原 著

Diuretic Effect of Oral Clonidine Premedication during Hypotensive Anesthesia

Ryohei Kudo, MD*, Takashi Horiguchi, MD, PhD*,
Toshiaki Nishikawa, MD, PhD*

Abstract

Clonidine, an α_2-agonist, increases urine output and electrolyte excretion, and reduces the dose requirement of vasodilator for induced hypotension. We examined whether oral clonidine would provide these effects during hypotensive anesthesia.

Twenty patients randomly received oral clonidine either 5 μg/kg (clonidine group, n=10), or none (control group, n=10). General anesthesia was maintained with isoflurane and 67% N_2O. During hypotensive period, mean arterial pressure (MAP) was kept at 50–60 mmHg. Urine output, urine osmolality, urinary excretion of electrolytes, and plasma ADH level were examined.

Urine output and absolute urinary excretion of potassium were greater during the first 30 minutes of hypotensive period in the clonidine group than the control group. Five patients in the control group and one in the clonidine group had no urine output during the hypotensive period ($p<0.05$). Absolute urinary excretion of sodium and potassium increased in the control group after MAP recovered. However, plasma ADH levels did not change over time in both groups, and were similar between groups. No difference was found between the two groups in the dose requirement of nicardipine during hypotensive period.

Oral preanesthetic medication of clonidine 5 μg/kg provided a diuretic effect during hypotensive anesthesia.

*Department of Anesthesia and Intensive Care Medicine, Akita University Graduate School of Medicine, Akita, Japan

Key words; diuresis, hypotensive anesthesia, oral clonidine premedication

Introduction

Previous clinical reports show that systemic as well as regional administration of clonidine, a preferential α_2-adrenergic agonist, modifies perioperative care by reducing requirements of anesthetics[1~3] or β-adrenoceptor antagonist for induced hypotension[3], and providing hemodynamic stability[4~6] and analgesia[7]. In addition, clonidine alters the responses to sympathomimetic or parasympatholytic agents[8,9], attenuates the sympathoadrenal responses[10], and provides diuresis[11].

It is well known that induced-hypotension causes a rapid rise in the activity of the renin-angiotensin system, resulting in a fivefold increase in plasma renin activity[12,13], since the section of renin by the juxtaglomerular apparatus is stimulated by a decrease in blood pressure. Renin cleaves angiotensinogen to angiotensin I, which is then cleaved to angiotensin II by the action of angiotensin-converting enzyme in the pulmonary circulation. Angiotensin II, in turn, causes vasoconstriction with greater influence on the arterial system of the kidney, an increase in aldosterone secretion, and the retention of water and sodium in the body. These net effects are likely to decrease urine output and urinary excretion of electrolytes during induced-hypotension.

Therefore, the aim of the present study is to assess whether preanesthetic clonidine medication would

induce clinically significant diuresis in patients undergoing surgical interventions under deliberate hypotensive anesthesia, and further, to evaluate the effect of clonidine on vasodilator requirement during induced-hypotension and on ADH secretion.

Methods

Twenty adult patients, who were in ASA physical status 1 or 2, gave their informed consent to participate in research approved by Human Investigation Committee. The subjects scheduled for elective surgery in the morning for otorhinolaryngological procedures or thyroidetomy were included. The subjects had neither medical history nor been taking any drugs. Those who had diabetes insipidus, diabetes mellitus, serum electrolyte abnormalities, anemia, renal dysfunction, hypertension, sinus bradycardia (heart rate $<$ 60 beats/min), and obesity exceeding standard body weight by 20% or more, were excluded from this study.

