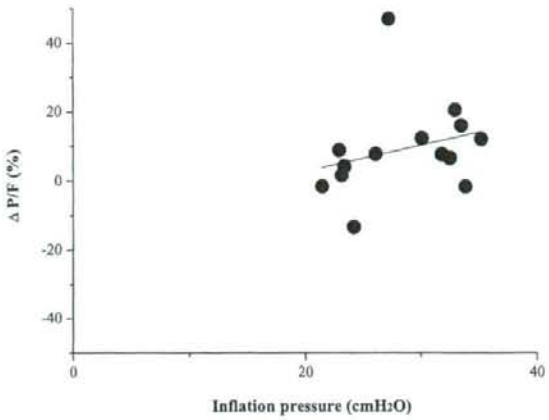

Fig. 3. The inflation pressure was not correlated with the improvement of the P/F ratio at 15 min after RM ($r^2 = 0.07$; $P = 0.18$; linear regression analysis). *P/F*, partial pressure arterial oxygen/inspiratory fraction of oxygen

The preservation of hemodynamic stability should be the first priority for the postoperative management of cardiac surgery. The RM should be used to avoid hemodynamic changes after cardiac surgery because cardiac compensation is insufficient in post-CPB patients, owing to myocardial stunning [6,12]. Indeed, in our clinical experience, a substantial decline in CO and MAP occurs in some patients. Therefore, the application of up to 20 cmH_2O continuous positive airway pressure (CPAP) for 25 s, associated with minimal and short-term changes in CO, was selected for the control procedure. It was obvious that this application was insufficient to improve pulmonary oxygenation or compliance in our pilot study.

The inflation pressure of the individualized RM was relatively higher than that of the control method (28 cmH_2O vs 20 cmH_2O); however, hemodynamic changes were similar in the two groups. The individualized RM in our study reduced MAP by only 3% and changed CI by 1% and HR by about 2%, while an RM with high inflation pressure (40 cmH_2O, 10 s or 20 s) has been reported to reduce CO by more than 50%, left ventricular end-diastolic area by about 45%, and MAP by 20% [6]. This discrepancy between the studies may be explained in terms of intrathoracic pressure (ITP) and sympathetic withdrawal [13]. Increasing airway pressure is elevated in ITP and this leads to decreased venous return and CO. Decreasing lung compliance, however, has been shown to decrease the transmission of the airway pressure to the ITP [13]. In our patients, in whom lung injury was mild to moderate, there was not much difference in ITP, even though there were about 8-cmH_2O differences in inflation pressure between the groups. On the other hand, large-volume inflation of the lung (>15 $ml \cdot kg^{-1}$) decreased HR in an animal model [14]. Lung volume in an RM with 40 cmH_2O may reach more than 15 $ml \cdot kg^{-1}$, and lead to sympathetic withdrawal in post-CPB patients. Indeed, an RM with high inflation pressure (40 cmH_2O, 20 s), as opposed to our methods, was shown to decrease HR by about 20% [6]. Therefore, an RM with high inflation pressure may contribute to hemodynamic instability.

An injured lung often shows nonhomogeneous alveolar distension and high airway pressure is needed to recruit alveoli. Previous studies have shown that, if inflation volume is constant, ITP will be equally increased, which will not reflect a change in the cardiovascular status, although the alveolar distention is not homogeneous [13,15]. In our study, inflation pressure varied, while the inflation volume of the individualized RM was theoretically constant (= 15 × real body weight). Accordingly, the individualized RM would change hemodynamic stability only slightly.

The impairment of pulmonary gas exchange after cardiac surgery contributes to the requirement for prolonged mechanical ventilation [16]. A previous study showed that the P/F ratio in patients with extubation failure was only 7% lower than that in the patients without extubation failure after cardiac surgery [17]. Another study demonstrated that the relative risk of delayed extubation was 0.935 when the P/F ratio increased by 10 [18]; in that study, the patients' P/F ratio at baseline was similar to that in our study. Determining the effect of the RM on long-term outcome after the procedure was not the purpose of our study; however, 2 of the 14 patients in the control RM group were ventilated with a noninvasive positive-pressure ventilator as a result of hypoxemia, whereas none of the patients in the individualized RM group needed such ventilation. Therefore, this slight improvement, without hemodynamic instability, could have some relevance for patients with CPB, although our individualized RM increased the P/F ratio by only about 38 from baseline.

