controlled infusion provides an excellent method to maintain constant plasma and effect site concentrations of propofol, but the pharmacokinetic and dynamic parameters of propofol are not available for the rhesus monkey. Even mild hypothermia would have a suppressive effect on the metabolism of propofol, but its nature in this species is not well understood. Thus, we used constant dosage infusion in our study.

In conclusion, it is possible to reduce cerebral metabolism throughout the entire brain, as well as in any brain region, by increasing the propofol dose or by inducing hypothermia during propofol anesthesia. When these two interventions are combined, the reduction in metabolism is additive, and the coupling of cerebral metabolism and blood flow is not impaired. We consider the concurrent use of these two interventions as a superior alternative to either overdosage of propofol or profound hypothermia for the reduction of CBF and $CMRO_2$ without increasing the risk of complications.

Acknowledgments. This work was supported in part by a Grant-in-Aid for Creative Scientific Research, from the Japan Society for the Promotion of Science.

References

1. Drummond JC, Patel PM (2000) Cerebral physiology and the effects of anesthetics and techniques. In: Miller RD (ed) Anesthesia, 5th edn. Churchill Livingstone, Philadelphia, pp 695–733
2. Vandesteene A, Trempont V, Engelman E, Deloof T, Focroul M, Schoutens A, DeRood M (1988) Effect of propofol on cerebral blood flow and metabolism in man. Anaesthesia 43 (Suppl):42–43
3. Oshima T, Karasawa F, Satoh T (2002) Effects of propofol on cerebral blood flow and the metabolic rate of oxygen in humans. Acta Anaesthesiol Scand 46:831–835
4. Kaisti K, Långsjö J, Aalto S, Oikonen V, Sipilä H, Teräs M, Hinkka S, Metsähonkala L, Scheinin H (2003) Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99:603–613
5. Pinaud M, Lelausque JN, Chetanneau A, Fauchoux N, Ménégalli D, Souron R (1990) Effects of propofol on cerebral hemodynamics and metabolism in patients with brain trauma. Anesthesiology 73:404–409
6. Kaisti K, Metsähonkala L, Teräs M, Oikonen V, Aalto S, Jääskeläinen S, Hinkka S, Scheinin H (2002) Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 96:1358–1370
7. Enlund M, Andersson J, Hartvig J, Valtysson J, Wiklund L (1997) Cerebral normoxia in the rhesus monkey during isoflurane- or propofol-induced hypotension and hypocapnia, despite disparate blood-flow patterns. A positron emission tomography study. Acta Anaesthesiol Scand 41:1002–1010
8. Werner C, Hoffman W, Kochs E, Schulte am Esch J, Albrecht F (1993) The effects of propofol on cerebral and spinal cord blood flow in rats. Anesth Analg 76:971–975
9. Haberer J, Audibert G, Saunier C, Muller C, Laxenaire M, Hartemann D (1993) Effect of propofol and thiopentone on regional blood flow in brain and peripheral tissues during normoxia and hypoxia in the dog. Clin Physiol 13:197–207
10. Strebel S, Lam A, Matta B, Mayberg T, Aaslid R, Newell D (1995) Dynamic and static cerebral autoregulation during isoflurane, desflurane and propofol anesthesia. Anesthesiology 83:66–76
11. Matta B, Lam A, Strebel S, Mayberg T (1995) Cerebral pressure autoregulation and carbon dioxide reactivity during propofol-induced EEG suppression. Br J Anaesth 74:159–163
12. Kimme P, Ledin T, Sjöberg F (2002) Cortical blood flow autoregulation revisited using laser Doppler perfusion imaging. Acta Physiol Scand 176:255–262
13. Fox J, Gelb A, Enns J, Murkin J, Farrar J, Manninen P (1992) The responsiveness of cerebral blood flow to changes in arterial carbon dioxide is maintained during propofol-nitrous oxide anesthesia in humans. Anesthesiology 77:453–456
14. Strebel S, Kaufmann M, Guardiola P, Schaefer H (1994) Cerebral vasomotor responsiveness to carbon dioxide is preserved during propofol and midazolam anesthesia in humans. Anesth Analg 78:884–888
15. Krafft P, Frietsch T, Lenz C, Piepgras A, Kuschinsky W, Waschke K (2000) Mild and moderate hypothermia (α-stat) do not impair the coupling between local cerebral blood flow and metabolism in rats. Stroke 31: 1393–1401
16. Mori K, Maeda M, Miyazaki M, Iwase H (1998) Effects of mild (33 degrees C) and moderate (29 degrees C) hypothermia on cerebral blood flow and metabolism, lactate, and extracellular glutamate in experimental head injury. Neurol Res 20:719–726
17. Walter B, Bauer R, Kuhnen G, Fritz H, Zwiener U (2000) Coupling of cerebral blood flow and oxygen metabolism in infant pigs during selective brain hypothermia. J Cereb Blood Flow Metab 20:1215–1224
18. Sakoh M, Gjedde A (2003) Neuroprotection in hypothermia linked to redistribution of oxygen in brain. Am J Physiol Heart Circ Physiol 285:H17–25
19. Watanabe M, Okada H, Shimizu K, Omura T, Yoshikawa E, Kosugi T, Mori S, Yamashita T (1997) A high resolution animal PET scanner using compact PS-PMT detectors. IEEE Trans Nucl Sci 44:1277–1282
20. Lagerkranser M, Stänge K, Sollevi A (1997) Effects of propofol on cerebral blood flow, metabolism, and cerebral autoregulation in the anesthetized pig. J Neurosurg Anesthesiol 9:188–193
21. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T (1990) Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg 71:49–54
22. Rosomoff H, Holaday D (1954) Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 179:85–88
23. Kaneko T, Ochiai R, Yoshikawa T, Takeda J, Fukushima K, Tsukada H, Okada H, Seki C (1997) The effect of cerebral perfusion pressure on cerebral blood flow in the rhesus monkey during sevoflurane anesthesia (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 46:166–172
24. Yoshikawa T, Ochiai R, Kaneko T, Takeda J, Fukushima K, Tsukada J, Seki C, Kakiuchi T (1997) The effect of sevoflurane on regional cerebral metabolism and cerebral blood flow in rhesus monkeys (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 46:237–243
25. Deutsch G, Samra SK (1990) Effects of nitrous oxide on global and regional cortical blood flow. Stroke 21:1293–1298
26. Reinstrup P, Ryding E, Algotsson L, Berntman L, Uski T (1994) Effects of nitrous oxide on human regional cerebral blood flow and isolated pial arteries. Anesthesiology 81:396–402
27. Gyulai F, Firestone L, Mintun M, Winter P (1996) In vivo imaging of human limbic responses to nitrous oxide inhalation. Anesth Analg 83:291–298
28. Field L, Dorrance D, Krzeminska E, Barsoum L (1993) Effect of nitrous oxide on cerebral blood flow in normal humans. Br J Anaesth 70:154–159

Platelet Dysfunction During Cardiopulmonary Bypass Assessed by a Novel Whole-Blood Aggregometer

Yoshifumi Kotake, MD, PhD, Naomi E. Ogawa, MD, Nobuyuki Katori, MD, Ryohei Serita, MD, Hiroshi Morisaki, MD, and Junzo Takeda, MD

Objective: **The purpose of this study was to assess perioperative platelet function with 2 types of monitors (a whole-blood aggregometer [WBA analyzer; Mebanix, Tokyo, Japan]) and the Sonoclot monitor [Sienco, Wheat Ridge, CO]) in patients undergoing hypothermic cardiopulmonary bypass (CPB).**

Design: **Prospective, observational study.**

Setting: **Single-center study at a university hospital.**

Participants: **Twenty-six patients who underwent coronary artery bypass grafting or valve replacement under hypothermic CPB without platelet transfusion or fresh frozen plasma administration.**

Interventions: **Blood sampling was performed at the following time periods: after anesthetic induction, after CPB, and on the first postoperative day. These samples were assessed with the WBA analyzer and the Sonoclot.**

Measurements and Main Results: **Significant attenuation of adenosine diphosphate–induced platelet aggregation was detected shortly after CPB by 2 WBA analyzer-derived parameters: a decrease in the filtration pressure rate and an increase in the platelet aggregatory threshold index. Platelet aggregation returned to the preoperative level on the next day. There was no correlation between the amount of postoperative mediastinal drainage and defects in platelet aggregation. On the other hand, time to peak obtained by the Sonoclot did not show any significant changes.**

Conclusions: **Whole-blood aggregation measured with the WBA analyzer detected transient platelet dysfunction shortly after CPB, whereas the Sonoclot was less sensitive to this change.**

***KEY WORDS:** cardiopulmonary bypass, bleeding, platelet, aggregation, viscoelastic, Sonoclot analysis*

PLATELET DYSFUNCTION IS one of the critical hemostatic changes caused by cardiopulmonary bypass (CPB).[1] More than 50% of excessive bleeding after cardiac surgery is because of nonsurgical causes, and platelet-related microvascular bleeding accounts for a significant part of these cases.[2] Although several components of coagulation, such as dilutional thrombocytopenia, interaction with leukocytes, hypothermia, heparin, and protamine, are implicated,[3] a defect in platelet aggregation has been recognized to be an important event in postoperative bleeding.[4-7] Therefore, monitoring platelet function could provide crucial information about the hemostatic profile during and after CPB.[8] However, it has been difficult to monitor platelet aggregation during the perioperative period because conventional aggregometry requires time-consuming and complicated preparation.[9]

The WBA analyzer (Mebanix, Tokyo, Japan), a commercially available platelet aggregometer using a screen filtration pressure method, may overcome the aforementioned shortcomings of the conventional analyzer. This device monitors platelet aggregation by measuring the resistance of a whole-blood sample as it flows through a microsieve after platelet activation.[10-14] It can simultaneously measure 4 samples; therefore, the dose response of platelet aggregation against an agonist can be obtained. Other characteristics of this device include semiautomatic operation and a short analytical sequence. These potential benefits warrant evaluation of this device, but it has not been reported in the setting of cardiovascular surgery.

