

The Effect of Deliberate Hypercapnia and Hypocapnia on Intraoperative Blood Loss and Quality of Surgical Field During Functional Endoscopic Sinus Surgery

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BACKGROUND: Anesthetic management during functional endoscopic sinus surgery is aimed at minimizing bleeding and establishing a near-perfect surgical field. We investigated whether deliberate intraoperative hypercapnia and hypocapnia may affect blood loss and quality of surgical field through a proposed modulating effect of different carbon dioxide (CO₂) tension levels on nasal vasculature.

METHODS: One hundred and eighty patients were randomly assigned to normocapnia (end-tidal CO₂ [ETCO₂] 37 ± 2 mm Hg), hypercapnia (ETCO₂ 60 ± 2 mm Hg), and hypocapnia (ETCO₂ 27 ± 2 mm Hg) groups. Anesthetic management was with propofol and remifentanyl infusions, nitrous oxide, and moderate controlled hypotension. Blood loss and operating conditions were assessed by the surgeon who was blinded to group assignment. Differences among the study groups, the effect of the study group and time on ETCO₂ levels and hemodynamic variables, and the association of blood loss with surgical covariates were analyzed.

RESULTS: There were no differences in blood loss and quality of surgical field among the study groups. Patients in the hypocapnia group demonstrated the highest, and in the hypercapnia group, the lowest, requirements for remifentanyl, labetalol, and administration of the antihypertensive medications in general. The computed tomography-graded severity of sinonasal disease and duration of surgery were the only independent predictors of intraoperative blood loss.

CONCLUSIONS: CO₂ management during functional endoscopic sinus surgery does not influence operating conditions or blood loss.

(Anesth Analg 2007;105:1404-9)

Since its introduction in the United States in 1985, functional endoscopic sinus surgery (FESS) has become the state-of-the-art technique for surgical management of chronic rhinosinusitis (1). There is general consensus that when FESS is performed under general anesthesia, maintaining moderate controlled hypotension (mean arterial blood pressure [MAP] 60–70 mm Hg) is important in improving surgical visibility (2–6), which results in faster surgery and reduced risk of such major complications as massive hemorrhage, skull base defects, orbital hemorrhage, and blindness (3,4,7–9). However, different modes of ventilation are electively used by anesthesiologists during FESS, which may potentially affect surgical bleeding and

operating conditions independently, through the carbon dioxide (CO₂)-mediated effect on nasal vasculature. Although most published studies appear to favor normocapnia by using intermittent positive pressure ventilation (3,4,6,9), others allow patients undergoing FESS to breathe spontaneously, either through the endotracheal tube or laryngeal mask airway (10,11). Yet, maintaining a patient's spontaneous ventilation is not routinely recommended during most otolaryngological procedures, for fear that rapidly ensuing hypercapnia will promote microvascular and mucosal bleeding due to the CO₂-induced peripheral vasodilation (12,13), a situation particularly undesirable during FESS. Consequently, some of our practicing colleagues (personal communications) strongly prefer maintenance of mild-to-moderate deliberate intraoperative hypocapnia, in an attempt to induce vasoconstriction and further improve visualization of the surgical field.

Physiological considerations of the effect of CO₂ on nasal vascular reactivity deserve attention, as the incidence of diffuse, intraoperative mucosal bleeding during FESS can reach 21% (14). Although the intensity of arterial bleeding during FESS will be mainly influenced by MAP and heart rate (HR) (2,5,9), mucosal capillary blood inflow may be affected by the direct CO₂-mediated effect on the smooth muscle tone of

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Accepted for publication July 10, 2007.

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DOI: 10.1213/01.ane.0000282781.56025.52

arterioles and precapillary sphincters (15–17). In addition, the arterial inflow into the ethmoid, sphenoid, and frontal sinuses, which is largely supplied by the branches of the internal carotid artery, may potentially be modulated through the effects of CO₂ on cerebral blood flow (6).

Nevertheless, whether different CO₂ tension levels have any clinically significant effect on microvascular bleeding during FESS, especially under the conditions of deliberate hypotension, is unknown. We, therefore, investigated the effect of different ventilatory strategies on intraoperative bleeding and quality of surgical field during FESS, to help further define standards of anesthesia care for this widely used surgical procedure.