Each patient was randomly assigned (sealed envelopes) to one of two groups. Subjects fasted for 8 hours before the operation, and no intravenous fluid was administered until subjects arrived at operating room. The patients received either oral clonidine approximately 5 μg/kg (clonidine group; n = 10) or none (control group; n = 10), in addition to famotidine 20 mg p.o., 90 minutes prior to arrival at operating room. Because clonidine (Catapres®, Boehringer Ingelheim & Tanabe) is available only in tablet forms of 75 μg or 150 μg dose in Japan, administration doses of clonidine were determined by choosing the closest doses calculated by multiplying 37.5 μg (half a tablet) as a unit. Prescription of preanesthetic drugs and observation during anesthesia were performed by the same anesthesiologist who was in charge of each anesthetic case. After an electrocardiogram monitor, a blood pressure cuff and a pulse oximeter were established, a 20 G intravenous cannula was placed into the forearm cutaneous vein. Lactated Ringer's solution was thereafter infused through the IV cannula at a rate of 10 mL/kg/h until the end of study. General anesthesia was induced with thiamylal, 4–5 mg/kg IV, and tracheal intubation was facilitated with vecuronium approximately 0.2 mg/kg IV. Anesthesia was maintained by inhalation of isoflurane 0.5–1.5% expired, and 67% nitrous oxide in oxygen with 6 L/min of the background gas flow. The lungs were mechanically ventilated to control arterial blood carbon dioxide tension ($PaCO_2$) between 33 and 37 mm Hg. Each patient's blood pressure was kept within $\pm$20% of the preoperative value by regulating the concentration of isoflurane throughout the study period except during hypotensive period. When blood pressure decreased below 80% of the preoperative value, or heart rate decreased below 40 beats/min, intravenous ephedrine 0.1 mg/kg or atropine 0.01 mg/kg was administered, respectively, during normotenive periods. During surgery, end-tidal isoflurane concentration was increased to 1.5% and nicardipine was infused to keep mean arterial pressure (MAP) of 50–60 mmHg for 60 minutes. Thereafter, nicardipine infusion was discontinued along with reducing isoflurane concentration, so that MAP recovered for the next 60 minutes.

An arterial cannula and a urinary catheter were placed in the radial artery and in the bladder, respectively, immediately after induction of general anesthesia. Urine was collected thereafter during anesthesia and surgery to gauge urine output immediately after the induction of anesthesia, and then every 30 minutes. Urine samples were obtained at the time for urine output measurement to examine urine electrolyte concentrations and osmolality, along with arterial blood gas tensions, pH and base excess (BE) analyses. All patients in each group were examined for plasma concentrations of ADH at every 30 minutes during hypotension and following normotension. The proposed surgery was started approximately 20 minutes after induction of anesthesia. This study was continued until three hours after induction of anesthesia and no further collection of data were performed, because all surgical procedures were accomplished within 3 hours after induction of anesthesia.

Blood samples were collected into heparinized tubes for analysis of ADH. Plasma was quickly sepa-

rated by centrifugation and stored frozen at −40℃ until assayed in a week. Urine electrolyte concentrations and osmolality, and blood gas tensions were determined with a multichannel electrolyte analyzer (NOVA 6; Nova, MA, U.S.A.), a freezing-point depression analyzer (Osmometer OM801; Vogel, Germany), and a pH/blood gas analyzer (GEM® PREMIER 400, Instrumentation Laboratory, United Kingdom), respectively. Expiratory isoflurane concentrations were determined by an anesthetic gas analyzer (Capnomac Ultima™, Datex, Helsinki, Finland). Concentrations of plasma ADH were analyzed using RIA kits (Mitsubishi Petrochemical, Tokyo, Japan) and a gamma-scintillation counter (ARC950, Aroka, Tokyo, Japan).

Results were reported as means±standard error of the mean (SEM). Urine output index (mL/kg/h) was calculated as hourly urine output (mL/h) divided by body weight (kg). Intergroup differences in demographic, drugs and fluid data were compared by an unpaired Student's *t*-test. Testing for significance in the incidence of between the two groups was accomplished by a chi-square analysis. Statistical analysis was performed by two-way analysis of variance to compare changes in hemodynamic variables and arterial blood gas values between groups. When a significant difference was identified, this was followed by an unpaired Student's *t*-test with Bonferroni correction. Changes in hemodynamic variables, urinary data, and plasma ADH levels over time within each group were analyzed by repeated-measures analysis of variance, followed by paired Student's *t*-test. A P value < 0.05 was considered significant for all of the statistic tests.