Another clinically available monitor of platelet aggregation is The Sonoclot Coagulation and Platelet Function Monitor (SNC; Sienco, Wheat Ridge, CO). Although this device does not specifically monitor platelet aggregation, previous reports showed that time to peak (TP) obtained from the SNC reflected collagen-induced platelet aggregation during CPB.[15,16]

This prospective, observational study assessed the time course of CPB-induced functional changes in platelet aggregation using both the WBA analyzer and SNC and compared the clinical usefulness of these devices as a platelet function monitor during the perioperative period of cardiac surgery.

METHODS

The protocol was approved by the Institutional Review Board of Keio University. Patients who underwent cardiac surgery with CPB from August to December 2001 were screened for possible participation in this study. A written informed consent was obtained from each participant. Exclusion criteria consisted of patient's refusal, preoperative nonsteroidal antiinflammatory drugs, antiplatelet drugs, or anticoagulant medication within 1 week before operation. Patients who received either platelet concentrates or fresh frozen plasma during the perioperative period were also excluded from subsequent analysis.

An oral histamine H2 blocker and diazepam plus intramuscular meperidine were administered as premedication. Anesthesia was induced and maintained with intravenous fentanyl, midazolam, and vecuronium. Patients were mechanically ventilated with an O_2-air mixture to maintain the PaO_2 above 200 mmHg and $PaCO_2$ between 35 to 45 mmHg. Hypothermic CPB (core temperature 28°-32°C), using a roller pump and a membrane oxygenator, was used in these patients. In each case, anticoagulation was achieved by initially administering 300 U/kg of heparin before CPB; additional heparin was given as necessary to maintain the activated coagulation time (Hemochron 401; Helthdyne, Edison, NJ) over 400 seconds. Heparin was antagonized with the same amount of intravenous protamine sulfate after rewarming (core temperature >36.5°C) and cession of CPB. The adequacy of heparin reversal was confirmed with the return of the activated coagulation time to the pre-CPB level. The total volume of mediastinal chest drainage was recorded hourly and was counted for 3 defined periods: 0 to 3, 3 to 8, and 8 to 24 hours.

Blood samples were obtained from the arterial catheter at the following time points: after induction of anesthesia, at the end of surgery, and on postoperative day (POD) 1 in the morning. An aliquot of arterial

From the Department of Anesthesiology, Keio University School of Medicine, Tokyo, Japan.

Address reprint requests to Yoshifumi Kotake, MD, PhD, Department of Anesthesiology, Keio University, 35 Shinanomachi, Shinjuku, Tokyo, 160-8582, Japan. E-mail: ykotake@sc.itc.keio.ac.jp

1053-0770/06/2004-0011$32.00/0

doi:10.1053/j.jvca.2005.11.013

blood was drawn into a tube containing citrate sodium and was used for the WBA analyzer. The analyzing principle and procedures for this device have been reported previously.[10-14] Briefly, the citrated blood was continuously stirred and incubated at 37°C in 4 glass tubes for 1 minute. Four different concentrations of adenosine diphosphate (ADP; 2, 4, 8, and 16 μmol/L) were added to these samples and incubated for another 5 minutes to allow platelet aggregation. These samples were automatically and sequentially aspirated at a rate of 200 μL/6.4 seconds through needles equipped with a microsieve and pressure sensor. The microsieve had 300 openings of 30 μm^2 in size. The platelet aggregation increased resistance to the samples' passage, and the negative pressure that was built up during aspiration was determined as the pressure rate. A negative pressure of −130 mmHg was established as 100% aggregation, whereas −6 mmHg was the 0% pressure rate. The percentage of filtration pressure through the mesh filter at each ADP concentration was measured. A previous investigation revealed the highly significant correlation between the pressure rate and the amount of platelet aggregation.[10] Another parameter, platelet aggregatory threshold index (PATI), was automatically calculated as the concentration of ADP that elicited 50% of maximal pressure rate and was used as an index of sensitivity to agonist-induced aggregation.

Simultaneously, another aliquot of nonanticoagulated blood was used for the SNC analysis within 2 minutes after sampling. A celite-containing cuvette was used for the analysis. SonACT and clot rate were automatically calculated with the SNC monitor. The TP on the SNC signature was manually calculated according to previous reports.[15,16]

Data were expressed as either mean ± SD or mean (range). The perioperative changes of each parameter were statistically analyzed with a Friedman test because these data did not follow normal distribution. A nonparametric Spearman rank correlation was used to establish any correlation between WBA-derived parameters and TP derived from SNC, as well as between those parameters and postoperative chest tube drainage. All the data were statistically analyzed with Prism software (Version 4; Graphpad, San Diego, CA), and $p < 0.05$ was considered statistically significant.

RESULTS

Thirty-three patients originally enrolled in this study. Seven patients were excluded from the analysis because of perioperative platelet transfusion, and the remaining 26 patients were included in the analysis. Demographic and operative data of these patients are summarized in Table 1. The data derived from the WBA analyzer are summarized in Figures 1 and 2. The filtration pressure rate was significantly decreased at all ADP concentrations at the end of surgery (Fig 1), which indicated impaired platelet aggregation at this time. Concurrently, PATI significantly increased at the same time and indicated decreased sensitivity of platelet aggregation to ADP (Fig 2). These parameters returned to preoperative levels on POD 1, suggesting platelets regained normal sensitivity to ADP-induced aggregation by then (Table 2).

Data derived from the Sonoclot analyzer are summarized in Table 3. Because TP was not clearly defined in 2 SNC signatures, the remaining 24 datasets were used for analysis. TP from the SNC analyzer showed no significant changes between the preoperative and postoperative samples. There was no linear relationship between filtration pressure rate and TP or between PATI and TP at any measurement period. There also was no significant correlation between postoperative blood loss and either WBA- or SNC-derived parameters.

Table 1. Patient Demographics and Operative Data

Age (y)	55 ± 15
Male/Female	21/5
Surgery (CABG/valve replacement)	11/15
Duration of surgery (min)	401 ± 64
Duration of CPB (min)	190 ± 49
Total heparin dose (U)	3100 ± 800
Total protamine dose (mg)	290 ± 60
Total drainage 0-3 h (mL)	203 (85-597)
Total drainage 3-8 h (mL)	125 (28-327)
Total drainage 8-24 h (mL)	318 (103-844)

NOTE. Data were expressed as mean ± SD, n or mean (range).
Abbreviation: CABG, coronary artery bypass grafting.

DISCUSSION

The present study showed that whole-blood aggregometry using a screen filtration method unmasked transient, but significant, platelet aggregation defects after CPB and that SNC failed to show such alterations of platelet aggregation. Although platelet dysfunction plays an important role in postoperative bleeding after CPB, the assessment of platelet function to achieve better hemostasis has not been widely used. Conventional platelet aggregometry using optical or impedance changes caused by platelet aggregation requires time-consuming preparation and considerable technical skills. On the other hand, viscoelastic analysis of clot formation and retraction, which is used in SNC, can provide integrated information about coagulation factors, fibrinogen, and platelet activity.[17] However, many issues remain unresolved in regards to how to interpret data derived from the SNC in perioperative hemostatic management. These considerations prompted the authors to investigate the clinical feasibility of a relatively new method, the WBA analyzer, and to compare it with SNC as a platelet function monitor during cardiac surgery.