METHODS

With the Stanford University Medical Center IRB approval and written patient informed consent, we prospectively studied 180 ASA physical status I and II patients with chronic rhinosinusitis presenting for bilateral FESS. A clinically meaningful 100 mL difference in intraoperative blood loss among the groups was selected as a target criterion. Prospective power analysis indicated that studying 60 patients in each group would detect that difference with 80% probability and Type I error of 5%.

Specific exclusion criteria included patients with a history of bleeding disorders or taking medications that may affect surgical hemostasis; a history of seizures; poorly controlled hypertension or cerebrovascular disease; a history of significant coronary artery disease or arrhythmias; a compromised renal or hepatic function; electrolyte and metabolic abnormalities; chronic obstructive pulmonary disease; severe asthma or other severe pulmonary disorders; a history of peptic ulcer disease; or pregnancy.

Patients were randomly assigned to one of the three study (treatment) groups, depending on the targeted intraoperative end-tidal CO₂ (ETCO₂) value: normocapnia (ETCO₂ 37 ± 2 mm Hg), hypercapnia (ETCO₂ 60 ± 2 mm Hg), and hypocapnia (ETCO₂ 27 ± 2 mm Hg). All patients had normal preoperative platelet count and coagulation studies. Anesthetic management of all patients was standardized and conducted by a single attending anesthesiologist (V.N.). The surgery was performed by a single attending surgeon (W.V.), with participation of the closely supervised sinus surgery fellows (E.H., A.C., and C.C.). All surgeons were blinded to patient study groups.

Preoperatively, patients received premedication with IV midazolam (1–2 mg), and topical vasoconstrictor (four puffs of oxymetazoline spray in each nostril) was administered to decongest nasal mucosa. General anesthesia was induced with IV fentanyl 2 µg/kg and propofol 2 mg/kg, and tracheal intubation was facilitated with IV vecuronium (0.1 mg/kg). Patients' lungs were mechanically ventilated in a volume-controlled

mode (tidal volume 10 mL/kg) with 70%–50% nitrous oxide in oxygen, to maintain SpO₂ at 95% or higher. Minute ventilation (tidal volume was held constant) and gas flows were adjusted to achieve the targeted ETCO₂ level, as measured by sidestream capnometry (Datex Capnomac Ultima, Datex, Helsinki, Finland). Anesthesia was maintained with manually adjusted continuous IV infusions of propofol (50–140 µg · kg⁻¹ · min⁻¹) and remifentanyl (0.1–0.25 µg · kg⁻¹ · min⁻¹), titrated to maintain MAP within 60–70 mm Hg range, as measured on the patient's arm every 5 min by oscillometric technique (Dinamap[™] 1846 SX Vital Signs Monitor, Criticon, Tampa, FL). Acute increases in MAP were treated with additional boluses of IV remifentanyl (0.5–1 µg/kg) and escalating doses of IV labetalol (up to 2 mg/kg total dose), followed by incremental doses of IV hydralazine (up to 20 mg total dose) and IV nitroglycerin infusion (0.25–1.0 µg · kg⁻¹ · min⁻¹), if needed. Propofol and remifentanyl infusions were discontinued 10–15 min before the end of the surgery, to promote early patient awakening.

Local control of bleeding in the surgical field was facilitated by incremental submucosal injections of epinephrine (1:100,000) by the surgeon. Crystalloid solution was administered to replace overnight fluid deficits, provide maintenance fluid requirements, and replace blood loss on a 3:1 basis. Normothermia was maintained in all patients by forced air warming.

Final intraoperative blood loss was confirmed by the surgeon (W.V.) at the end of each procedure by accounting for loss of blood and irrigation fluid into the 25 mL-graded suction canister, the patient's stomach (measured volume of gastric contents, aspirated at regular time intervals during surgery) and nasopharyngeal packing (measured weight of packing on the electronic scale). The overall quality of the surgical field was assessed at the end of each procedure by the operating surgeon (W.V.) on a scoring scale adapted from Boezaart et al. (3) (Table 1).