The present study has some limitations. First, our ventilation setting of V_T was relatively high and may be unsuitable for the management of patients with acute lung injury. Pulmonary dysfunction in most patients with CPB is reported to range from subclinical functional changes to moderate lung injury [19,20]. In our patient population, lung injuries were not severe but mild, and no patient had a P/F ratio of less than 200. All patients had been ventilated with an inspiratory plateau pressure of about 20 cmH_2O. It remains controversial whether or not V_T should be reduced when the inspiratory plateau pressure is lower than 30 cmH_2O [21,22]. Therefore, we used a V_T of 10–12 ml to avoid increasing pulmonary atelectasis. Second, we did not try to obtain static pressure-volume loop values because it was our desire to simplify the individualized RM in terms

of daily management. We considered that static pressure—volume loop values did not always provide clear inflection points without neuromuscular agents and the use of these parameters was not necessarily of advantage for post-CPB patients [23]. Recent studies indicate that the application of dynamic respiratory mechanics as a diagnostic tool in ventilated patients could be more appropriate than using static pressure-volume curves [9]. Similarly, we did not correct for the influence of the tracheal tube on airway pressure, and this influence possibly modifies the measurement of dynamic lung compliance. Correction of the airway pressure could make it possible to accurately calculate the dynamic compliance of the respiratory system. By the monitoring of airway pressure in the trachea, respiratory mechanics can be assessed more accurately [24]. Third, in the present study, we chose the pressure to be 15 × real body weight/dynamic compliance + PEEP (cmH_2O), and did not investigate other pressures or hold-times. There may be another combination of pressure and hold-time which is even more effective for the improvement of oxygenation. Nevertheless, we believe that our method, based on dynamic compliance, facilitates the identification of the optimal pressure and hold-time. Finally, based on the P/F ratio, lung injuries in our patient population were not severe but mild, and no patient had a P/F ratio of less than 200. Therefore, it remains unclear whether our individualized RM would be effective for patients with ARDS.

Conclusion

In conclusion, this preliminary study suggests that an individualized RM, defined on the basis of dynamic compliance, slightly improves oxygenation and lung compliance, without hemodynamic instability, for post-CPB patients. We expect to propose a new RM concept by seeking to optimize the inflation pressure for each individual patient, but a large-scale study will be required to determine the optimal pressure and hold-time, and other parameters.