Previous studies showed that post-CPB platelet aggregation using whole-blood impedance aggregometry decreased to nearly 10% of the preoperative value.[5,7] The present data agree with these reports, indicating the validity of the WBA analyzer as a platelet function monitor. Although this study was not designed to clarify the mechanisms of bleeding, the findings underscore the significance of CPB-induced platelet dysfunction. In addition, the present study showed that the defect of platelet function was transient and returned to the baseline value by the first POD, possibly through recovery of damaged platelets or mobilization of normal platelets from storage sites as previously described.[18-20]

It should be noted that no statistical relationship was shown between the platelet aggregatory defect and the amount of postoperative bleeding in this study. Previous studies reported conflicting results on this issue.[5,7] Several possibilities could account for such a discrepancy. First, the small sample size might preclude enough statistical power to show a significant correlation. Second, the relatively stable hemostatic profiles of these patients may have obscured the possible relationship between the WBA analyzer-derived parameter and postoperative bleeding. Third, the choice of agonist may have a significant impact on the data. In this respect, studies using different agonists, such as collagen and thrombin-receptor-activating

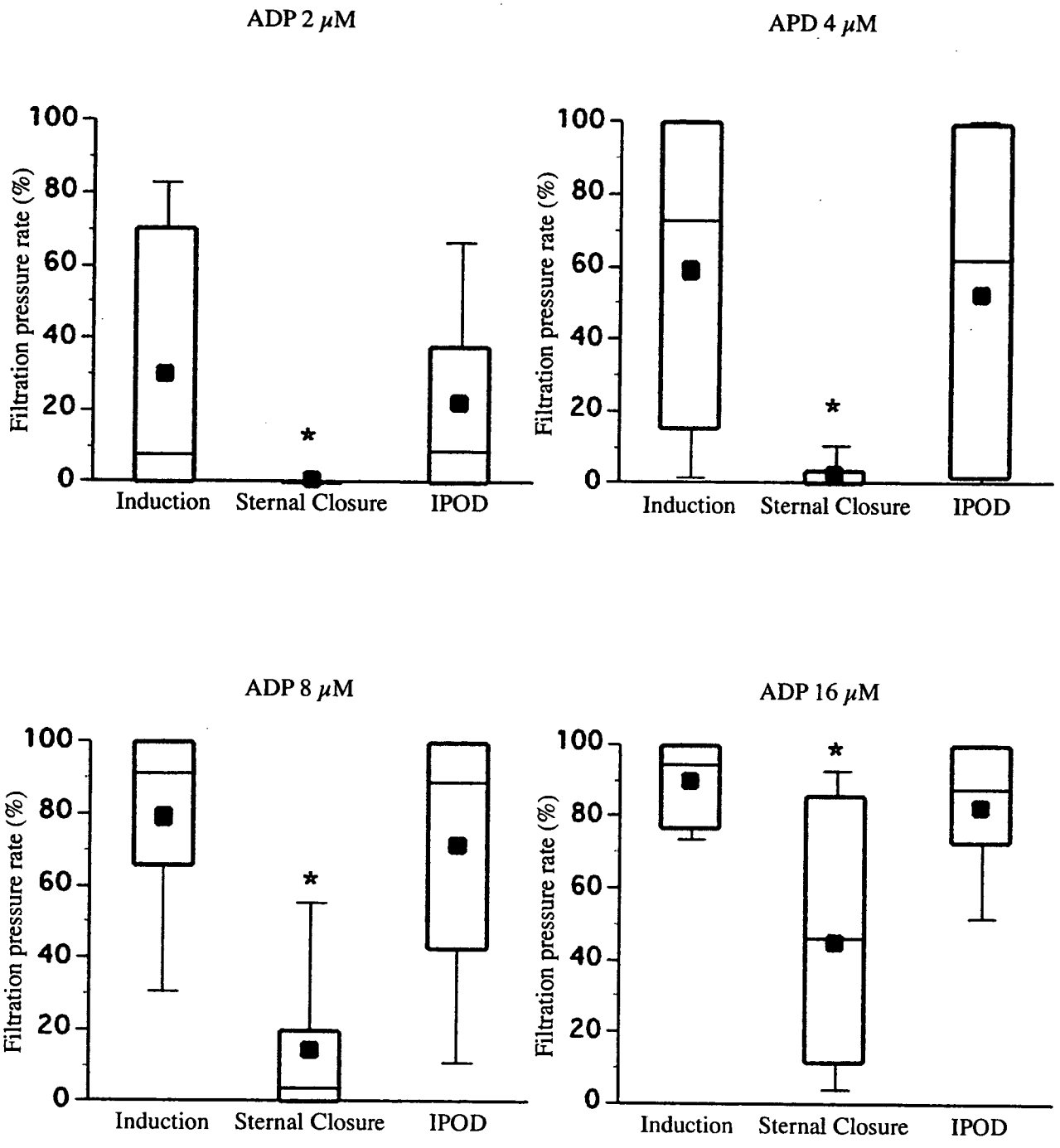


Fig 1. Time-dependent change of platelet aggregation assessed with filtration pressure rate elicited by 4 different ADP concentrations. Data were expressed as a box graph. Closed square represents mean value; *$p < 0.05$ versus preoperatively.

peptide, are warranted to find the most suitable agonist in predicting postoperative bleeding. Finally, the effects of the platelet count possibly impact the results because CPB is frequently accompanied with substantial thrombocytopenia. However, a previous study showed that PATI was stable over a wide range of platelet counts.[11]

The TP obtained from the Sonoclot signature was not consistent with the data from the WBA analyzer. The finding contradicts a previous report, indicating that TP was negatively correlated with platelet count and platelet aggregation measured with impedance aggregometry.[15] In the previous report, however, prolongation of TP was noted in patients with advanced hemostatic derangements, such as marked thrombocytopenia and/or low fibrinogen levels, suggesting that TP lacks

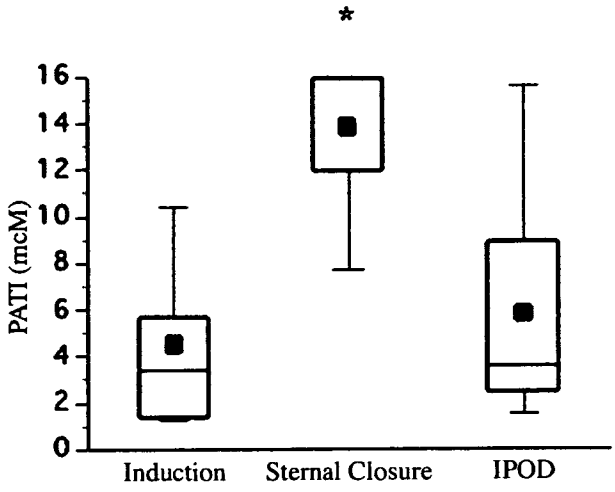


Fig 2. Time-dependent change of platelet aggregation assessed with platelet aggregatory threshold index (PATI). Data were expressed as a box graph. Closed box represents median value; *$p < 0.05$ versus preoperatively.

adequate sensitivity for evaluating platelet aggregation in uncomplicated cases and is only elongated in cases with severe hemostatic compromise. Additionally, the interpretation of TP is somewhat subjective. Given these findings, SNC may be suitable to detect severe platelet dysfunction, whereas the WBA analyzer could be used to investigate more subtle changes of platelet function in the majority of cardiac surgical patients. In this respect, the WBA analyzer could be useful to assess

Table 2. Platelet Count and ACT

	Induction	Sternal Closure	1 POD
Platelet count ($\times$1,000/mm^6)	195 ± 55	112 ± 39	103 ± 31
ACT (s)	134 ± 12	137 ± 14	130 ± 13

NOTE. Data were expressed as mean ± SD.

Table 3. Sonoclot-Derived Parameters

	Induction	Sternal Closure	1 POD
SonACT (s)	230 ± 65	231 ± 59	202 ± 48
Clot rate (/min)	17.1 ± 6.0	14.0 ± 4.4	18.8 ± 5.5
Time to peak (min)*	15.3 ± 6.7	17.5 ± 7.3	15.8 ± 5.1

NOTE. Data were derived from celite-activated analysis and were expressed as mean ± SD.

*Data from 24 signatures were used for calculation of time to peak.

pharmacologic interventions to preserve platelet function (eg, GPIIb/IIIa blockers).[10] Additionally, platelet function is one of the key components of a transfusion algorithm,[21-24] and further study is warranted to determine whether the WBA analyzer can be incorporated.

This study has several limitations. First, the authors could not compare the performance of the WBA analyzer with a more conventional analysis of perioperative hemostasis, such as the thromboelastograph or classic platelet aggregometry. Second, any clear relationship between the aggregatory deficit and the amount of postoperative chest tube drainage was not found in this study. Furthermore, this study was not intended to investigate whether the WBA analyzer and Sonoclot would prompt the need of hemostatic intervention. In this respect, previous investigations clarified that another device, the Clot Signature Analyzer, was able to detect clinical coagulopathic states after CPB and predicted the need for transfusion.[25] Further evaluation is required of the clinical implications of the functional change in platelets detected by the WBA analyzer. Additionally, the functional status of platelets in high-risk patients remains to be investigated because this study was focused on the CPB-induced physiologic changes of platelet function rather than the effects of pharmacologic intervention.

In conclusion, ADP-induced platelet aggregation, assessed with a novel screen filtration aggregometer, the WBA analyzer, was transiently but significantly attenuated after CPB in patients at relatively low risk for perioperative bleeding. In contrast, the TP value obtained by the Sonoclot analyzer was less sensitive to this pathophysiologic change. The WBA analyzer may be useful to assess platelet function intraoperatively because of its high sensitivity, easy operation, rapid assay time, and easy interpretation.