Potential individual surgical predictors (covariates) of intraoperative bleeding were recorded in all patients. These included the presence of sinonasal polypoid disease and endoscopically documented active infection, computed tomography (CT)-graded severity of sinus disease based on the Lund-MacKay scoring system (18),¹ the extent of the performed surgical procedure (surgical volume scale, adopted by the surgeons),² duration of surgery, history of previous

¹CT-graded severity of disease is scored on 0–2 scale in each of the following: maxillary sinus, anterior ethmoid sinus, posterior ethmoid sinus, frontal sinus, sphenoid sinus and osteomeatal complex, yielding the maximum score of 12 per side.

²Surgical volume was scored on 0–1 scale for surgery on the maxillary and sphenoid sinuses, 0–2 scale for ethmoid, frontal sinuses and dissection of bulky polypoid disease from the nasal cavity, yielding the maximum score of eight per side. Increased score was given to the surgical dissection of the ethmoid, frontal sinuses, and nasal polypoid disease because of the frequently encountered higher blood loss in these regions.

Table 1. Quality of Intraoperative Surgical Field During Functional Endoscopic Sinus Surgery

0–1	No bleeding; excellent to outstanding surgical conditions
2–3	Slight bleeding; surgery fairly easy. No stops for hemostasis and/or suctioning are required
4–5	Slight bleeding; surgery mildly difficult. One stop for hemostasis and/or suctioning is required
6–7	Moderate bleeding; surgery moderately difficult. Occasional stops for hemostasis and/or suctioning are required
8–9	Moderate to severe bleeding; surgery very difficult. Multiple stops for hemostasis and/or suctioning are required
10	Surgery terminated due to severe bleeding in the surgical field

FESS and history of taking oral steroids within 2 wk before surgery.

Between-group differences were assessed for significance by the Kruskal–Wallis rank sum test, followed by Dunn’s test or the Pearson’s χ^2 test. The association of intraoperative blood loss with surgical covariates was determined by univariate analysis using the Wilcoxon’s ranked sum test. Stepwise multivariate regression analysis was used to identify the factors that were independent predictors of blood loss. Akaike’s information criterion and the F-test were used to assess significant model improvement. The data are reported as median (25–75th percentile or interquartile range) or incidence of observations. The effect of the factors treatment group and time on the ET CO_2 levels and hemodynamic variables was determined by two-way analysis of variance for repeated measurements, followed by Bonferroni-corrected *t*-tests. A *P* value <0.05 was considered statistically significant. All analyses were performed using S-PLUS version 6.2 (Insightful Corp., Seattle, WA).

RESULTS

A total of 180 patients were recruited, and all patients completed the study. The targeted ET CO_2 values were achieved in all three patient groups (Fig. 1).

All groups were comparable with respect to demographic characteristics and all surgical covariates (Table 2). No differences in blood loss and quality of surgical field were observed among the groups (Table 2), although there was a statistically significant effect of the treatment group and time on MAP and HR (Figs. 2 and 3). Mean MAP and HR differences, however, were small and transient, not exceeding 10 U of measurements over the course of 40 min.

In the univariate analysis, the presence of sinonasal polypoid disease, higher CT grading score, higher surgical volume score, and longer duration of surgery were associated with increased surgical blood loss. Multivariate regression analysis revealed that the CT-graded severity of disease (not the mere presence of nasal polypoid) and duration of surgery were the

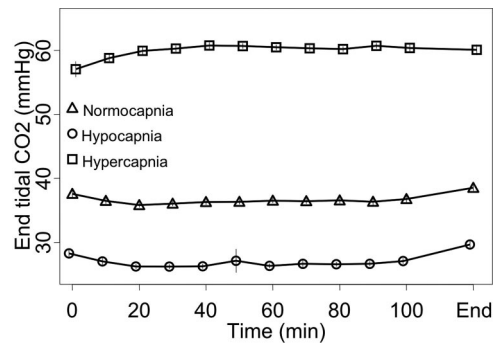


Figure 1. End-tidal carbon dioxide tension levels achieved in each of the treatment groups over the course of surgery. The symbols are the mean values, the vertical lines are the Bonferroni corrected 95% confidence intervals. Nonoverlapping confidence intervals suggest a statistically significant difference. For clarity purposes, data are presented at 10-min intervals, up to 100 min. The “0” and “End” values refer to the start and end of surgery, respectively.

only independent predictors of intraoperative blood loss.