Results

There were no significant differences between the two groups in patient demographic characteristics, drugs for anesthesia and hypotension, and the amount of fluid given during the study (**Table 1**). Clonidine dose administered for the clonidine group was 4.92±0.07 μg/kg, while the total doses of nicardipine given for induced hypotension were similar between groups (**Table 1**). The volume, sodium and potassium concentrations, and osmolality of urine gauged and discarded at the beginning of anesthesia did not differ significantly between the two groups (data not shown). Blood losses during surgery were within 100 mL. No additional intravenous fluid rather than lactated Ringer's solution of 10 mL/kg/h were administered.

Two patients in the clonidine group and two patients in the control group received ephedrine, while two patients in the clonidine group and one patient in the control group received atropine, for the treatments of hypotension and bradycardia, respectively.

Table 1 Patient demographic characteristics, doses or end-expiratory concentration of anesthetic agents used during induction and maintenance of general anesthesia, dose of nicardipine given for hypotension, and amount of fluid administered during the study

Group	Clonidine (n=10)	Control (n=10)
Age (year)	38±5	39±3
Weight (kg)	56±4	56±3
Height (cm)	162±3	159±3
Gender (M/F)	3/7	4/6
Clonidine dose (μg/kg)	4.92±0.07	−
Thiamylal dose (mg/kg)	4.8±0.03	4.8±0.07
Vecuronium dose (mg/kg)	0.20±0.01	0.19±0.01
End-expiratory concentration of isoflurane (%)		
Before hypotensive period	0.77±0.03	0.73±0.02
During normotensive period	0.74±0.03	0.70±0.04
Nicardipine dose (mg/kg)	0.12±0.08	0.26±0.15
Lactated Ringer's solution (mL/kg/h)	10.8±1.4	10.2±1.3

Values are mean±SEM. There were no significant differences between the two groups.

Table 2 Hemodynamic variables and values of arterial blood gas analysis before, during 1 hour-hypotension and subsequent 1 hour-normotension in the clonidine (n=10) and control (n=10) groups

Variables	Group	Before	Hypotensive period		Normotensive period	
			30 min	60 min	90 min	120 min
MAP (mmHg)	Clonidine	75±3	54±3*	55±3*	70±4+	73±4+
	Control	77±4	55±3*	56±4*	72±4+	75±5+
HR (beats/min)	Clonidine	64±2	75±3*	75±3*	69±3+	70±3+
	Control	66±5	74±4*	73±5*	69±4+	71±5+
pHa	Clonidine	7.45±0.01	7.44±0.01*	7.44±0.01*	7.43±0.01	7.43±0.01
	Control	7.46±0.01	7.44±0.01*	7.44±0.01*	7.44±0.01	7.43±0.01
$PaCO_2$ (mmHg)	Clonidine	35±1	35±2	34±2	36±3	35±2
	Control	34±1	35±2	35±2	34±2	36±3
PaO_2 (mmHg)	Clonidine	160±12	155±11	158±13	157±13	155±12
	Control	159±9	156±10	155±11	153±10	152±9
BE (mEq/L)	Clonidine	1.5±0.6	0.9±0.5*	0.8±0.5*	0.7±0.6	0.5±0.7
	Control	1.8±0.5	0.8±0.6*	0.8±0.6*	0.6±0.7	0.5±0.8

Values are mean±SEM. MBP=mean arterial pressure. HR=heart rate. pHa=arterial pH. $PaCO_2$=arterial carbon dioxide tension. PaO_2=arterial oxygen tension. BE=arterial base excess. *$p<0.05$ versus values before hypotensive period. +$p<0.05$ versus values at 30 and 60 min of hypotensive period. However, there were no significant differences between the two groups during any study periods.