REFERENCES

1. Khuri SF, Wolfe JA, Josa M, et al: Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. J Thorac Cardiovasc Surg 104:94-107, 1992

2. Despotis GJ, Goodnough LT: Management approaches to platelet-related microvascular bleeding in cardiothoracic surgery. Ann Thorac Surg 70:S20-S32, 2000

3. Despotis GJ, Gravlee G, Filos K, et al: Anticoagulation monitoring during cardiac surgery: A review of current and emerging techniques. Anesthesiology 91:1122-1151, 1999

4. Menys VC, Belcher PR, Noble MI, et al: Macroaggregation of platelets in plasma, as distinct from microaggregation in whole blood (and plasma), as determined using optical aggregometry and platelet counting respectively, is specifically impaired following cardiopulmonary bypass in man. Thromb Haemost 72:511-518, 1994

5. Ray MJ, Hawson GA, Just SJ, et al: Relationship of platelet aggregation to bleeding after cardiopulmonary bypass. Ann Thorac Surg 57:981-986, 1994

6. Menys VC, Belcher PR, Noble MI, et al: Impaired platelet aggregation after cardiopulmonary bypass in man: Enhancement of collagen-induced aggregation in whole blood and plasma by adrenaline ex vivo. Clin Sci (Lond) 88:269-275, 1995

7. Irani MS, Izzat NN, Jones JW: Platelet function, coagulation tests, and cardiopulmonary bypass: lack of correlation between preoperative and intraoperative whole blood lumiaggregometry and perioperative blood loss in patients receiving autologous platelet-rich plasma. Blood Coagul Fibrinolysis 6:428-432, 1995

8. Despotis GJ, Levine V, Saleem R, et al: Use of point-of-care test in identification of patients who can benefit from desmopressin during cardiac surgery: A randomised controlled trial. Lancet 354:106-110, 1999

9. Faraday N: Platelets, perioperative hemostasis, and anesthesia. Anesthesiology 96:1042-1043, 2002

10. Ozeki Y, Sudo T, Toga K, et al: Characterization of whole blood aggregation with a new type of aggregometer by a screen filtration pressure method. Thromb Res 101:65-72, 2001

11. Sudo T, Ito H, Ozeki Y, et al: Estimation of antiplatelet drugs on human platelet aggregation with a novel whole blood aggregometer by a screen filtration pressure method. Br J Pharmacol 133:1396-1404, 2001

12. Inoue T, Hayashi M, Uchida T, et al: Significance of platelet aggregability immediately after blood sampling and effect of cigarette smoking. Platelets 12:415-418, 2001

13. Sudo T, Ito H, Kimura Y: Characterization of platelet aggregation in whole blood of laboratory animals by a screen filtration pressure method. Platelets 14:239-246, 2003

14. Arakawa K, Takeyoshi I, Muraoka M, et al: Measuring platelet aggregation to estimate small intestinal ischemia-reperfusion injury. J Surg Res 122:195-200, 2004

15. Miyashita T, Kuro M: Evaluation of platelet function by Sonoclot analysis compared with other hemostatic variables in cardiac surgery. Anesth Analg 87:1228-1233, 1998

16. Waters JH, Anthony DG, Gottlieb A, et al: Bleeding in a patient receiving platelet aggregation inhibitors. Anesth Analg 93:878-882, 2001

17. Hett DA, Walker D, Pilkington SN, et al: Sonoclot analysis. Br J Anaesth 75:771-776, 1995

18. Kestin AS, Valeri CR, Khuri SF, et al: The platelet function defect of cardiopulmonary bypass. Blood 82:107-117, 1993

19. Gries A, Bode C, Gross S, et al: The effect of intravenously administered magnesium on platelet function in patients after cardiac surgery. Anesth Analg 88:1213-1219, 1999

20. Parolari A, Guarnieri D, Alamanni F, et al: Platelet function and anesthetics in cardiac surgery: An in vitro and ex vivo study. Anesth Analg 89:26-31, 1999

21. Tuman KJ, McCarthy RJ, Djuric M, et al: Evaluation of coagulation during cardiopulmonary bypass with a heparinase-modified thromboelastographic assay. J Cardiothorac Vasc Anesth 8:144-149, 1994

22. Spiess BD, Gillies BS, Chandler W, et al: Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. J Cardiothorac Vasc Anesth 9:168-173, 1995

23. Spiess BD: Thromboelastography and cardiopulmonary bypass. Semin Thromb Hemost 21:27-33, 1995 (suppl 4)

24. Shore-Lesserson L, Manspeizer HE, DePerio M, et al: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 88:312-319, 1999

25. Faraday N, Guallar E, Sera VA, et al: Utility of whole blood hemostatometry using the clot signature analyzer for assessment of hemostasis in cardiac surgery. Anesthesiology 96:1115-1122, 2002

Activation of a Neutrophil-Derived Inflammatory Response in the Airways During Cardiopulmonary Bypass

Toru Kotani, MD*
Yoshifumi Kotake, MD†
Hiroshi Morisaki, MD†
Junzo Takeda, MD†
Hideyuki Shimizu, MD‡
Toshihiko Ueda, MD‡
Akitoshi Ishizaka, MD§

Cardiopulmonary bypass (CPB) is believed to cause postoperative lung dysfunction. To more closely examine the inflammatory processes occurring in the airways during CPB, we serially measured inflammatory mediators, with the assistance of a new bronchoscopic microsample probe, in 11 patients undergoing repair of aortic arch aneurysms. Epithelial lining fluid (ELF) and arterial blood were sampled simultaneously after induction of anesthesia, at the time of pulmonary reperfusion, and at the end of surgery. A decrease in the Pao_2/Fio_2 ratio was observed at the end of surgery ($P = 0.029$). Although the ELF concentrations of interleukin (IL)-8, IL-6, and neutrophil elastase had increased significantly at the end of surgery (median = 23,200, 1818, and 12,900 μg/mL, respectively), they did not correlate with the degree of hypoxemia. Neutrophil elastase increased significantly at the time of pulmonary reperfusion, before IL-8 and IL-6, and independently of blood transfusions. At the end of surgery, IL-6 in ELF correlated with total blood transfusion volume ($\rho = 0.731$, $P = 0.011$). These results indicate that a neutrophil-derived inflammatory response is activated in the airway in the early phase of CPB.
(Anesth Analg 2006;103:1394-9)

Postoperative respiratory failure, apparent as hypoxemia, a common complication of cardiac surgery performed under cardiopulmonary bypass (CPB) (1), correlates with major morbidity and mortality (2,3). A higher incidence of prolonged mechanical ventilation has been reported in patients undergoing repair of aortic arch aneurysms (4). Circulating humoral and cellular factors account primarily for the inflammatory processes, such as activation of neutrophils and complement system, associated with exposure to foreign material during and after CPB, and the subsequent pulmonary injury (5). However, other events, including ischemia and reperfusion, abundant allogenic transfusions, or bacterial and endotoxin translocation from the hypoperfused gut, contribute to triggering this process (6,7). In view of the pivotal role played by systemic proinflammatory cytokines, such as interleukin (IL)-6 and IL-8, (7,8) monitoring of their concentrations may help us to understand the clinical status of patients and design treatments.

Several studies have confirmed that resident lung cells are the source of inflammatory mediators involved in the pulmonary dysfunction observed after CPB (9,10). While monitoring of cytokines in bronchoalveolar lavage (BAL) fluid was useful for following the development of pulmonary dysfunction after CPB (11), this method is limited by its invasive nature. A less invasive method of pulmonary epithelial lining fluid (ELF) collection would obviously be preferred in high-risk surgical patients. We have developed a bronchoscopic microsample probe and described its use for the serial assessment of intrapulmonary events in critically ill patients (12) and for the evaluation of the therapeutic effects of pharmaceuticals (13).

The aim of the current study was to test the feasibility of the bronchoscopic microsample method in patients who underwent prolonged CPB for the repair of aortic arch aneurysms. Serial measurements of several mediators with this new method would help to monitor the CPB-activated inflammatory response in the airways and could facilitate future analysis of airway cytokines and post-CPB pulmonary dysfunction.

METHODS

The study protocol was approved by the IRB of Keio University Hospital, and informed consent was obtained from each patient. We prospectively studied 10 men and 1 woman who underwent elective aortic arch repair during the study period. Meperidine hydrochloride, 1 mg/kg, i.m., and atropine sulfate, 0.5 mg, i.m., were administered 1 h before anesthesia, which was induced and maintained by continuous infusions of fentanyl, midazolam, and vecuronium.

From the *Department of Anesthesiology, Tokyo Women's Medical University, Shinjuku, Tokyo 162-8666, Japan; and Department of †Anesthesiology, ‡Cardiovascular Surgery, and §Medicine, Keio University School of Medicine, Tokyo, Japan.

Accepted for publication August 14, 2006.

Supported by an unrestricted departmental grant.

Address correspondence and reprint requests to Toru Kotani, MD, Department of Anesthesiology, Tokyo Women's Medical University, 8-1, Kawadacho, Shinjuku, Tokyo 162-8666, Japan. Address e-mail to trkotani@aol.com.