References

1. Dyhr T, Laursen N, Larsson A. Effects of lung recruitment maneuver and positive end-expiratory pressure on lung volume, respiratory mechanics and alveolar gas mixing in patients ventilated after cardiac surgery. Acta Anaesthesiol Scand. 2002;46:717–25.
2. van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol. 2002;92:1223–31.
3. Federici A, Ciccone M, Gattullo D, Losano G. Systolic and diastolic changes in human coronary blood flow during Valsalva maneuver. Clin Physiol. 2000;20:19–29.
4. van den Berg PC, Grimbergen CA, Spaan JA, Pinsky MR. Positive pressure inspiration differentially affects right and left ventricular outputs in postoperative cardiac surgery patients. J Crit Care. 1997;12:56–65.
5. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. Anesthesiology. 2002;96:795–802.
6. Nielsen J, Ostergaard M, Kjaergaard J, Tingleff J, Berthelsen PG, Nygard E, Larsson A. Lung recruitment maneuver depresses central hemodynamics in patients following cardiac surgery. Intensive Care Med. 2005;31:1189–94.
7. Richard JC, Maggiore S, Mercat A. Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome? Curr Opin Crit Care. 2003;9:22–7.
8. Kacmarek RM. Strategies to optimize alveolar recruitment. Curr Opin Crit Care. 2001;7:15–20.
9. Stahl CA, Moller K, Schumann S, Kuhlen R, Sydow M, Putensen C, Guttmann J. Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome. Crit Care Med. 2006;34:2090–8.
10. Karason S, Sondergaard S, Lundin S, Wiklund J, Stenqvist O. A new method for non-invasive, maneuver-free determination of "static" pressure-volume curves during dynamic/therapeutic mechanical ventilation. Acta Anaesthesiol Scand. 2000;44:578–85.
11. Lichtwarck-Aschoff M, Kessler V, Sjostrand UH, Hedlund A, Mols G, Rubertsson S, Markstrom AM, Guttmann J. Static versus dynamic respiratory mechanics for setting the ventilator. Br J Anaesth. 2000;85:577–86.
12. Royster RL. Myocardial dysfunction following cardiopulmonary bypass: recovery patterns, predictors of inotropic need, theoretical concepts of inotropic administration. J Cardiothorac Vasc Anesth. 1993;7:19–25.
13. Lueke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. Crit Care. 2005;9:607–21.
14. Pinsky MR. Cardiovascular issues in respiratory care. Chest. 2005;128 (5 Suppl 2):592–7.
15. Romand JA, Shi W, Pinsky MR. Cardiopulmonary effects of positive pressure ventilation during acute lung injury. Chest. 1995;108:1041–8.
16. Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest. 2002;121:1269–77.
17. Rady MY, Ryan T. Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. Crit Care Med. 1999;27:340–7.
18. Suematsu Y, Sato H, Ohtsuka T, Kotsuka Y, Araki S, Takamoto S. Predictive risk factors for delayed extubation in patients undergoing coronary artery bypass grafting. Heart Vessels. 2000;15:214–20.
19. Hachenberg T, Tenling A, Nystrom SO, Tyden H, Hedenstierna G. Ventilation-perfusion inequality in patients undergoing cardiac surgery. Anesthesiology. 1994;80:509–19.
20. Asimakopoulos G, Smith PL, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg. 1999;68:1107–15.
21. Hager DN, Krishnan JA, Hayden DL, Bower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172:1241–5.
22. Deans K, Minneci P, Cui X, Banks S, Natanson C, Eichaker P. Mechanical ventilation in ARDS: one size does not fit all. Crit Care Med. 2005;33:1141–4.
23. Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. Lancet. 2003;361:332–40.
24. Karason S, Sondergaard S, Lundin S, Wiklund J, Stenqvist O. Evaluation of pressure/volume loops based on intratracheal pressure measurements during dynamic conditions. Acta Anaesthesiol Scand. 2000;44:571–7.

J Anesth (2009) 23:115–118
DOI 10.1007/s00540-008-0691-6

Journal of
Anesthesia

Recurrent ST-segment elevation on ECG and ventricular tachycardia during neurosurgical anesthesia

Yoshifumi Kotake[1], Midori Matsumoto[2], Tomoko Yorozu[3], and Junzo Takeda[4]

[1] Department of Anesthesiology, Toho University School of Medicine, 6-11-1 Ohmori-nishi, Ohta-ku, Tokyo 143-8541, Japan
[2] Department of Anesthesiology, Tachikawa Kyosai Hospital, Tokyo, Japan
[3] Department of Anesthesiology, Kyorin University School of Medicine, Tokyo, Japan
[4] Department of Anesthesiology, Keio University School of Medicine, Tokyo, Japan

Abstract
This article reports an unusual case of repeated intraoperative myocardial ischemia and ventricular arrhythmia during neurosurgical anesthesia. The presentation was clinically diagnosed as coronary spasm after successful resuscitation. Intraoperative prostaglandin E_1 and β-adrenergic blockade, as well as vagal stimulation due to surgical manipulation, may have contributed to the episode.

Key words Coronary spasm · Anesthesia · Neurosurgical · Prostaglandin E_1 · Propranolol

Introduction

Coronary vasospasm may occur intraoperatively and cause serious ventricular arrhythmia and hemodynamic instability [1,2]. However, recurrent episodes of intraoperative coronary spasm in one patient during a single procedure is very rare. We present a case of multiple intraoperative episodes of ST change and ventricular tachycardia in a neurosurgical patient. These episodes were clinically diagnosed as coronary spasm, and the administration of a β-blocker and prostaglandin E_1 for deliberate hypotension may have been involved in the pathophysiology of the recurrent symptoms.

