The use of a volatile anesthetic regimen protects against acute normovolemic hemodilution induced myocardial depression in patients with coronary artery disease

Sratwadee Lorsomradee, Suraphong Lorsomradee

Abstract:
Background: Previous studies indicated that acute normovolemic hemodilution (ANH) was associated with a depression of myocardial function in coronary surgery patients with baseline heart rate faster than 90 bpm. It was suggested that this phenomenon could be explained by the occurrence of myocardial ischemia. In the present study, we hypothesized that the cardioprotective properties of a volatile anesthetic regimen might protect against the ANH related myocardial functional impairment. Materials and Methods: Forty elective coronary surgery patients with baseline heart rate faster than 90 bpm were randomly allocated to receive different anesthetic regimens. Group A (n = 20) received midazolam-based anesthesia. Group B (n = 20) received a sevoflurane-based anesthesia. Five-lead electrocardiogram, pulse oximetry, capnography, radial arterial pressure, and Swan Ganz continuous thermodilution cardiac output via right internal jugular vein were monitored. Measurements were obtained before and after ANH. Data were compared using paired t test. All data were expressed as mean ± SD. Data were considered significant if \( P < 0.05 \).

Results: After ANH, systemic vascular resistance was slightly decreased in group A while there was a significant decrease in group B. In group A, cardiac output was slightly decreased from 5.07±1.17 l/min to 5.02±1.28 l/min after ANH, whereas in group B, cardiac output was significantly increased from 4.84±1.21 l/min to 6.02±1.28 l/min after ANH.

Conclusion: In coronary surgery patients, with baseline heart rate faster than 90 bpm, anesthesia with sevoflurane during ANH was associated with an improvement in myocardial function after ANH, which was not present in patients anesthetized with midazolam.

Key words: Acute normovolemic hemodilution, coronary artery disease, volatile anesthetic

Introduction
Recently, the premise that hemoglobin (Hb) levels should be kept above 9 to 10 g per dL has been challenged by clinical and experimental studies suggesting that acute normovolemic hemodilution (ANH) and restrictive transfusion strategies (Hb target of 7-8 g/dL) in critically ill and surgical patients can reduce blood transfusion requirements without compromising clinical outcome.[1,2] With this technique, the adequacy of tissue oxygenation and organ function is maintained by compensatory increases in cardiac output, improved blood flow distribution, and higher oxygen extraction ratios.[3-5] In the myocardium, hemodilution-induced lowering of blood viscosity is thought to facilitate blood flow through stenotic and collateral vessels, thereby counteracting the reduced blood oxygen-carrying capacity.[6] However, a previous study[7] indicated that acute normovolemic hemodilution (ANH) was associated with a depression of myocardial function in coronary surgery patients with baseline heart rate faster than 90 bpm. It was suggested that this phenomenon would be explained by the occurrence of myocardial ischemia. In the present study, we hypothesized that the cardioprotective properties of a volatile anesthetic regimen[8,9] might protect against the ANH related myocardial functional impairment. To test this hypothesis, we compared the effects of a midazolam-based intravenous anesthetic and a sevoflu-urane-based volatile anesthetic regimen on hemodynamic and cardiac function after ANH in coronary surgery patients.

Materials and Methods
The study was approved by the institutional ethical committee, and written informed consent was obtained. Forty patients, with baseline heart rate faster than 90 bpm, undergoing elective coronary surgery with cardiopulmonary bypass (CPB) were included. Inclusion criteria were as follows: a screening hemoglobin concentration > 12 g/dL in men or 11 g/dL in women; stable angina; left ventricular ejection fraction > 30%; and absence of significant coexistent diseases, namely, valvular disease, recent myocardial infarct (< 6 weeks), significant carotid stenosis (> 70%) or recent stroke.

Correspondence to: Dr. Suraphong Lorsomradee, Division of Cardiothoracic and Vascular Anesthesia, Department of Anesthesiology, Chiangmai University Hospital, Chiang Mai, Thailand. E-mail: slorsmr@mail.med.cmu.ac.th
Patients were randomly allocated to two different anesthetic regimens. Group A (n = 20) received midazolam-based anesthesia. Group B (n = 20) received sevoflurane-based anesthesia. The surgeon, an independent investigator, and the patient were blinded to the type of anesthesia by positioning of sheets covering the vapor, and by connecting a midazolam infusion pump to the intravenous line or a hidden syringe, respectively. After preoxygenation with 100% oxygen, anesthesia was induced by fentanyl (Fentanyl-Janssen, Janssen-Gilig, Beerse, Belgium) 0.01 mg/kg and relaxation with cisatracurium (Nimbex, GlaxoSmithKline, Parma, Italy) 0.2 mg/kg together with midazolam (Dormicum, Roche, Fontenay-sous-Bois, France) or sevoflurane (Sevorane, Abbott). In group A, anesthesia was performed with midazolam based total intravenous anesthesia (TIVA) by constant intravenous midazolam infusion at 1-5 µg/kg/min after a bolus dose of 0.15 mg/kg. In group B, anesthesia was performed with sevoflurane based volatile induction and maintenance anesthesia (VIMA) by mask induction follow by 0.5-2% end-tidal sevoflurane. In both groups, anesthetic depth was adjusted and maintained to keep bispectral index at 40-60.