All of the patients responded well to these treatments. The incidence of either ephedrine or atropine administration was not significantly different between the two groups.

There were no differences between the two groups in hemodynamic variables and arterial blood gas analyses before hypotensive period (**Table 2**). Mean arterial pressure decreased during hypotensive period and returned to pre-hypotensive values during normotensive period in both groups. Heart rate increased during hypotensive period and returned to pre-hypotensive values during normotensive period in both groups. However, no significant differences were noted in these variables between groups. Arterial pH and base excess decreased to the same extent in both groups during hypotensive period (**Table 2**).

The patients receiving clonidine 5 μg/kg had larger amounts of urine output and urinary potassium excretion during the first 30-minute hypotensive epoch than did the patients in the control group ($p<0.05$, **Table 3**). Five patients in the control group and one in the clonidine group had no urine output during the hypotensive period ($p<0.05$). Urine output indices increased significantly during normotensive period following 60-minute hypotensive epoch in both groups, as compared with the values during hypotensive period ($p<0.05$, **Table 3**), with greater magnitude noted during the second 30-minute period of normotension in the control group.

Urine osmolality during normotensive period showed comparably significant reductions from the values during hypotensive period in both groups. Absolute urinary excretion of sodium during normotensive period was significantly greater than those during hypotensive period in the control group, with a significant increase than the clonidine group during the 2nd 30-minute normotension (**Table 3**). Also absolute urinary excretion of potassium increased significantly during the 2nd 30-minute normotension in the control group, as compared with the value at 30-minute hypotensive period ($p<0.05$). However, plasma ADH levels did not change over time in both groups, and were similar between groups (**Table 3**).

Discussion

The present results show that clonidine 5 μg/kg as an oral preanesthetic medication significantly reduced the number of patients with anuria, along with increasing urine output and urinary potassium excretion during nicardipine-induced hypotension in surgical

Table 3 Urine output index, urine osmolality, absolute urinary excretion of sodium and potassium, and plasma ADH concentrations during 1 hour-hypotension and subsequent 1 hour-normotension in the clonidine (n=10) and control (n=10) groups

Variables	Group	Hypotensive period		Normotensive period	
		30 min	60 min	90 min	120 min
UOI (mL/kg/h)	Clonidine	0.24±0.1*	0.49±0.1	2.70±0.5^{+}	3.10±0.5*$^{+}$
	Control	0.05±0.4	0.90±0.4	3.86±0.8^{+}	5.50±0.7^{+}
UOsm (mOsm/kg)	Clonidine	792±55	605±93	147±23^{+}	130±30^{+}
	Control	799±144	373±86	161±40^{+}	104±6^{+}
UNa (mEq/h)	Clonidine	2.03±0.8	1.44±0.4	2.17±0.4	2.71±0.4*
	Control	0.51±0.4	1.81±0.8	4.66±1.4^{+}	6.16±1.3^{+}
UK (mEq/h)	Clonidine	0.75±0.2*	0.98±0.2	1.39±0.2	1.20±0.1
	Control	0.15±0.1	1.17±0.6	1.54±0.4	1.45±0.2#
ADH (pg/mL)	Clonidine	1.0±0.2	1.3±0.3	1.5±0.4	1.5±0.3
	Control	1.2±0.2	1.1±0.2	1.0±0.1	1.1±0.1

Values are mean±SEM. UOI=urine output index. UOsm=urine osmolality. UNa=absolute urinary sodium excretion. UK=absolute urinary potassium excretion. ADH=plasma antidiuretic hormone concentrations. *$p<0.05$ versus control group. $^{+}p<0.05$ versus values at 30 and 60 min. #$p<0.05$ versus values at 30 min.

patients under isoflurane-nitrous oxide general anesthesia. This effect of clonidine appears not to be mediated primarily by its effect on ADH release. Although mechanisms of clonidine-induced diuresis during deliberate hypotension remains to be proved, preanesthetic clonidine premedication is likely to provide one of clinically useful adjuvants in patients undergoing hypotensive anesthesia and surgery.