Case report

A 60-year-old, 54-kg, 157-cm-tall woman underwent neck clipping of an unruptured cerebral aneurysm. She had already undergone neck clipping of a ruptured cerebral aneurysm 10 years prior to this procedure, without any neurological sequelae. She had no history of coronary artery disease, and all the preoperative tests, including chest radiograph and ECG, revealed no abnormalities. Premedication consisted of oral famotidine and intramuscular meperidine, midazolam, and atropine sulfate. General anesthesia was induced with intravenous propofol and fentanyl, supplemented with vecuronium and maintained with continuous infusion of propofol and inhaled N_2O-O_2 (fractional inspired oxygen; $F_{I_{O_2}} = 0.33$). The maintenance dose of propofol was 4 $mg \cdot kg^{-1} \cdot h^{-1}$. The patient was mechanically ventilated to maintain Pa_{CO_2} at 30 to 35 mmHg. Before incision, administration of intravenous propranolol (0.6 mg) and continuous infusion of prostaglandin E_1, at a rate of 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, were started for deliberate hypotension. Twenty minutes after incision, a brief episode of bradycardia (heart rate [HR], 45 bpm), atrioventricular (AV) block, ST elevation, and T wave inversion with hypotension (arterial pressure, 74/48 mmHg) was noted (Fig. 1, trace 1A). Two minutes later, these changes disappeared, and only ST depression persisted (Fig. 1, trace 1B). After another minute, the ECG spontaneously returned to normal (Fig. 1, trace 1C). At this time, the HR was 74 bpm, and the blood pressure was 94/56 mmHg. The attending anesthesiologist diagnosed this episode as coronary vasospasm, and a transdermal isosorbide dinitrate patch was applied as a prophylactic measure. Prostaglandin E_1 administration was temporarily stopped and then restarted at the same dose 20 min later when microscopic manipulation was started. Eighty minutes after the first episode and during the microscopic manipulation of cerebral aneurysm, significant ST elevation and premature ventricular contractions were noted (Fig. 1, trace 2). At this time, the HR was 84 bpm, and the blood pressure was 89/46 mmHg. One minute later, ventricular tachycardia was noted on the ECG and was successfully treated with 60 mg of intravenous lidocaine. Two minutes after this event, the ECG returned to normal following transient ECG evidence of ST depression and T wave inversion. After this

Address correspondence to: Y. Kotake
Received: April 10, 2008 / Accepted: September 1, 2008