DOI: 10.1213/01.ane.0000243391.05091.bb

Percutaneous arterial oxygen saturation, brachial arterial pressure, and continuous thermodilution cardiac output (Vigilance, Edwards Lifesciences, Irvine, CA) were continuously monitored. The lungs were ventilated with a 10-mL/kg tidal volume, and the respiratory frequency was adjusted to maintain a $Paco_2$ within the normal range. No positive end-expiratory pressure was applied during CPB to facilitate the surgical procedure. The CPB circuit included a centrifugal pump (HC-011S, Terumo, Tokyo, Japan) and a heparin-coated membrane oxygenator (Affinity NT oxygenator, Medtronic, Inc., MN) and heat exchanger. Ultrafiltration (Capiox Hemoconcentrator CX-HC11S, Terumo, Tokyo, Japan) was systematically performed. Anticoagulation was performed with porcine heparin in an initial dose of 300 U/kg, and neutralized with protamine. Additional heparin administration and the protamine dose needed for its neutralization were calculated by monitoring of the activated coagulation time. Blood was transfused to maintain a hemoglobin concentration >8 g/dL. Adrenergic agonists, including dopamine, dobutamine, and norepinephrine were used to support the systemic blood pressure and promote urinary output. The patients were sedated postoperatively with a continuous propofol infusion, and mechanically ventilated for at least 12 h in the intensive care unit. The hemodynamic fluid and ventilatory management were left to the discretion of attending physicians. No steroids, antiprotease, nonsteroidal anti-inflammatory drugs, aprotinin, aminocaproic acid, or tranexamic acid were administered during the study period. Chest radiographs were obtained immediately after the operation and daily thereafter until the patients left the intensive care unit, to monitor the development of acute lung injury, diagnosed according to the criteria of the American–European Consensus Conference (14).

Bronchoscopic sampling of ELF was performed after induction of anesthesia (baseline), at re-establishment of pulmonary circulation (reperfusion), and at the end of surgery. Patients' lungs were continuously ventilated throughout the procedure via a Bodai Suction Safe™ Swivel Y connector (Sontek Medical, Hingham, MA). The inspired O_2 concentration was set at 100% and other ventilator settings remained unchanged during the procedure. The design of the bronchoscopic microsample probe and the ELF sampling method has been described elsewhere (12). Briefly, a commercially available bronchoscopic microsample probe (OD, 2.4 mm) loaded with absorptive material (BC-401C, Olympus, Tokyo, Japan) was directed to the right S4 or S5 bronchus through the channel of the bronchoscope. The catheter was advanced to the subsegmental bronchus and placed in contact with the epithelial surface for 5 s. Three samples without blood contamination were obtained at each time point. Serial ELF samples were obtained from the same distal subsegmental bronchus in each patient. The ELF samples were stored at −80°C until assayed.

Table 1. Patient Characteristics and P/F Ratio

Patient no.	Age (yr)/sex	Height (cm)/weight (kg)	DOV (days)	Pao_2/Fio_2 BL	PR	ES
1	71/M	164/81	16	537	350	301
2	80/F	156/71	6	352	521	326
3	66/M	162/66	1	364	556	228
4	72/M	165/81	2	242	293	224
5	71/M	163/69	1	360	479	301
6	67/M	158/64	1	434	528	427
7	73/M	172/63	1	569	640	648
8	68/M	164/89	2	425	243	252
9	70/M	170/69	1	308	467	368
10	65/M	165/70	1	343	780	373
11	65/M	165/69	1	288	688	464

DOV = duration of ventilation, BL = baseline, PR = pulmonary reperfusion, ES = end of surgery.

Arterial blood samples for blood gas analyses were collected at the time of ELF sampling. The remainder of the blood samples was centrifuged at 3000 rpm for 10 min at 4°C, and the supernatant was stored at −80°C until assayed.

The absorbed material collected with the bronchoscopic microsample probe and the plasma samples underwent enzyme linked immunosorbent assay for IL-8, IL-6, and neutrophil elastase. The human albumin concentration in the extract was also measured by a colorimetric method (Beckman, Fullerton, CA). The original concentrations of these mediators in ELF were calculated with the correction of wet-to-dry ratio of the absorptive material and used for analysis. Measurement was performed by the laboratory staff unaware of the clinical situation and profile of the patients. All results of chemical mediator assay and albumin concentration are means of two measurements.

The results were expressed as means and SD or medians, where appropriate. Changes in Pao_2 were tested by one-way repeated measures analysis of variance and by paired *t*-test with Bonferroni correction. Time-dependent changes were analyzed with Friedman analysis and Wilcoxon's ranked sum test since the data were skewed. The correlation of log-transformed mediator concentrations with Pao_2/Fio_2 ratio (P/F ratio) or total volume of blood transfusion was analyzed with Spearman correlation coefficient. A P value <0.05 was considered significant.

RESULTS

One of the 12 patients enrolled was excluded from the analysis because of postoperative bleeding and need for surgical re-exploration. Data from one patient who needed prolonged postoperative ventilatory support for late-onset ventilator-associated pneumonia were included in this analysis. The postoperative course of the other 10 patients was uneventful. The demographic characteristics, duration of ventilation, and P/F ratio in the 11 patients included in the study are shown in Table 1. No patient developed postoperative bilateral

Table 2. Operative and Blood Transfusion Characteristics

Patient no.	Anesthesia time (min)	Operation time (min)	Total CPB time (min)	Aortic cross clamp time (min)	Blood transfusions (mL)	
					Total volume	Before reperfusion
1	550	445	290	198	0	0
2	540	320	170	110	0	0
3	575	434	268	170	520	0
4	555	474	280	152	2470	0
5	570	480	257	171	3510	0
6	428	350	183	112	4680	0
7	515	435	281	146	0	0
8	550	462	262	159	1820	260
9	685	553	300	168	6760	0
10	715	542	269	177	6760	0
11	712	602	365	250	7410	1040

CPB = cardiopulmonary bypass.

infiltrates on roentgenographic examination. Significant changes in oxygenation were found by Friedman analysis ($P = 0.029$). Pao_2 decreased at the end of surgery compared with reperfusion ($P = 0.008$). However, nine patients were weaned from the ventilator on Day 1 or 2 after the operation, and were discharged from intensive care the next day. Table 2 summarizes the operative and blood transfusion characteristics. The mean duration of CPB was 266 ± 53 min. Allogenic blood transfusions were administered to eight patients, representing a mean total volume of 3085 ± 2925 mL. The majority of blood products were given at the time of weaning from CPB, though three patients were transfused before the onset of pulmonary reperfusion.

The ELF sampling procedure was completed within 10 min, and no adverse hemodynamic or respiratory event was observed. FIo_2 returned to previous levels immediately after the procedure in all patients. The concentrations of inflammatory mediators and albumin in ELF are shown in Figure 1. The changes in IL-8, IL-6, and neutrophil elastase in ELF were statistically significant ($P = 0.029$, 0.006, and 0.003, respectively). The median concentrations of IL-8 (23,200 pg/mL) and IL-6 in ELF (1,818 pg/mL) were significantly higher at the end of surgery than at baseline ($P = 0.008$ and 0.003, respectively). The median concentration of neutrophil elastase also increased significantly at the time of reperfusion (5000 μg/mL) and at the end of surgery (12,900 μg/mL) when compared with baseline ($P = 0.017$ and 0.004, respectively). The albumin concentration in ELF remained unchanged throughout the study period. The log-transformed measurements of IL-6, IL-8, and neutrophil elastase did not correlate with the P/F ratio (data not shown).

The plasma concentrations of IL-6 and IL-8 increased significantly after reperfusion and at the end of surgery when compared with baseline (Table 3). Although time-dependent increases in plasma concentrations in IL-6 and IL-8 were observed by Friedman analysis ($P = 0.001$ and 0.002, respectively), the difference between the concentrations at reperfusion versus at the end of surgery did not reach statistical significance.

No correlation was found between the concentrations of neutrophil elastase, IL-6, and IL-8 and P/F ratio. The log-transformed mean IL-6 concentration at the end of surgery correlated closely with total transfusion volume (Fig. 2, $\rho = 0.731$, $P = 0.011$).

DISCUSSION

This study is the first to show that neutrophil elastase increases at the time of pulmonary reperfusion after CPB, preceding the increase in IL-6 and IL-8. We also found significant increases in ELF IL-6, IL-8, and neutrophil elastase after CPB, an observation in agreement with previous studies. One report has highlighted the importance of the alveolar space as a source of inflammatory mediators, as several inflammatory mediators were increased in BAL fluid (9). Kotani et al. (10) have reported that the gene expression of IL-6, IL-8, and tumor necrosis factor-α were up to 8 times greater in alveolar macrophages than in plasma monocytes after CPB. In addition, the activation of mitogen-activated protein kinase in BAL after CPB, which leads to a variable inflammatory cytokine production in the air spaces, has been observed in an animal model (15). However, the time course of these responses during CPB has not been studied. Our observations suggest that neutrophil activation in the airway is the earliest stage of the inflammatory response induced by CPB. They further suggest that a neutrophil-derived inflammatory reaction plays a role in CPB-induced lung dysfunction, although the increase in concentrations of mediators did not correlate with the impairment of oxygenation in this study. The unchanged ELF albumin concentration (Fig. 1) and mild decrease in P/F ratio (Table 1) indicate that this severe reaction did not cause extensive endothelial or epithelial injury. Therefore, a concomitant anti-inflammatory reaction in the airway and in the systemic circulation might play a role in the mitigation of lung dysfunction (16). It