Major determinants for urine output during anesthesia and surgery include renal blood flow, glomerular filtration ratio, blood volume, plasma osmolality, and activities of autonomic nervous and endocrine systems[14]. Because arterial blood pressure is most likely to affect renal blood flow and thus urine output during anesthesia and surgery[14], lower blood pressure should contribute to decrease urine output through baroregulatory mechanisms to stimulate ADH secretion[15]. But it is unlikely in the current study, because mean arterial pressure decreased to the same extent during hypotensive period in both groups and there were no significant differences between the two groups in hemodynamics as well as in plasma ADH concentrations throughout the entire study period. Similarly, isoflurane has been demonstrated to decrease renal blood flow and glomerular filtration ratio[16], though cardiac output was well maintained at 0.9–1.9 minimum alveolar concentration of isoflurane[17]. But, because expired concentrations of isoflurane were comparable between groups before, during and after hypotensive period, the magnitude of detrimental, renal effects of isoflurane seemed to be similar in both groups.

More importantly, the patients receiving clonidine 5 μg/kg in the current study had larger amounts of urine output and urinary potassium excretion (**Table 3**), and lower incidence of anuria during the hypotensive period, as compared with the patients of the control group. These findings may be supported by a previous investigation showing that acute deliberate hypotension by clonidine did not reduce renal blood flow in rats[18]. The result that urine output increased during normotensive period following hypotension in both groups (**Table 3**) seems to be attributed to restoration of renal blood flow secondary to a rise in arterial blood pressure. But, the reason for its greater magnitude found during the second 30-minute period of normotension in the control group remains unclear. Similarly, significant reductions in urine osmolality during normotension following hypotensive period in both groups (**Table 3**) are probably due to an increase in water excretion secondary to recovery of renal blood flow associated with normotension. Also, significant increments in absolute excretion sodium and potassium during the same period in the control group

(**Table 3**) presumably are ascribed to increased renal blood flow.

Several mechanisms for diuretic effect of α_2-adrenoceptor agonists have been proposed. According to several experimental evidences, α_2-adrenoceptor agonists directly inhibited the action of ADH on the renal collecting tubules in various animals[19~22]. This inhibitory effect of ADH on the renal collecting tubules has been evidenced by significant reduction of ADH-stimulated cyclic AMP accumulation[23]. However, there seems to be a marked inter-species difference in this ability of α_2-adrenoceptor agonists[23]. While, diminished central secretion of vasopressin may account for diuretic effect of α_2-adrenoceptor agonists[24,25]. There are some reports showing reductions of ADH levels in both plasma and cerebrospinal fluid following oral or intravenous clonidine in awake humans[25~28]. However, since plasma ADH levels in the present results did not differ between groups, this mechanism for the diuretic action of clonidine is unlikely to be involved in patients undergoing hypotensive anesthesia and surgery. As another mechanism for the diuretic action of clonidine, clonidine's releasing effect of atrial natriuretic peptide (ANP) may be proposed[29,30]. However, ANP has been demonstrated not be involved in the diuretic effect of clonidine in patients undergoing minor surgery under isoflurane and nitrous oxide anesthesia[11]. Thus, ANP is unlikely to account for the diuretic effect of clonidine, although plasma ANP concentrations were not measured in the current study. Sympathetic inhibition by clonidine may rather be a plausible mechanism of diuresis during hypotensive anesthesia, since renal sympathetic nerve activity is suppressed by clonidine[2,31,32], thus resulting in diuresis[33,34].

There are some controversies regarding the effect of isoflurane upon plasma ADH levels as well as upon hormoral effect[35]. According to a clinical study, 1.1% isoflurane with 65% nitrous oxide in oxygen reduced plasma ADH levels by approximately 50% of the mean control value (9.9 pg/mL) prior to surgery, but was unable to suppress ADH secretion in response to surgical stimuli, resulting in a fourfold increase in plasma ADH levels[36]. However, plasma ADH levels remained within low ranges during all study periods, did not change significantly over time, and did not differ between groups in our study (**Table 3**). Thus, the influence of isoflurane on the plasma ADH levels might be minimal due to relatively smaller surgical stress response in each patient of the present study.