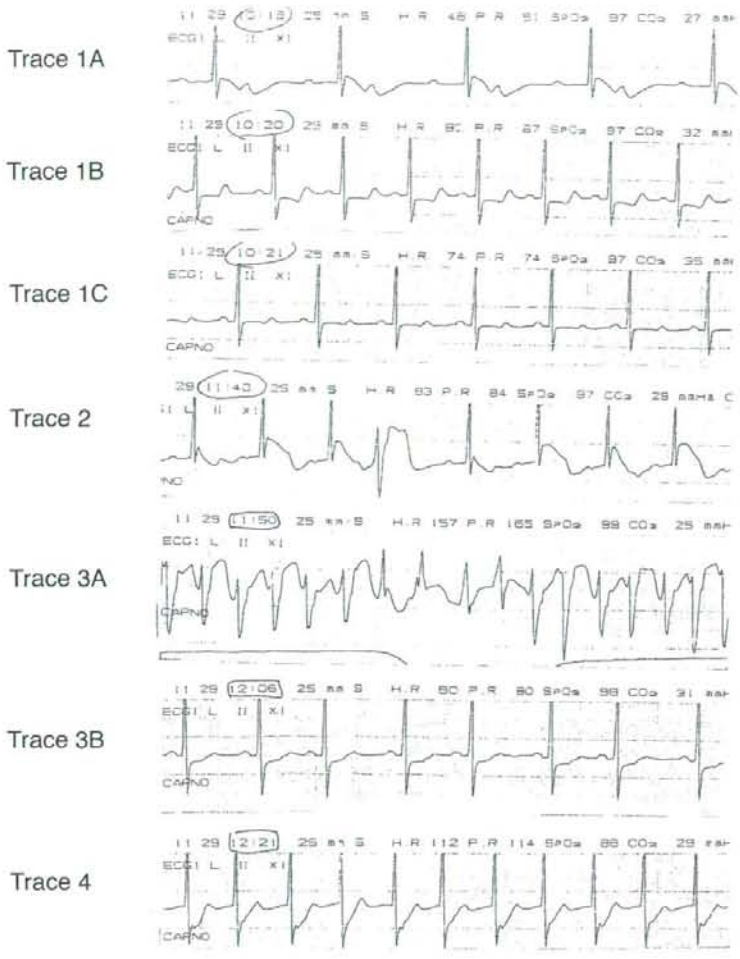

Fig. 1. Electrocardiographic recordings of repeated intraoperative ST changes and ventricular arrhythmia. Time of the recording and the heart rate (HR) of each trace are shown in the *upper left corner of each trace. Traces 1A through 1C.* First episode of electrocardiographic (ECG) change (trace 1A); subsequent ST depression and T wave inversion (trace 1B) spontaneously normalized (trace 1C). *Trace 2.* Second episode of ECG change. ST elevation and ventricular premature contractions were successfully treated with intravenous lidocaine. *Traces 3A and 3B.* The third episode of ECG change. Ventricular tachycardia, which necessitated DC defibrillation, temporary chest compression, and epinephrine administration, was recorded in lead II at 10 min after the second episode (*trace 3A*). Only slight ST depression was noted in the ECG after treatment (*trace 3B*). *Trace 4.* The fourth episode of ECG change. Junctional rhythm, ST depression, and severe hypotension, which required external chest compression and intravenous epinephrine administration, were noted 30 min after the episode of coronary spasm

second event, the prostaglandin administration was terminated. At this time, the HR was between 80 and 90 bpm, and the systolic blood pressure was between 90 and 110 mmHg. The surgical procedure proceeded after consultation with the neurosurgeon, as the second episode of ECG change had been successfully treated with lidocaine. The rest of the anesthetic regimen remained constant during these periods, and arterial blood gas analysis revealed no abnormalities (pH, 7.45; Pa_{CO_2}, 38 mmHg; Pa_{O_2}, 170 mmHg; hemoglobin [Hb], 13.1 $g \cdot dl^{-1}$). Ten minutes after the second episode, significant ST elevation and pulseless ventricular tachycardia was noted (Fig. 1, trace 3A). This life-threatening arrhythmia did not respond to 100 mg intravenous lidocaine and was immediately treated with DC defibrillation and 1 mg of intravenous epinephrine. The ECG returned to sinus rhythm with a rate of 90 bpm and moderate ST depression. The systolic blood pressure was stabilized around 120 mmHg after transient hypertension due to intravenous epinephrine administration (Fig. 1, trace 3B). After this event, N_2O was terminated but propofol was continued at the same rate as previously. Cardiovascular support and vasospasm prophylaxis consisted of a continuous infusion of dopamine, nicardipine, lidocaine, and diltiazem, and the surgery was postponed due to these adverse cardiovascular conditions. Multiple episodes of hypotension with systolic blood pressure around 80 mmHg occurred during dural and cranial closure and these were treated with intravenous ephedrine and phenylephrine. Thirty minutes after the third event, clinical cardiac arrest following severe hypotension (systolic blood pressure below 60 mmHg) occurred and was successfully treated with 1.5 min of chest compression and repeated epinephrine administration. ECG monitoring at this time revealed an AV junctional rhythm with a rate of 112 bpm and marked

ST depression (Fig. 1, trace 4). High-dose continuous epinephrine ($0.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) administration was added to the medications, and stable hemodynamics was achieved during craniotomy closure. At the end of the surgery, these intraoperative events were diagnosed as coronary vasospasm by a consulting cardiologist. Subsequent echocardiographic study demonstrated no pathologic lesion, no signs of inadequate preload, and well-preserved ventricular contractility. Postoperative chest radiograph and blood gas analysis revealed no abnormal findings, and the patient was transferred to the neurological intensive care unit (ICU) and mechanically ventilated. On arrival in the ICU, the HR was 86 with a sinus rhythm, and the systolic blood pressure was between 120 and 140 mmHg with dopamine infusion at a rate of $3\ \mu g \cdot kg^{-1} \cdot min^{-1}$. Neurologically, the patient showed dilated pupils with a sluggish light reflex at the end of surgery, but she had regained consciousness 60 min later without any neurological signs or symptoms. The patient was extubated after the administration of epinephrine was terminated. During and after this recovery period, no ECG abnormality was found, and the patient was discharged without invasive diagnostic testing.

