Brief Reports

Nicardipine did not activate renin-angiotensin-aldosterone system during isoflurane or sevoflurane anesthesia

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Purpose: To investigate the changes of renin-angiotensin-aldosterone system by nicardipine administration during isoflurane or sevoflurane anesthesia.

Methods: Twenty patients aged 40 to 70 yr for elective neurosurgery were studied. Anesthesia was induced with thiopental, midazolam and fentanyl and was maintained with nitrous oxide in oxygen and isoflurane or sevoflurane. When blood pressure was constant, $0.017 \text{ mg}\cdot\text{kg}^{-1}$ nicardipine was administered as a bolus. Blood pressure, heart rate, and plasma concentrations of nicardipine, angiotensin I and II, aldosterone and renin activity were measured for 30 min after nicardipine administration.

Results: Blood pressure decreased for 30 min after nicardipine administration in both groups with lower values during sevoflurane anesthesia. Heart rate increased only in the isoflurane group. Plasma nicardipine concentrations did not differ between isoflurane and sevoflurane groups. Plasma renin activity and concentrations of angiotensin II and aldosterone did not change in either groups and there were no differences between groups. Plasma concentration of angiotensin I increased at 20 and 30 min after nicardipine administration in the isoflurane group but not in the sevoflurane group.

Conclusion: The activity of renin-angiotensin-aldosterone system did not increase by a single dose administration of nicardipine in isoflurane or sevoflurane anesthesia.

Objectif : Examiner les changements du système rénine-angiotensine-aldostérone produits par l'administration de nicardipine pendant une anesthésie avec de l'isoflurane ou du sévoflurane.

Méthode : On a étudié 20 patients de 40 à 70 ans, en chirurgie élektive. L'anesthésie a été induite avec du thiopental, du midazolam et du fentanyl et a été maintenue avec du protoxyde d'azote dans de l'oxygène et avec de l'isoflurane ou du sévoflurane. Une fois la tension artérielle constante, on a administré un bolus de $0,017 \text{ mg}\cdot\text{kg}^{-1}$ de nicardipine. La tension artérielle, la fréquence cardiaque et les concentrations plasmatiques de nicardipine, d'angiotensine I et II et d'aldostérone ainsi que l'activité de la rénine ont été mesurées pendant 30 min après l'administration de nicardipine.

Résultats : La tension artérielle a diminué pendant 30 min après l'administration de nicardipine chez tous les patients, mais davantage avec le sévoflurane. La fréquence cardiaque a augmenté avec l'isoflurane seulement. Les concentrations plasmatiques de nicardipine ne présentaient pas de différence entre les groupes. L'activité de la rénine plasmatique et les concentrations d'angiotensine II et d'aldostérone n'ont pas été modifiées et n'ont pas présenté de différence intergroupe. La concentration plasmatique d'angiotensine I a augmenté 20 et 30 min après l'administration de nicardipine dans le groupe isoflurane, mais non dans le groupe sévoflurane.

Conclusion : L'activité du système rénine-angiotensine-aldostérone n'a pas augmenté après l'administration d'une seule dose de nicardipine lors d'anesthésie avec de l'isoflurane ou du sévoflurane.

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SYMPATHETIC activity and the renin-angiotensin-aldosterone system induce circulatory, hormonal and fluid-balance changes. They are stimulated by surgical stress and are modulated by general anesthesia¹ and hypotensive therapy.² In our previous study, nicardipine increased serum catecholamine concentrations during isoflurane but not sevoflurane anesthesia.³ Catecholamine stimulates renin release.⁴ Thus, we expected that nicardipine would increase renin activity during isoflurane anesthesia so that the combination of isoflurane and nicardipine should be avoided in critically ill patients. There are no studies comparing the activity of renin-angiotensin-aldosterone system modified by hypotensive therapy during isoflurane or sevoflurane anesthesia. In the present study, we compared the changes of renin-angiotensin-aldosterone system by nicardipine administration in isoflurane anesthesia with those in sevoflurane anesthesia.