While the total dose of IV propofol was not different among the study groups, patients in the hypocapnia group demonstrated the highest, and in the hypercapnia group, the lowest, requirements for IV remifentanyl, labetalol, and administration of antihypertensive medications in general (Tables 2 and 3). Two patients (one in the hypocapnia and one in the normocapnia group) required short-term, small-dose IV nitroglycerin infusion to maintain MAP within the desired range (data not shown). There were no intraoperative and immediate postoperative anesthesia-related or surgical complications in any group.

DISCUSSION

Our study demonstrates that both mild intraoperative hypercapnia and hypocapnia, relative to normocapnia do not affect blood loss and quality of surgical field during FESS, suggesting limited clinical impact of CO_2 on nasal vascular reactivity under the current study conditions.

It seems unlikely that a small, transient difference in MAP between the hypocapnia and hypercapnia groups (Fig. 2) may have confounded the results of the study by negating a respective modulating effect of CO_2 on nasal vasculature. Previous FESS studies (3,4,9) found no correlation between MAP and intraoperative blood loss, likely reflecting the predominantly capillary bleeding during FESS (4,9) and the complexity of the nasal vascular structure. Blood supply in rich capillary networks of nasal mucosa is balanced between the inflow through the arterioles, outflow via large cavernous sinusoids into the thick-walled collecting venules, and shunting through numerous arteriovenous anastomoses, all of which receive dense autonomic innervation (19,20). Therefore, whereas intraoperative MAP may largely affect

Table 2. Patient Demographic Characteristics, Total Intraoperative Blood Loss, Quality of Surgical Field and Surgical Predictors of Blood Loss During Functional Endoscopic Sinus Surgery^a

	Hypocapnia N = 60	Normocapnia N = 60	Hypercapnia N = 60	P
Age (yr)	47 (42–55)	53 (42–59)	47 (38–56)	0.3
Height (cm)	170 (163–178)	173 (165–188)	173 (165–182)	0.3
Weight (kg)	79 (67–91)	77 (69–89)	86 (73–97)	0.1
Gender (M/F)	28/32	30/30	33/27	0.7
Surgical blood loss (mL)	125 (74–250)	100 (50–200)	150 (94–267)	0.3
Surgical field (0–10)	2 (1–3)	2 (1–3)	2 (2–3)	0.4
Duration of surgery (min)	117 (85–146)	105 (75–145)	105 (80–135)	0.7
CT score (0–24)	14 (10–18)	12 (8–20)	14 (10–17)	0.5
Surgical volume (0–16)	12 (12–16)	12 (8–16)	12 (10–16)	0.1
Polypoid disease (Y/N)	45/15	44/16	47/13	0.8
Active infection (Y/N)	24/36	24/36	20/40	0.7
Revision surgery (Y/N)	38/22	37/23	39/21	0.9
Preoperative steroids (Y/N)	26/34	14/46	19/41	0.06

^a The data are reported as median (25–75th percentile or interquartile range) or incidence of observations.

CT = computed tomography.

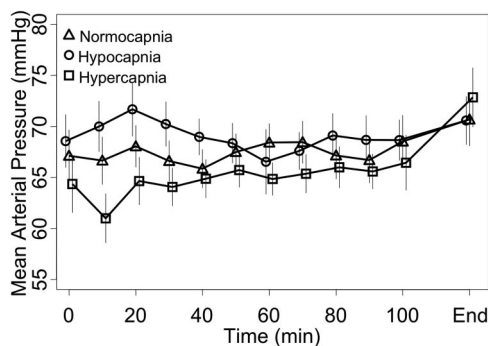


Figure 2. Mean arterial blood pressure values in each of the treatment groups over the course of surgery. The symbols are the mean values, the vertical lines are the Bonferroni corrected 95% confidence intervals. Nonoverlapping confidence intervals suggest a statistically significant difference. For clarity purposes, data are presented at 10-min intervals, up to 100 min. The “0” and “End” values refer to the start and end of surgery, respectively.