In the present study, a comparison of urine outputs between groups before induction of hypotension was not performed, because it does not make sense for the purpose of the study and it was obscure how long urine filled the patient's bladder; some of the patients voided just before leaving the ward, or some of those did not. Since the peak plasma concentration of clonidine reaches 1 to 3 hours after oral administration[37], the diuretic effect of clonidine should have been evident after anesthesia induction (approximately 2 hours after clonidine administration). Furthermore, we could not measure the urine output more than 3 hours due to brief surgical procedures, but the diuretic effect of clonidine is expected to last for a considerable period, because the elimination half-life of clonidine is approximately 12 hours, ranging from 6 to 24 hours[37]. Thus, the diuretic action of clonidine is likely to persist into a long postoperative period.

Based on a previous investigation showing that clonidine premedication caused a greater incidence of hypotension and more frequent requirements of vasopressor agents[3], we assumed lesser requirement of nicardipine for induced-hypotension in patients receiving oral clonidine premedication. However, the total doses of nicardipine given for induced hypotension were statistically similar between groups in our study (**Table 1**). The failure to detect a difference between the clonidine and control groups in the requirement of nicardipine was likely to be due to larger individual variations of nicardipine doses in both groups, especially in the control group. Nicardipine also has been demonstrated to exert a diuretic effect through increasing renal blood flow as well as glomerular filtration rate in rats or dogs[38,39], but the current results might not have been affected by this confound-

ing factor because of the statistically comparable total dose of nicardipine given for induced hypotension in the two groups.

It is recommended to use diuretics to counteract oliguria or anuria during anesthesia[40], since a decrease in urine output during anesthesia is of little clinical importance in low-risk patients, provided adequate circulatory volume is maintained. Among agents used for preanesthetic medications, there has been no description as to whether premedicants affect urine output during anesthesia. For example, although morphine in anesthetic dose reduced urine output in some animals[41,42] presumably through increasing ADH release, its preanesthetic medication seems not affect urine output in humans during anesthesia[43], and data on other premedicants are not available in this regard.

Although the results from previous clinical investigations as to the effects of α_2-adrenoceptor agonists on plasma ADH concentrations are conflicting[26~28], no data have been available whether preanesthetic oral clonidine medication induces diuresis in surgical patients undergoing hypotensive anesthesia. Since anesthetic agents[16,44,45] or techniques[46~48] including hypotensive anesthesia[12,13] may impair renal hemodynamics and decrease urine output, a diuretic effect of clonidine, a unique, valuable action, should provide a certain clinical importance for care of patients during anesthesia.

In conclusion, the current results show that oral preanesthetic medication of clonidine 5 μg/kg provided a diuretic effect during surgical procedure under hypotensive anesthesia with isoflurane and nitrous oxide.

Acknowledgements

This study was supported solely by institutional resources (Department of Anesthesia and Intensive Care Medicine, Akita University Graduate School of Medicine).

The authors declare that they have no conflicts of interests pertinent to the topics addressed in the present article.