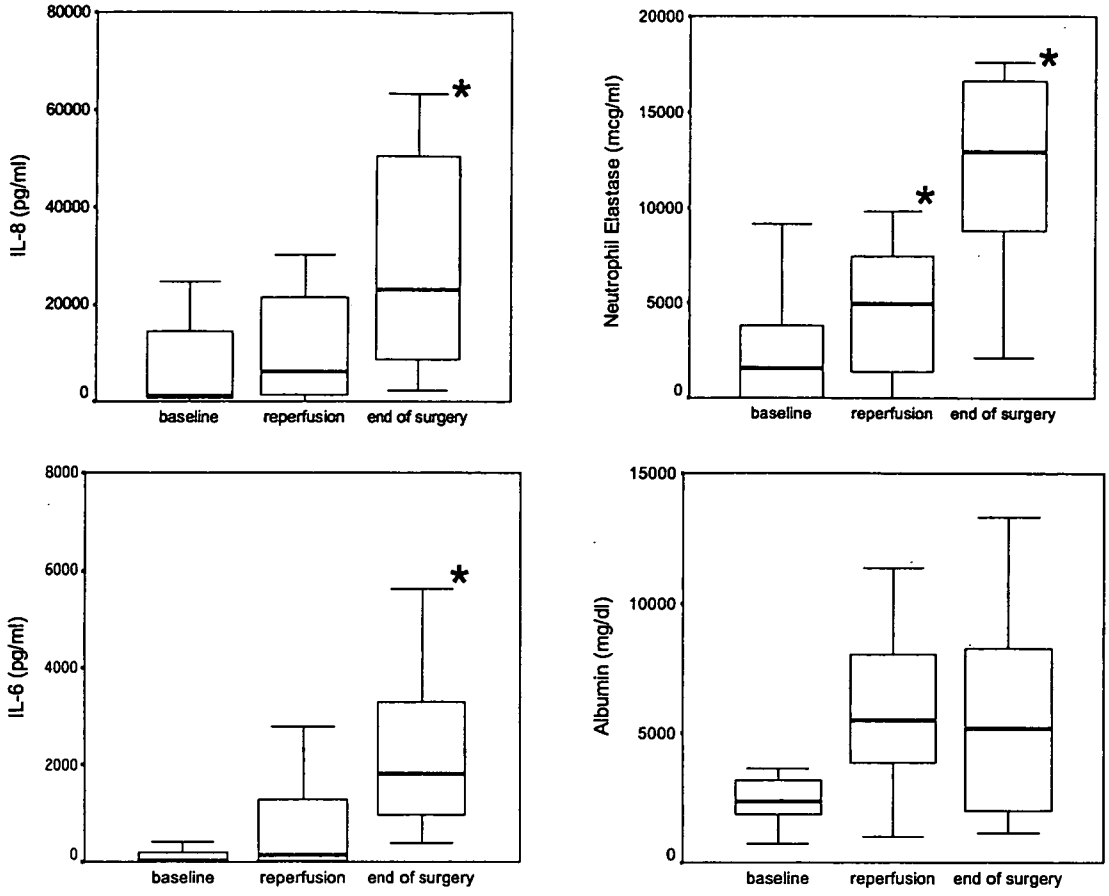


Figure 1. The concentrations of interleukin (IL)-8, IL-6, neutrophil elastase, and albumin in epithelial lining fluid (ELF) collected by the microsampling method are shown in the box graph. The data are presented as medians, 5, 25, 75, and 95%, and means (closed box). *$P < 0.05$ by Wilcoxon's ranked sum test versus baseline.

Table 3. Plasma Levels of Interleukin (IL)-6 and IL-8

	IL-6 (pg/mL)			IL-8 (pg/mL)		
Patient no.	Baseline	Reperfusion	End of surgery	Baseline	Reperfusion	End of surgery
1	1.2	446.0	92.9	0.0	36.7	18.4
2	2.4	159.0	223.0	0.0	21.1	44.4
3	1.5	1.2	73.9	0.0	0.0	326.0
4	2.3	5.1	77.1	0.0	0.0	14.2
5	0.9	177.0	71.9	0.0	26.7	27.1
6	0.8	192.0	71.0	0.0	32.4	0.0
7	2.2	66.9	224.0	0.0	29.8	53.1
8	3.1	20.9	151.0	0.0	36.1	17.8
9	2.0	6.9	202.0	0.0	29.4	44.6
10	0.6	39.3	92.5	0.0	21.4	36.3
11	1.6	143.0	52.4	0.0	23.4	0.0
Median	1.6	66.9*	92.5*	0.0	26.7*	27.1*

BL = baseline, PR = pulmonary reperfusion, ES = end of surgery.

* $P < 0.05$ when compared with baseline.

is noteworthy that, despite the absence of postoperative lung injury, IL-6 and neutrophil elastase were higher in ELF at the end of surgery than the peak concentrations we previously observed in seven patients with acute respiratory distress syndrome (median, 342.2 pg/mL and 9829.1 μg/L, respectively). (12) This may be an indication that lungs exposed to CPB become susceptible to even subtle stimuli, such as infection or mechanical over-distension, that can induce further cytokine upregulation.

Hauser et al. (17) reported that IL-6 was significantly increased in BAL at the time of removal of the aortic cross-clamp and remained increased for 24 h after pediatric open heart surgery. Although the sampling method and study population were different, our results showed a concordant time-dependent evolution. In the study of Hauser et al., a correlation was also observed between concentrations of serum IL-6 and postoperative mortality. While plasma IL-6 in the current study also increased in a time-dependent manner, the increase was considerably

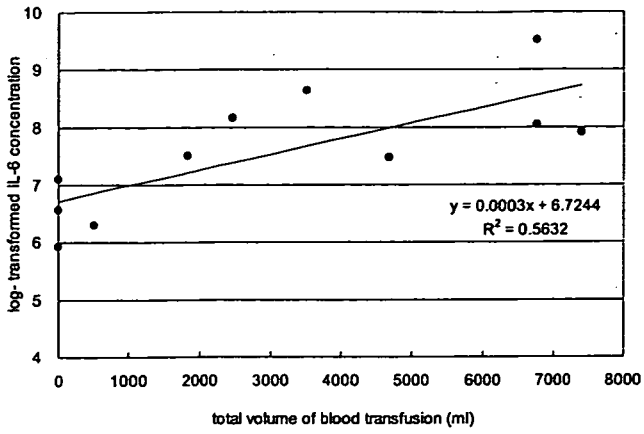


Figure 2. Correlation between log-transformed interleukin (IL)-6 concentration in epithelial lining fluid (ELF) and total blood transfusion volume.

less than that measured among the survivors in that study, probably due to differences in the patients' clinical conditions.

We also found that the increase in neutrophil elastase was independent of blood transfusion, since few blood products had been administered before pulmonary reperfusion (Table 2), whereas the increase in IL-6 in ELF at the end of surgery correlated with the volume of blood transfusion. Direct contact of the neutrophils with foreign materials or ischemia during CPB are mechanisms that are susceptible, alone or in combination, to activating neutrophils, and which warrant further investigation. Other mechanisms may also be responsible for activation of neutrophils during cardiac surgery.

While several studies emphasized the importance of lung epithelium as a source of inflammatory mediators (9,11), few clinical studies have detailed the evolution of these inflammatory changes, probably because of the lack of a safe procedure applicable to critically ill patients during CPB. While BAL has become a bedside procedure used to diagnose respiratory disorders, it causes temporary, though sometimes severe, O_2 desaturation (18). It is noteworthy that our bronchoscopic microsample technique often enabled us to collect ELF without the saline instillation that carries such risks as hypoxia or dissemination of infection. It also allowed us to understand the contribution of blood transfusions to the evolution of the inflammatory response in the airway, and its time course during and after CPB. This study will prompt further applications of bronchoscopic microsampling in the study of the pathophysiology of postoperative pulmonary dysfunction.

LIMITATIONS OF OUR STUDY

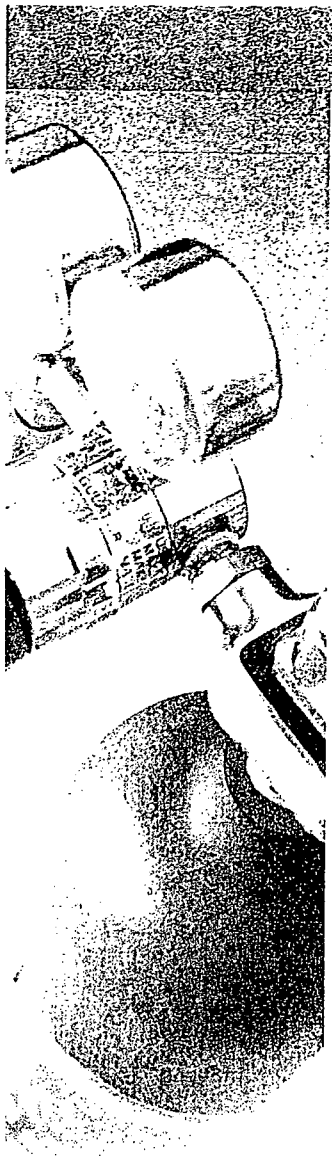
It might not be legitimate to compare measurements made in ELF obtained by the bronchoscopic microsample technique to that obtained by BAL, since the former is not diluted by saline. However, we (12) have previously demonstrated that the concentrations of biochemical substances obtained by bronchoscopic microsample showed a similar trend as those obtained by BAL in healthy subjects, and that it is a reliable method to grade the severity of lung injury in patients with acute respiratory distress syndrome (19), and in the diagnosis of lung cancer (20). Our study had a weak statistical power because of the small number of patients, perhaps explaining the discordant absence of correlation between ELF mediators and decreased arterial oxygenation after cardiac surgery (11). To exclude biases introduced by the surgical procedure and techniques, we limited our patient population to those operations that were elective and performed by a single surgeon. This design did not allow the inclusion of a control group, and our study was observational. However, the baseline values measured in each patient were used as intra-individual controls, allowing an assessment of the time-dependent changes as a means of mitigating this limitation. Mechanical ventilation could affect inflammatory mediator production, especially in critically ill patients. A previous report showed that ventilation with 15 mL/kg of tidal volume on zero positive end-expiratory pressure did not result in higher cytokine levels compared with 6 mL/kg in essentially normal patients' lungs (21). Thus, the ventilation applied in this study had little effect on cytokine production in the airway. Finally, fewer emigrated neutrophils might change the results, although cells were not counted since the bronchoscopic microsample method does not provide enough cells in the airspace.