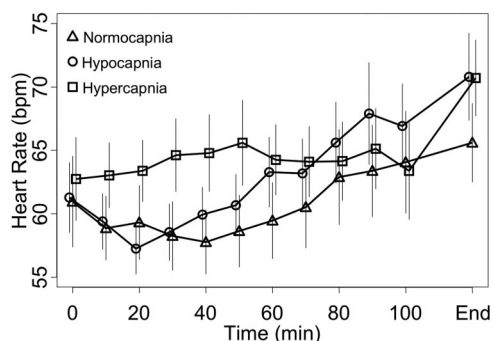


Figure 3. Heart rate in each of the treatment groups over the course of surgery. The symbols are the mean values, the vertical lines are the Bonferroni corrected 95% confidence intervals. Nonoverlapping confidence intervals suggest a statistically significant difference. For clarity purposes, data are presented at 10-min intervals, up to 100 min. The “0” and “End” values refer to the start and end of surgery, respectively.

the arterial inflow, other factors, such as the preexisting condition of the vascular network (4,9), local metabolic, humoral, neural, and myogenic mechanisms regulating functional capillary density, and

local venous pressure (6,19,20), play a significant role in regulating overall nasal capillary perfusion.

Multivariate analysis of our data refutes a popular belief among surgeons (7,8,21) that those FESS patients who present with active preoperative infection, for a revision surgery, or those not receiving preoperative oral steroid therapy, may be at higher risk for intraoperative hemorrhage. In our study, blood loss during FESS was best predicted by the severity of preexisting sinus disease and duration of surgery, corroborating a conventional assumption about positive association between the degree of the polypoid disease and length of surgery and intraoperative bleeding (7,8,14,21,22). This suggests that such surgical factors as adherence to meticulous surgical technique and the obligatory and judicious use of injectable vasoconstrictors to decongest nasal mucosa (8,23) may be more important in reducing intraoperative bleeding than any single anesthesia-related intervention.

Proper anesthetic management, however, can indirectly decrease blood loss during FESS by improving the operating conditions, which should translate into a more rapid surgery (4,22). Under the conditions of moderate controlled hypotension, the quality of the surgical field during FESS is most favorably affected by achieving a reduction in HR (2–5) and intraoperative use of propofol-based total IV anesthesia (optionally supplemented by nitrous oxide), to promote superior hemodynamic stability and minimize direct peripheral vasodilation (2,5,6,9,23). All these strategies were successfully used in our study, further emphasizing an apparent lack of effect of different CO₂ tensions on nasal vascular reactivity, as reflected in similar surgical field scores and duration of surgery in the study groups (Table 2). Although there was a transient increase in HR in the hypercapnia group (Fig. 3), overall surgical visibility was not adversely affected, most likely because HR was still appropriately reduced.

Table 3. Perioperative Anesthetic and Antihypertensive Drug Requirements During Functional Endoscopic Sinus Surgery^a

	Hypocapnia N = 60	Normocapnia N = 60	Hypercapnia N = 60	P
Propofol (mg)	1160 (675–1651)	900 (680–1310)	1000 (885–1245)	0.17
Remifentanyl (μg)	1965 (1190–2852)	1695 (937–2275)	1500 (955–2000)	0.05
Labetalol (Y/N)	49/11	42/18	35/25	0.02
Labetalol (mg)	90 (40–135)	40 (20–87.5)	20 (15–45)	0.0001
Hydralazine (Y/N)	25/35	9/51	1/59	0.0001
Hydralazine (mg)	20 (15–20)	10 (5–15)	20	0.13

^a The data are reported as median (25–75th percentile or interquartile range) or incidence of observations. There was a statistically significant difference in the administered doses of remifentanyl and labetalol between the hypocapnia and hypercapnia groups. There was also a statistically significant difference in the administered dose of labetalol between the hypocapnia and normocapnia groups.

Significantly smaller doses of IV remifentanyl and labetalol were required in the hypercapnia group to maintain intraoperative MAP within the desired range (Table 3). This likely reflects the direct cardiovascular effects of hypercapnia (24), effective suppression of the hypercapnia-mediated sympathetic responses by propofol (18), and augmented negative inotropic and direct vasodilating effects of labetalol and remifentanyl (24–27). The most frequent administration of the antihypertensive drugs and the largest doses of IV remifentanyl and labetalol for maintenance of deliberate hypotension were required in the hypocapnia group (Table 3), likely because of the hypocapnia-induced systemic arterial vasoconstriction (28). The question of whether these pharmacological interventions could have overcome local vasoconstriction in nasal mucosa, confounding the results of the study, is debatable, considering the sparse vascularity and largely denervated blood vessels in nasal polypoid tissue (20,29) and the weak α_1 adrenergic blocking potency of labetalol.