References

1) Ghignone M, Calvillo O, Quintin L: Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 1987; 67: 3–10.
2) Flacke JW, Bloor BC, Flacke WE, et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987; 67: 11–9.
3) Woodcock TE, Millard RK, Dixon J, et al: Clonidine premedication for isoflurane-induced hypotension. Sympathoadrenal responses and a computer-controlled assessment of the vapour requirement. Br J Anaesth 1988; 60: 388–94.
4) Engelman E, Lipszyc M, Gilbart E, et al: Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. Anesthesiology 1989; 71: 178–87.
5) Wright PM, Carabine UA, McClune S, et al: Preanaesthetic medication with clonidine. Br J Anaesth 1990; 65: 628–32.
6) Fukuda T, Dohi S, Naito H: Comparisons of tetracaine spinal anesthesia with clonidine or phenylephrine in normotensive and hypertensive humans. Anesth Analg 1994; 78: 106–11.
7) Nishikawa T, Dohi S: Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. Anesthesiology 1990; 73: 853–9.
8) Nishikawa T, Kimura T, Taguchi N, et al: Oral clonidine preanesthetic medication augments the pressor responses to intravenous ephedrine in awake or anesthetized patients. Anesthesiology 1991; 74: 705–10.
9) Nishikawa T, Dohi S: Oral clonidine blunts the heart rate response to intravenous atropine in humans. Anesthesiology 1991; 75: 217–22.
10) Muzi M, Goff DR, Kampine JP, et al: Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology 1992; 77: 864–71.
11) Hamaya Y, Nishikawa T, Dohi S: Diuretic effect of clonidine during isoflurane, nitrous oxide, and oxygen anesthesia. Anesthesiology 1994; 81: 811–9.
12) Khambatta HJ, Stone JG, Khan E: Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979; 51: 127–30.
13) Mirenda JV, Grissom TE: Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. Anesth Analg 1991; 72: 667–83.
14) Sladen RN: Renal Physiology. In: Miller RD, editor. Anesthesia. New York: Churchill Livingstone; 2000. p.663–93.