Discussion

The three episodes of ST segment elevation and ventricular arrhythmia described in this report were most likely caused by coronary spasm, because the patient had no signs of preoperative myocardial ischemia and no apparent imbalance of the myocardial oxygen demand-and-supply relationship at the time of these events [3]. Based on our MEDLINE literature search, 17 relevant case reports written in English about intraoperative coronary spasm during noncardiac surgery were located. Additionally, 21 case reports with English abstracts were found in the Japanese literature. The case we have described is characterized by the fact that the multiple events of coronary spasm took place during a single anesthesia course. From this perspective, we believe this report may provide some additional information about the interaction between coronary spasm and anesthesia. Although the pathophysiology of coronary spasm remains to be elucidated, involvement of endothelial dysfunction and the autonomic nervous system is suggested [4]. In the context of anesthetic management, sympathetic activation due to inadequate depth of anesthesia, parasympathetic activation due to vagal stimulation, neostigmine and neuraxial blockade, alkalosis, and hypotension have been implicated as triggers of coronary spasm [2,4,5]. We believe that the HR and blood pressure in our patient precluded inadequate anesthetic depth or myocardial hypoperfusion at the time of the coronary spasm. At this time, the blood gas analysis revealed no hypocapnia or alkalosis. It is not readily known whether all episodes were triggered by the same mechanism, however, three possible causes may have been involved. First, the administration of propranolol and prostaglandin E_1 may have triggered a coronary spasm. Several reports implicate propranolol as a triggering agent of coronary spasm, by blocking sympathetic activity and causing parasympathetic dominance [6–8]. Although the majority of investigations have revealed a protective effect of β-blockade on myocardial ischemia [9], β-blockade may cause spastic vasoconstriction under certain conditions. Whether β-blockade may trigger coronary spasm or protect the post-ischemic myocardium warrants further investigation. Prostaglandin E_1 is generally regarded to have a myocardial protective effect [10]. However, several anecdotal reports in the Japanese literature have demonstrated a temporal coincidence between prostaglandin E_1 administration and the occurrence of coronary spasm [11–13]. In our patient, the fact that ECG change relevant to coronary spasm occurred only during prostaglandin E_1 infusion may suggest this possibility. Second, stimulation of the vagal nerve during neurosurgical manipulation may be involved as an underlying mechanism of coronary spasm [12]. As each episode in our patient occurred during craniotomy and during surgical exposure of the cerebral aneurysm, it is possible that the vagal nerve may have been stimulated at the time of each episode. Third, propofol-based anesthesia may have contributed to the coronary spasm. One laboratory investigation demonstrated that propofol was less protective against coronary spasm than sevoflurane [14]. Of the 115 cases of coronary spasm reported during the period from 1968 to 1998, 32% of the patients were anesthetized with an inhalational agent, while 11% were anesthetized with an intravenous agent [2]. However, the contribution of anesthetic choice to the occurrence of coronary spasm is not readily understood, because the total number of cases is not known.

In summary, we have reported a case of recurrent episodes of ST elevation and ventricular tachycardia during neurosurgical anesthesia. Coronary spasm is most likely implicated as an underlying mechanism of these symptoms. Although the precise mechanisms remain unclear, multiple factors, such as β-blockade, prostaglandin E_1 administration for deliberate hypotension, vagal stimulation elicited by surgical manipulation, and propofol may have been involved. This case reminds us that even transient ST elevation and a few ventricular premature contractions that are spontaneously alleviated may be a sign of more clinically significant coronary spasm. Meticulous attention is needed to circumvent possible triggering conditions and to provide definitive prophylaxis after these episodes.