Our study has several limitations. More accurate techniques for measuring intraoperative blood loss (6) could have been used. However, the careful calculation of intraoperative blood loss in all patients makes it reasonable to assume that there would be a similar finding of absent clinically relevant difference in blood loss, even with more precise measurements. The presence of continuous, invasive arterial blood pressure monitoring would have provided more accurate hemodynamic data and enabled determination of the arterial CO_2 (Paco_2) tension levels. Yet, the precision of the Dinamap devices is best at low to normal systolic blood pressures (30,31), similar to the conditions in our study. Despite an absence of intraoperative arterial blood gas analysis, the recorded ETCO_2 values likely closely reflect true Paco_2 tension levels in the study groups. Studies have demonstrated largely unchanged and stable Paco_2 - ETCO_2 gradients during mild deliberate hypocapnia (32) and hypercapnia (33), and very small effects of pharmacologically induced moderate controlled hypotension on physiological dead-space over a wide range ($30\text{--}50 \pm 5$ mm Hg) of Paco_2 values (31).

As in other studies (2), we elected to record an overall assessment of the quality of the surgical field,

as opposed to its evaluation at predefined time intervals (5) or during the operation on a specific sinus (6). The similar severity of sinonasal disease, surgical volume and duration of surgery in all study groups (Table 2) suggest that the operating conditions were likely comparable throughout the procedure. Finally, the results of our study do not necessarily apply to situations when the vapor-based or balanced FESS anesthesia techniques are selected to produce and maintain moderate controlled hypotension, especially in conjunction with the use of direct-acting peripheral vasodilators (e.g., sodium nitroprusside). A lower quality of surgical field (2,3,5,6) and a clear trend towards increased blood loss (2,23) are observed under these circumstances, even in normocapnic patients.

In conclusion, we have demonstrated an absence of an independent effect of mild deliberate hypocapnia and hypercapnia on blood loss and quality of the surgical field during FESS, performed under propofol, remifentanyl and nitrous oxide anesthesia, and moderate controlled hypotension. The most appropriate Paco_2 for any patient can, therefore, be decided based on other considerations.

REFERENCES

- Kennedy DW, Senior BA. Endoscopic sinus surgery. A review. *Otolaryngol Clin North Am* 1997;30:313–30
- Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. *Laryngoscope* 2003;113:1369–73
- Boezaart AP, Van der Merwe J, Coetzee A. Comparison of sodium nitroprusside- and esmolol-induced hypotension for functional endoscopic sinus surgery. *Can J Anaesth* 1995;42:373–6
- Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of beta-blocker premedication on the surgical field during endoscopic sinus surgery. *Laryngoscope* 2004;114:1042–6
- Wormald PJ, van Renen G, Perks J, Jones JA, Langton-Hewer CD. The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery. *Am J Rhinol* 2005;19:514–20
- Pavlin JD, Colley PS, Weymuller EA Jr, Van Norman G, Gunn HC, Koerschgen ME. Propofol versus isoflurane for endoscopic sinus surgery. *Am J Otolaryngol* 1999;20:96–101
- Stankiewicz JA. Complications of endoscopic sinus surgery. *Otolaryngol Clin North Am* 1989;22:749–58
- Bolger WE, Kennedy DW. Surgical complications and postoperative care. In: Kennedy DW, Bolger WE, Zinreich SJ, eds. *Diseases of the sinuses: diagnosis and management*. Hamilton, Ont., Lewiston, NY: B.C. Decker, 2001:303–16
- Jacobi KE, Bohm BE, Rickauer AJ, Jacobi C, Hemmerling TM. Moderate controlled hypotension with sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. *J Clin Anesth* 2000;12:202–7