After anesthesia induction, blood was withdrawn (60 to 80 mL/min) from a central vein by gravity into citrate-phosphate-dextrose collection bags that were placed on a rocking platform of a precision scale. In parallel, 6% hydroxyethyl starch (Voluven®; Kabi-Frezenius) was infused through a 16-gauge peripheral catheter on the opposite arm, to a ratio of 1.15:1 to the donated blood.

Global hemodynamic data (mean arterial pressure, pulmonary capillary wedge pressure, central venous pressure, cardiac index, stroke volume index, and systemic vascular resistance index) were registered before the start of ANH and 5 min after ANH. All data were collected by trained observers who did not participate in patient care.

Statistical analysis was performed using the SigmaStat 2.03 software package (SPSS, Leuven, Belgium). Patient characteristics and hemodynamic parameters were compared between groups using unpaired Student’s t test. Hemodynamic parameters were compared versus baseline using paired t test. Values are expressed as mean ± SD unless stated otherwise. Statistical significance was accepted at P < 0.05. All P values were two tailed.

**Results**

Preoperative patient characteristics are summarized in Table 1. There was no significant difference between the two groups in any of the variables. Following blood withdrawal and isovolemic compensation with colloids, hemoglobin decreased from 14.5 ± 0.9 to 9.1 ± 1.0 (P < 0.001) in group A, and from 14.6 ± 1.1 to 8.9 ± 1.0 (P < 0.001) in group B. It was compensated by a slight increase in heart rate. However, central venous pressure and mean arterial pressure were within baseline values [Table 2]. No patients exhibited signs of myocardial ischemia as judged by the analysis.
of automated ST-segment and left ventricular wall motion monitoring.

After ANH, systemic vascular resistance was slightly reduced from 1,089±187 to 1,042±198 mmHg/L/min in group A while there was a significant decrease from 1,162±144 to 884±137 mmHg/L/min in group B. In addition, the change in cardiac output was different between both groups. In group A, cardiac output was slightly decreased from 5.07±1.17 l/min to 5.02±1.28 l/min after ANH, whereas in group B, cardiac output was significantly increased from 4.84±1.21 l/min to 6.02±1.28 l/min after ANH.

Discussion

The results of the present study demonstrated that in coronary surgery patients, with baseline heart rate faster than 90 bpm, anesthesia with sevoflurane during ANH was associated with an improvement in myocardial function after ANH, which was not present in patients anesthetized with midazolam. Acute normovolemic hemodilution does not per se reflect ischemic status of the myocardium. Several factors are known to determine occurrence of myocardial and other organ damage and outcome after coronary surgery. Among these, patient characteristics and surgery-related events are the common reasons for possible complications. The degree of stenosis in coronary arteries and myocardial area are also important. In addition, ANH in severe left main stem coronary artery disease has also greater significance compared to triple or double vessel disease. However, all patient characteristics, anesthetic depth, surgical and cardioprotective strategies were similar in both groups. This implies that the only difference between the groups was the choice of associated anesthetic drug: midazolam or sevoflurane.

The effects of acute normovolemic hemodilution (ANH) on myocardial function in patients with coronary artery disease are still not fully elucidated. Experimental and clinical evidence has indicated that volatile anesthetics have cardioprotective effects that are related to a preconditioning and a post-conditioning effect.[10-18] The use of a volatile anesthetic regimen might also have beneficial effects on cardioprotection during acute normovolemic hemodilution. The safety of the hemodilution procedure was ascertained by maintaining circulatory normovolemia and by close monitoring of cardiovascular parameters with ECG and echocardiography. Presumably, general anesthesia and chronic ß-blockade decreased the metabolic needs (approximately 20 to 30%) and prevented the sympathetic-mediated inotropic and chronotropic response.[19] Occasional reports of myocardial ischemia have been attributed to extremely low hemoglobin levels, concomitant hypovolemia, reflex tachycardia in awake volunteers, and/or increased postoperative metabolic needs.[20-22]

Hibernating myocardium results in recovery of myocardial function dramatically and the increase in cardiac output can be attributed to that. This also puts the severity of disease into perspective, as the decrease in cardiac output in midazolam group was not statistically significant. However, a previous study[7] indicated coronary surgery patients anesthetized with midazolam, pacing at 90 bpm during ANH were associated with depression of myocardial function which was not present in patients paced at 70 bpm. Our hypothesis is that the cardioprotective properties of a volatile anesthetic regimen[8,9] might also protect against the ANH related myocardial functional impairment in patients with baseline heart rate faster than 90 bpm. In the present study, cardiac output was slightly decreased after ANH in patients anesthetized with midazolam, whereas cardiac output was significantly improved after ANH in patients anesthetized with sevoflurane. The results of this study indicated that beside the slow baseline heart rate which was associated with an improvement in myocardial function after ANH, the use of a volatile anesthetic regimen could preserve myocardial function in patients with faster baseline heart rate. The limitation in this study was whether the chosen parameters were the optimal parameters to describe the whole myocardial function. Further experimental and clinical study using other parameters such as ejection fraction using transesophageal echocardiography should be investigated. In addition, the present study was limited until ANH, however the process of CPB and after-effects should have been analyzed until completion of surgery to give insights. However, according to cardioprotective strategies of our institute, during and after CPB, all patients were anesthetized with sevoflurane. So, we could not assess cardiac output changes during and after CPB.