In conclusion, our study indicates that neutrophil elastase, IL-8 and IL-6, in the airway increases during CPB. Neutrophil elastase increased before IL-8 and IL-6, and independently of blood transfusions, suggesting that CPB triggered a neutrophil-related inflammatory process in the airway. The bronchoscopic microsample method was safely used in multiple samplings and chemical analyses of pulmonary epithelial fluid, including intra-operatively in cardiac patients.

REFERENCES

1. Rady MY, Ryan T, Starr NJ. Early onset of acute pulmonary dysfunction after cardiovascular surgery: risk factors and clinical outcome. Crit Care Med 1997;25:1831–9.
2. 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.
3. Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest 2002;121:1269–77.
4. Stowe CL, Baertlein MA, Wierman MD, et al. Surgical management of ascending and aortic arch disease: refined techniques with improved results. Ann Thorac Surg 1998;66:388–95.
5. Ito H, Hamano K, Gohra H, et al. Relationship between respiratory distress and cytokine response after cardiopulmonary bypass. Surg Today 1997;27:220–5.
6. Picone AL, Lutz CJ, Finck C, et al. Multiple sequential insults cause post-pump syndrome. Ann Thorac Surg 1999;67:978–85.
7. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 2002;97:215–52.

8. Kawamura T, Wakusawa R, Okada K, Inada S. Elevation of cytokines during open heart surgery with cardiopulmonary bypass: participation of interleukin 8 and 6 in reperfusion injury. Can J Anaesth 1993;40:1016–21.
9. Pugin J, Verghese G, Widmer MC, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 1999;27:304–12.
10. Kotani N, Hashimoto H, Sessler DI, et al. Cardiopulmonary bypass produces greater pulmonary than systemic proinflammatory cytokines. Anesth Analg 2000;90:1039–45.
11. Kotani N, Hashimoto H, Sessler DI, et al. Neutrophil number and interleukin-8 and elastase concentrations in bronchoalveolar lavage fluid correlate with decreased arterial oxygenation after cardiopulmonary bypass. Anesth Analg 2000;90:1046–51.
12. Ishizaka A, Watanabe M, Yamashita T, et al. New bronchoscopic microsample probe to measure the biochemical constituents in epithelial lining fluid of patients with acute respiratory distress syndrome. Crit Care Med 2001;29:896–8.
13. Yamazaki K, Ogura S, Ishizaka A, et al. Bronchoscopic microsampling method for measuring drug concentration in epithelial lining fluid. Am J Respir Crit Care Med 2003;168:1304–7.
14. Artigas A, Bernard GR, Carlet J, et al. The American–European Consensus Conference on ARDS, part 2: ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Acute respiratory distress syndrome. Am J Respir Crit Care Med 1998;157:1332–47.
15. Khan TA, Bianchi C, Araujo EG, et al. Activation of pulmonary mitogen-activated protein kinases during cardiopulmonary bypass. J Surg Res 2003;115:56–62.
16. McBride WT, Armstrong MA, Gilliland H, McMurray TJ. The balance of pro and anti-inflammatory cytokines in plasma and bronchoalveolar lavage (BAL) at paediatric cardiac surgery. Cytokine 1996;8:724–9.
17. Hauser GJ, Ben-Ari J, Colvin MP, et al. Interleukin-6 levels in serum and lung lavage fluid of children undergoing open heart surgery correlate with postoperative morbidity. Intensive Care Med 1998;24:481–6.
18. Guerra LF, Baughman RP. Use of bronchoalveolar lavage to diagnose bacterial pneumonia in mechanically ventilated patients. Crit Care Med 1990;18:169–73.
19. Ishizaka A, Matsuda T, Albertine KH, et al. Elevation of KL-6, a lung epithelial cell marker, in plasma and epithelial lining fluid in acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 2004;286:L1088–94.
20. Watanabe M, Ishizaka A, Ikeda E, et al. Contributions of bronchoscopic microsampling in the supplemental diagnosis of small peripheral lung carcinoma. Ann Thorac Surg 2003;76:1668–72; discussion 73.
21. Wrigge H, Zinserling J, Stuber F, et al. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. Anesthesiology 2000;93:1413–17.



麻酔科学レビュー

最新主要文献集

2007

監修
天羽敬祐

総合医学社

目次

麻酔科学レビュー
最新主要文献集
2007

麻酔科学
レビュー
最新主要文献集
2007

28. 日帰り麻酔

武田純三（たけだじゅんぞう）
慶應義塾大学医学部 麻酔学教室

最近の動向

日帰り手術の麻酔として，全身麻酔か局所麻酔かの検討が行われている．局所麻酔はさらに，脊髄くも膜下麻酔・硬膜外麻酔と末梢神経ブロックとに分けられる．末梢神経ブロックは覚醒や術直後の鎮痛には優れているが，帰宅後の鎮痛対策に問題があるため，痛みが強い手術には適さないとされてきた．しかし，その解決策としてカテーテルを末梢神経周囲に挿入し，局所麻酔薬を持続注入する方法が検討されてきており，その成績，合併症，在宅でのカテーテル管理などが今後の課題となっている．また，神経ブロックのスタンダードが無く，施行者による効果のばらつきが，全身麻酔との比較で帰宅までの時間などに，有意な結果が出ない原因と考えられる．

術前検査

術前 Hb 値は術前検査として必須と考えられてきたが，術前に症状の無い，リスクの小さい手術を受ける健康成人での貧血は大変稀と考えられる．そこでリスクの小さい手術を日帰りで受けた患者のうち，Hb 検査の記録のある患者を対象に，術前 Hb 検査の必要性を検討している[1]．対象患者のうち ASA Ⅰ-Ⅱは 9584 名で，その中で Hb<9g/dL は 75 名（0.8%）と少なかった．ASA Ⅲは 3499 名で，Hb<9g/dL は 138 名（3.9%），ASA Ⅳは 205 名で，Hb<9g/dL は 18 名（8.8%）であった．Hb<9g/dL は男性の 0.5%に比べて，女性は 0.9%で男性に比べて高かった．年齢では，13 歳以下が 4.6%と，13 歳以上の 1.6%に比べて高く，1 歳以下の乳児 66 名では 6.1%であったが，1～12 歳の 4.4%との間に差は認められていない．

ASA Ⅰ-Ⅱで 9g/dL であった 75 名の術前平均 Hb は 8.3±0.7g/dL で，最低値は 5.6g/dL であった．7g/dL 以下は 4 名で，出血の既往や HIV などの疾患を明らかに有しており，ASA Ⅰ-Ⅱに分類することに問題があったとしている．これら 75 名に関して，これ以上の検査や処置は何も行われていなかった．輸血の記録から，ASA Ⅰ-Ⅱの 9584 名のうち 4 名（0.05%）に赤血球輸血が，当日か翌日に行われていた．貧血の既往，ヘパリンの使用，進行癌などの疾患を

1) Olson RP, Stone A, Lubarsky D : The prevalence and significance of low preoperative hemoglobin in ASA 1 or 2 outpatient surgery candidates. Anesth Analg 101 : 1337-1340, 2005

有していた.

以前は10g/dL以下が輸血の対象とされていたが，現在は症状が無く，循環血液量が十分であれば7g/dL以下が対象になると考えられている．今回の結果からは，無症状の健康な成人であればHb<9g/dLである確率は低く，また輸血の実施は術前のHbの値と関連しておらず，さらにHb<9g/dLであっても術中管理に変わりはないことから，有症状，リスクの高い手術，リスクの高い患者，小児，老人を除いた成人でのHb値のスクリーニング検査の必要性は無いとしている.

術後リスク

日帰り手術では，術後24時間は車の運転をしないようにといわれている．しかし，全身麻酔24時間後までに，運転能力や意識状態が正常に戻っているとする十分な証拠も無い．そこで，日帰り手術患者を対象に，全身麻酔後2時～24時間の間に，運転注意力が回復しているかを検討している[2]．左膝関節内視鏡手術を受けた20名を対象に，術前，術後2時間，24時間の時点での，シミュレーターによる運転能力，脳波解析による眠気の判定，主観による眠気の判定，倦怠感，注意力，疼痛を計測し，対応した20名の健康者と比較している．正常者に比べて患者では，術前は有意に高度の注意力を必要とする試験の失敗と，低い注意力レベルにあったが，全身麻酔覚醒2時間後では，有意に運転能力と注意力の障害が認められ，反応の遅延，注意力喪失の頻度の増大，一瞬の睡眠がみられたが，24時間後には元に戻っていた.