10. Webster AC, Morley-Forster PK, Janzen V, Watson J, Dain SL, Taves D, Dantzer D. Anesthesia for intranasal surgery: a comparison between tracheal intubation and the flexible reinforced laryngeal mask airway. *Anesth Analg* 1999;88:421-5
11. Kaplan A, Crosby GJ, Bhattacharyya N. Airway protection and the laryngeal mask airway in sinus and nasal surgery. *Laryngoscope* 2004;114:652-5
12. Morison JD, Mirakhur RK, Craig HJL. Anaesthesia for eye, ear, nose and throat surgery. 2nd ed. Edinburgh: Churchill Livingstone, 1985
13. Koopman CF. Anesthetic considerations in facial plastic surgery: the surgeon's viewpoint. In: Brown BR Jr, Coulthard SW, eds. *Anesthesia and ENT surgery*. Philadelphia: FA Davis Co., 1987:117-25
14. Jakobsen J, Svendstrup F. Functional endoscopic sinus surgery in chronic sinusitis—a series of 237 consecutively operated patients. *Acta Otolaryngol Suppl* 2000;543:158-61
15. Harkin CP, Schmeling WT, Kampine JP, Farber NE. The effects of hyper and hypocarbia on intraparenchymal arterioles in rat brain slices. *Neuroreport* 1997;8:1841-4
16. Tominaga M, Stekiel TA, Bosnjak ZJ, Kampine JP. Contribution of carotid chemoreceptors to mesenteric venoconstriction during acute hypercapnia in rabbits. *Am J Physiol* 1999;277:H2305-10
17. Enoki T, Tsuchiya N, Shinomura T, Nomura R, Fukuda K. Effect of hypercapnia on arterial hypotension after induction of anaesthesia. *Acta Anaesthesiol Scand* 2005;49:687-91
18. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;31:183-4
19. Lung MA, Wang JC. Effects of hypercapnia and hypoxia on nasal vasculature and airflow resistance in the anaesthetized dog. *J Physiol* 1986;373:261-75
20. Howarth PH. Leukotrienes in rhinitis. *Am J Respir Crit Care Med* 2000;161:S133-6
21. Ramadan HH, Allen GC. Complications of endoscopic sinus surgery in a residency training program. *Laryngoscope* 1995;105:376-9
22. Kinsella JB, Calhoun KH, Bradfield JJ, Hokanson JA, Bailey BJ. Complications of endoscopic sinus surgery in a residency training program. *Laryngoscope* 1995;105:1029-32
23. Blackwell KE, Ross DA, Kapur P, Calcaterra TC. Propofol for maintenance of general anesthesia: a technique to limit blood loss during endoscopic sinus surgery. *Am J Otolaryngol* 1993;14:262-6
24. Stekiel TA, Stekiel WJ, Tominaga M, Stadnicka A, Bosnjak ZJ, Kampine JP. Effect of halothane and isoflurane on in situ diameter responses of small mesenteric veins to acute graded hypercapnia. *Anesth Analg* 1996;82:349-57
25. Sticher J, Muller M, Scholz S, Schindler E, Hempelmann G. Controlled hypercapnia during one-lung ventilation in patients undergoing pulmonary resection. *Acta Anaesthesiol Scand* 2001;45:842-7
26. Ouattara A, Boccara G, Kockler U, Lecomte P, Leprince P, Leger P, Riou B, Rama A, Coriat P. Remifentanyl induces systemic arterial vasodilation in humans with a total artificial heart. *Anesthesiology* 2004;100:602-7
27. Noseir RK, Ficke DJ, Kundu A, Arain SR, Ebert TJ. Sympathetic and vascular consequences from remifentanyl in humans. *Anesth Analg* 2003;96:1645-50
28. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med* 2002;347:43-53
29. Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax* 2000;55:S79-83
30. Precious DS, Splinter W, Bosco D. Induced hypotensive anesthesia for adolescent orthognathic surgery patients. *J Oral Maxillofac Surg* 1996;54:680-3
31. Grosenbaugh DA, Muir WW. Accuracy of noninvasive oxyhemoglobin saturation, end-tidal carbon dioxide concentration, and blood pressure monitoring during experimentally induced hypoxemia, hypotension, or hypertension in anesthetized dogs. *Am J Vet Res* 1998;59:205-12
32. Sharma SK, McGuire GP, Cruise CJ. Stability of the arterial to end-tidal carbon dioxide difference during anaesthesia for prolonged neurosurgical procedures. *Can J Anaesth* 1995;42:498-503
33. Akca O, Liem E, Suleman MI, Doufas AG, Galandiuk S, Sessler DI. Effect of intra-operative end-tidal carbon dioxide partial pressure on tissue oxygenation. *Anaesthesia* 2003;58:536-42