In conclusion, in coronary surgery patients with baseline heart rate faster than 90 bpm, anesthesia with sevoflurane during ANH was associated with an improvement in myocardial function after ANH, which was not present in patients anesthetized with midazolam.

Acknowledgment

We would like to express our gratitude to all those who gave us the opportunity to complete this study, especially the faculty of medicine, Chiangmai University Hospital, Thailand.

References

1. Carson JL, Hill S, Carless P, Hébert P, Henry D. Transfusion triggers: A systematic review of the literature. Transfus Med Rev 2002;16:187-99.
2. Shander A, Rijhwani TS. Acute normovolemic hemodilution. Transfusion 2004;44:26-34.
3. Kreimeier U, Messmer K. Hemodilution in clinical surgery: State of the art. World J Surg 1996;20:1208-17.
4. Mirhashemi S, Ertelai S, Messmer K, Intaglietta M. Model analysis of the enhancement of tissue oxygenation by hemodilution due to increased microvascular flow velocity. Microvasc Res 1987;34:290-301.
5. Hudetz AG, Wood JD, Biswal BB, Krolo P, Kampine JP. Effect of hemodilution on RBC velocity, supply rate and hematocrit in the cerebral capillary network. J Appl Physiol 1999;87:505-9.
6. Pries AR, Secomb TW. Rheology of the microcirculation. Clin Hemorheol Microcirc 2003;29:143-8.
7. Cromheecke S, Lorsomradee S, Van Damme V, Van der Linden Ph, De Hert S. Tolerance to acute normovolemic hemodilution with coronary artery surgery. J Cardiothorac Vasc Anesth 2006;20:684-90.
8. Lorsomradee S, Cromheecke S, De Hert SG. Effects of sevoflurane on biomechanical markers of hepatic and renal dysfunction after coronary artery surgery. J Cardiothorac Vasc Anesth 2006;20:684-90.
9. Cromheecke S, Pepermans V, Hendrickx E, Lorsomradee S, Ten Broecke PW, Stockman BA, et al. Cardioprotective properties of sevoflurane in patients undergoing aortic valve replacement with cardiopulmonary bypass. Anesth Analg 2006;103:289-96.
10. Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. Mechanism of myocardial protection by isoflurane: Role of adenosine triphosphate regulated-potassium (KATP) channels. Anesthesiology 1996;85:794-807.

11. Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC. Isoflurane mimics ischemic preconditioning via activation of KATP channels: Reduction of myocardial infarct size with an acute memory phase. Anesthesiology 1997;87:361-70.

12. Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anesthetics protect the ischemic rabbit myocardium from infarction. Anesthesiology 1997;86:699-709.

13. Toller WG, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. Anesthesiology 1999;91:1437-46.

14. Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. Anesthesiology 2002;97:4-14.

15. Hanouz JL, Yvon A, Massei M, Lepage O, Babatasi G, Khayat A, et al. Mechanisms of desflurane-induced preconditioning in isolated human right atria in vivo. Anesthesiology 2002;97:33-41.

16. Preckel B, Schlack W, Comfère T, Obal D, Barthel H, Thämer V. Effects of enflurane, isoflurane, sevoflurane and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart in vivo. Br J Anaesth 1998;81:905-12.

17. Schlack W, Preckel B, Stunneck D, Thämer V. Effects of halothane, enflurane, isoflurane, sevoflurane and desflurane on myocardial reperfusion injury in the isolated rat heart. Br J Anaesth 1998;81:913-9.

18. Obal D, Preckel B, Scharbatke H, Müllenheim J, Höterkes F, Thämer V, et al. One MAC of sevoflurane provides protection against reperfusion injury in the rat heart in vivo. Br J Anaesth 2001;87:905-11.

19. Spahn DR, Schmid ER, Seifert B, Pasch T. Hemodilution tolerance in patients with coronary artery disease who are receiving chronic β-adrenergic blocker therapy. Anesth Analg 1996;82:687-94.

20. Herregods L, Foubert L, Moerman A, François K, Rolly G. Comparative study of limited intentional normovolaemic haemodilution in patients with left main coronary artery stenosis. Anaesthesia 1995;50:950-3.

21. Rehm M, Orth VH, Kreimeier U, Thiel M, Mayer S, Brechtelsbauer H, et al. Changes in blood volume during acute normovolemic hemodilution with 5% albumin or 6% hydroxyethylstarch and intraoperative retransfusion. Anasthesist 2001;50:569-79.

22. Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983;58:277-80.

Source of Support: Nil, Conflict of Interest: None declared.