15) Baylis PH: Osmoregulation and control of vasopressin secretion in healthy humans. Am J Physiol 1987; 253: R671-8.
16) Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 1974; 40: 536-42.
17) Stevens WC, Cromwell TH, Halsey MJ, et al: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971; 35: 8-16.
18) Takishita S, Muratani H, Kawazoe N, et al: Neural effects on renal blood flow during acute hypotension vary with antihypertensive drugs. Hypertension 1994; 23: I 97-101.
19) Olsen UB: Clonidine-induced increase of renal prostaglandin activity and water diuresis in conscious dogs. Eur J Pharmacol 1976; 36: 95-101.
20) Pettinger WA, Umemura S, Smyth DD, et al: Renal α_2-adrenoceptors and the adenylate cyclase-cAMP system: biochemical and physiological interactions. Am J Physiol 1987; 252: F199-208.
21) Gellai M, Edwards RM: Mechanism of α_2-adrenoceptor agonist-induced diuresis. Am J Physiol 1988; 255: F317-23.
22) Rouse D, Williams S, Suki WN: Clonidine inhibits fluid absorption in the rabbit proximal convoluted renal tubule. Kidney Int 1990; 38: 80-5.
23) Edwards RM, Stack EJ, Gellai M, et al: Inhibition of vasopressin-sensitive cAMP accumulation by α_2-adrenoceptor agonists in collecting tubules is species dependent. Pharmacology 1992; 44: 26-32.
24) Roman RJ, Cowley AW Jr, Lechene C: Water diuretic and natriuretic effect of clonidine in the rat. J Pharmacol Exp Ther 1979; 211: 385-93.
25) Reid IA, Naolan PL, Wolf JA, et al: Suppression of vasopressin secretion by clonidine: effect of α-adrenoceptor antagonists. Endocrinology 1979; 104:1403-6.
26) Pouttu J, Scheinin B, Rosenberg P, et al: Oral premedication with clonidine: effects on stress responses during general anaesthesia. Acta Anaesthesiol Scand 1987; 31: 730-4.
27) Peskind ER, Raskind MA, Leake RD, et al: Clonidine decreases plasma and cerebrospinal fluid arginine vasopressin but not oxytocin in humans. Neuroendocrinology 1987; 46: 395-400.
28) Brown GM, Mazurek M, Allen D, et al: Dose-response profiles of plasma growth hormone and vasopressin after clonidine challenge in man. Psychiatry Res 1990; 31: 311-20.
29) Baranowska B, Gutkowska J, Cantin M, et al: Plasma immunoreactive atrial natriuretic factor (IR-ANF) increases markedly after α_2-adrenergic stimulation with clonidine in normally-hydrated rats. Biochem Biophys Res Commun 1987; 143: 159-63.
30) Feng QP, Hedner T, Hedner J, et al: Blunted renal response to atrial natriuretic peptide in congestive heart failure rats is reversed by the α_2-adrenergic agonist clonidine. J Cardiovasc Pharmacol 1990; 16: 776-82.
31) Pouttu J, Tuominen M, Scheinin M, et al: Effects of oral clonidine premedication on concentrations of cortisol and monoamine neurotransmitters and their metabolites in cerebrospinal fluid and plasma. Acta Anaesthesiol Scand 1989; 33: 137-41.
32) Veith RC, Best JD, Halter JB: Dose-dependent suppression of norepinephrine appearance rate in plasma by clonidine in man. J Clin Endocrinol Metab 1984; 59: 151-5.
33) DiBona GF: The function of the renal nerves. Rev Physiol Biochem Pharmacol 1982; 94: 75-181.
34) DiBona GF: Neural control of renal function: cardiovascular implications. Hypertension 1989; 13: 539-48.
35) Diltoer M, Camu F: Glucose homeostasis and insulin secretion during isoflurane anesthesia in humans. Anesthesiology 1988; 68: 880-6.
36) Kataja J, Viinamäki O, Punnonen R, et al: Renin-angiotensin-aldosterone system and plasma vasopressin in surgical patients anaesthetized with halothane or isoflurane. Eur J Anaesth 1988; 5: 121-9.
37) Lowenthal DT, Matzek KM, MacGregor TR: Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988; 14: 287-310.
38) Takenaka T, Asano M, Shiono K, et al: Cardiovascular pharmacology of nicardipine in animals. Br J Clin Pharmacol 1985; 20 Suppl 1: 7-22S.
39) Abe Y, Komori T, Miura K, et al: Effects of the calcium antagonist nicardipine on renal function and rennin release in dogs. J Cardiovasc Pharmacol 1983; 5: 254-9.
40) Aronson S: Renal Function Monitoring. In: Miller RD, editor. Anesthesia. New York: Churchill Livingstone; 2000. p.1296-323.
41) Leander JD, Zerbe RL, Hart JC: Diuresis and suppression of vasopressin by kappa opioids: comparison with mu and delta opioids and clonidine. J Pharmacol Exp Ther 1985; 234: 463-9.
42) Rockhold RW, Crofton JT, Wang BC, et al: Effect of intracarotid administration of morphine and naloxone on plasma vasopressin levels and blood pressure in the dog. J Pharmacol Exp Ther 1983; 224: 386-90.
43) Papper S, Papper EM: The effects of pre-anesthetic, anesthetic, and postoperative drugs on renal function. Clin Pharmacol Ther 1964; 5: 205-15.
44) Deutsch S, Goldberg M, Stephen GW, et al: Effects of halothane anesthesia on renal function in normal man. Anesthesiology 1966; 27: 793-804.
45) Deutsch S, Bastron RD, Pierce EC Jr, et al: The effects of anaesthesia with thiopentone, nitrous oxide, narcot-

ics and neuromuscular blocking drugs on renal function in normal man. Br J Anaesth 1969; 41: 807–15.
46) Kennedy WF Jr, Sawyer TK, Gerbershagen HY, et al: Systemic cardiovascular and renal hemodynamic alterations during peridural anesthesia in normal man. Anesthesiology 1969; 31: 414–20.
47) Amory DW, Sivarajan M, Lindbloom LE: Systemic and regional blood flow during epidural anesthesia with epinephrine in the Rhesus monkey. Acta Anaesthesiol Scand 1977; 21: 423–9.
48) Kennedy WF Jr, Sawyer TK, Gerbershagen HU, et al: Simultaneous systemic cardiovascular and renal hemodynamic measurements during high spinal anaesthesia in normal man. Acta Anaesthesiol Scand Suppl 1969; 37: 163–71.