疼痛，嘔気，眠気などの小さい症状は，日帰り手術患者では帰宅直後にしばしば起こることから，術後1週間の症状の発生と強さを調査し，予測因子を検討している[3]．日帰り手術患者3,910名に質問表を送り，症状の強さを4点法によって記載してもらった．回答を得た中で記載が整っていた2,732名を解析に使用した．2,144名（79%）が15歳以上の成人で，588名（22%）が15歳未満の小児であった．成人の106名（5%）と，小児の3名（0.5%）が，疼痛，PONVなどの理由で入院している．患者は種々の症状を日帰り手術後1週間に経験しており，何も症状を訴えなかったのはすべての患者の10%で，術後初日には多くの人に症状が認められた．成人では疼痛が最も多く31%，出血19%，発熱あるいは感染徴候が17%，血腫や膨隆が15%，排尿困難が7%，PONVが2%であった．小児では，発熱あるいは上気道感染が主で55%であり，その90%が耳鼻咽喉科で，出血10%，排尿困難7%，疼痛5%，PONVが4%であった.

41名（1.5%）が帰宅後救急部門を訪れており，その理由は創部感染（24%），出血（22%），疼痛（12%），排尿困難（12%）であった．0PODが5%，1PODが20%，2PODが10%，3PODが24%，4PODが15%，5PODが17%，6POD

2) Chung F, Kayumov L, Sinclair D et al : What is the driving performance of ambulatory surgical patients after general anesthesia? Anesthesiology 103 : 951-956, 2005

3) Mattila K, Toivonen J, Janhunen L et al : Postdischarge symptoms after ambulatory surgery : First-week incidence, intensity, and risk factors. Anesth Analg 101 : 1643-1650, 2005

が7%，7PODは2%であった．9名が出血のため病院に戻り，2名が脊髄くも膜下麻酔後の頭痛で，硬膜外血液パッチを行った．2名で深部静脈血栓症が診断されたが，外来で対応可能であった．9名が主に感染のため入院となった．予定外で病院に電話をかけたり，医師を訪れたり，救急部門を訪れたのは，240名（9%）あり，小児が13%，成人が8%であった．1/5が2PODに接触しており，医学的アドバイスを要していることがわかる．

術後の初日には小さい症状がみられるのが一般的で，7PODでも1/4の成人に認められた．青年や年長児，女性では，より多くの小さい症状を経験する傾向にあった．長時間手術は疼痛や嘔気を起こしやすかった．成人では疼痛が最も多く，他の症状に比べて中等度から重度で，より疼痛対策の重要なことが再確認された．眠気も多い症状で，20%近くが訴えており，嗄声・咽頭痛は全身麻酔で増えている．帰宅後当日のより緻密な対応が望まれる．

全身麻酔と神経ブロック，局所麻酔

傍脊椎ブロックで日帰り鼠径ヘルニア手術を行った50名を対象に，0.75%ロピバカインによる傍脊椎ブロックにプロポフォールによる鎮静か，デスフルランによる全身麻酔に0.25%ブピバカインによる局所麻酔を行ったところ，傍脊椎ブロックの71%の患者がPACUをバイパスしたのに対して，全身麻酔では8%であった（$p<0.001$）[4]．在院中に傍脊椎ブロックの3名（13%）が痛みの治療が必要であったが，全身麻酔では局所麻酔をしたにもかかわらず12名（50%）が必要であった（$p=0.005$）．また，傍脊椎ブロックでは102±55分で歩行が可能となったが，全身麻酔では213±108分と遅かった（$p<0.001$）．帰宅可能あるいは帰宅までの時間は，傍脊椎ブロックで156±60分と253±37分で，全身麻酔の203±91分と218±93分より短かった（$p<0.001$）．24時間以内の治療を必要とする疼痛，嘔気・嘔吐，咽頭痛の発生も，全身麻酔より傍脊椎ブロックで少なかった．

前立腺の経会陰刺入法による小型密封放射線源埋込みに対して，TIVAあるいはイソフルランによる全身麻酔と，0.5%高比重ブピバカイン5mg単独か2.5mgに25μgフェンタニルによる脊髄くも膜下麻酔を比較した[5]．術後の嘔気・嘔吐，疼痛スコア，家での通常生活に戻るまでの時間，全体の満足度に差は無かった．手術室滞在時間は全身麻酔のほうが短く，TIVAは排尿までの時間が他の麻酔法に比べて有意に短かった．帰宅までの時間は，TIVAの119±42分は，イソフルラン全身麻酔の160±69分，ブピバカイン2.5mg＋フェンタニルの132±53分，ブピバカイン5mg単独の186±72分に比べて早かった．脊髄くも膜下麻酔では，ブピバカイン2.5mg＋フェンタニルのほうが術中の鎮静を多く必要としたが，排尿は早く，結果的に帰宅が早くなった．

MEDLINEやその他のデータベースをもとに，無作為化対照研究を選び出

4) Hadzic A, Kerimoglu B, Loreio D et al : Paravertebral blocks provide superior same-day recovery over general anesthesia for patients undergoing inguinal hernia repair. Anesth Analg 102 : 1076-1081, 2006

5) Flaishon R, Ekstein P, Matzkin H et al : An evaluation of general and spinal anesthesia techniques for prostate brachytherapy in a day surgery setting. Anesth Analg 101 : 1656-1658, 2005

し，日帰り手術における局所麻酔と全身麻酔を比較した[6]．局所麻酔は主たるブロック一つを選び，さらに15（1003名）のneuraxialブロックと7（359名）の末梢神経ブロックに分けた．全身麻酔に比べると，神経ブロックでは導入時間が長く，ペインスコアが低く，術後の鎮痛薬の使用が少なかった．しかし，neuraxialブロックではPACUの通過は減らず，鎮痛薬が少ないにもかかわらず嘔気が減っておらず，滞在時間が35分長かった．一方，末梢神経ブロックはPACUの必要性を減らし，嘔気を減少させたが，滞在時間を減らすことはできなかった．全身麻酔に比べると局所麻酔は，PACUの必要性の減少や嘔気の軽減，術後痛などの点で優れているにもかかわらず，滞在時間を減少させておらず，その理由として，解析方法や帰宅基準などの別の理由が考えられるとしている．これに対してHadzicは[7]，神経ブロックの成績がブロックの施行者に依存しており，スタンダードが無く，報告の再現性が低いことが問題であると指摘している．

局所麻酔薬持続投与

持続神経ブロックは長時間神経ブロックを維持するための唯一の方法である．有効な疼痛対策であり，PONVの低下，患者満足度の向上，リハビリテーションの改善，術後慢性痛症候群の発生を減少させるなどの医学的理由に加え，経済的側面からも日帰り手術患者への麻酔法として広がりを見せている．神経刺激装置を使わない方法，神経刺激装置を用いる方法があるが，後者は手技に時間を必要とするが成功率では高い．超音波を用いてのカテーテル挿入法はまだ十分には確立していないが，数多くの評価が試みられている[8]．

Ilfeldらは二つの持続注入の報告を行っている．一つは肩関節形成術をロピバカイン持続注入による斜角筋間ブロックを行うことで，従来の入院手術から日帰り手術にできるかを検討した[9]．第一段階として1泊する患者8名を対象にしたところ，5名が回復室で帰宅基準を満たした．続く第二段階では，回復室で帰宅基準を満たす6名のうち，5名が直接帰宅した．すべての患者で術後痛は十分にコントロールされ，鎮痛薬の必要性や睡眠障害も最小限であった．術者の期待以上に，患者の気分も安定しており，満足度も高かった．次いで，米国での膝関節形成術後の平均在院日数は4〜5日であるが，持続大腿神経ブロックを第4PODまで在宅で行うことで，1泊入院で行えるかの検討を行った[10]．10名の患者のうち9名が術翌日に帰宅基準を満たして帰宅した．疼痛は十分にコントロールされており，鎮痛薬の必要も睡眠障害も最小限であり，患者の満足度も高かった．これらのパイロットスタディで，局所麻酔薬の持続注入は有用であることが示唆されたが，より詳細な検討と合併症に関しての検討が必要であるとしている．また，在宅での安全なカテーテル管理も重要な課題となっている[11]．

6) Liu SS, Strodtbeck WM, Richman JM et al : A comparison of regional versus general anesthesia for ambulatory anesthesia : A meta-analysis of randomized controlled trials. Anesth Analg 101 : 1634-1642, 2005

7) Hadzic A : Is regional anesthesia really better than general anesthesia? Anesth Analg 101 : 1631-1633, 2005

8) Boezaart AP : Perineural infusion of local anesthetics. Anesthesiology 104 : 872-880, 2006

9) Ilfeld BM, Wright TW, Enneking K et al : Total shoulder arthroplasty as an outpatient procedure using ambulatory perineural local anesthetic infusion : A pilot feasibility study. Anesth Analg 101 : 1319-1322, 2005

10) Ilfeld BM, Gearen PF, Enneking K et al : Total knee arthroplasty as an overnight-stay procedure using continuous femoral nerve blocks at home : A prospective feasibility study. Anesth Analg 102 : 87-90, 2006

11) Klein SM, Evans H, Nielsen KC et al : Peripheral nerve block techniques for ambulatory surgery. Anesth Analg 101 : 1663-1676, 2005