Methods

After approval of the research committee and informed consent, 20 patients (without liver, renal or metabolic diseases; 40 to 70 yr, ASA class 1 or 2) scheduled for elective neurosurgery were randomly assigned by an envelope method to receive either isoflurane or sevoflurane anesthesia.

After premedication with 0.01 mg·kg⁻¹ atropine and 1 mg·kg⁻¹ hydroxyzine *im* 30 min before surgery, anesthesia was induced with 2 mg·kg⁻¹ thiopental, 0.1 mg·kg⁻¹ midazolam, and 1 µg·kg⁻¹ fentanyl and tracheal intubation was facilitated with 0.15 mg·kg⁻¹ vecuronium. Anesthesia was maintained with 4 L·min⁻¹ N₂O in 2 L·min⁻¹ oxygen and isoflurane or sevoflurane. The P_{ET}CO₂ (Ultima™, Datex, Helsinki, Finland) was controlled between 30 to 35 mmHg by artificial ventilation. During the study, the concentration of inhalational anesthetics and the infusion rate of lactated Ringer's solution were kept constant.

When the microsurgical procedure had started and blood pressure was stable ($\pm$ 5% compared with pre-anesthesia level), 0.017 mg·kg⁻¹ nicardipine was administered as a bolus. Blood pressure (radial artery), heart rate, and plasma concentrations of nicardipine, angiotensin I and II, aldosterone and renin activity were measured for 30 min. Plasma nicardipine concentration was measured with high-performance liquid chromatography (HPLC, UV detector SPD-2A, Shimadzu, Hamamatsu, Japan; detection limit 3 ng·mL⁻¹, coefficient of variation 2.0%). Plasma concentrations of angiotensin I and II and renin activity were measured with radioimmunoassay (ARC-950, Aroka, Tokyo, Japan) at BML Laboratory (Tokyo, Japan).

Data were expressed as mean $\pm$ standard deviation. Statistical analysis was performed with chi-square test for sex and type of surgery, with Student *t* test for other demographic data, with two-way repeated measures analysis of variance (ANOVA) followed by the contrast as a post-hoc test for blood pressure, heart rate, plasma concentration of nicardipine, angiotensin I, II, and aldosterone, and renin activity. A *P* value < 0.05 was considered statistically significant.

Results

Demographic data showed no differences between the two groups (Table I).

Blood pressure was lower in the sevoflurane group than in the isoflurane group. Heart rate increased significantly only in the isoflurane group (Table II).

Plasma nicardipine concentration did not differ between the two groups.

Plasma renin activity, angiotensin II, and aldosterone concentrations did not change during the study in either group. Plasma concentration of angiotensin I increased in the isoflurane group but did not increase in the sevoflurane group (Table II).

Discussion

In our previous study, nicardipine produced greater initial hypotension during sevoflurane than during isoflurane anesthesia.³ The present study also showed a greater decrease in blood pressure during sevoflurane anesthesia. Nicardipine increased heart rate by reflex sympathetic hypertonia due to hypotension under general anesthesia.³ That was confirmed in the present study while only in isoflurane anesthesia.

Nicardipine concentration did not differ between isoflurane and sevoflurane groups in the present study while clearance of nicardipine was greater during isoflurane than sevoflurane anesthesia in our previous study.³ This difference might be attributed to differ-

TABLE I Demographic data of the patients

	<i>Isoflurane</i>	<i>Sevoflurane</i>
Age (yr)	64 $\pm$ 4	62 $\pm$ 7
Sex (Male/Female)	6/4	5/5
Body weight (kg)	59 $\pm$ 8	58 $\pm$ 10
Surgery (Vascular/Tumour)	5/5	6/4
Duration of anesthesia (min)	611 $\pm$ 95	574 $\pm$ 88
MAC at nicardipine administration	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1
Time between start of surgery and nicardipine administration (min)	105 $\pm$ 16	121 $\pm$ 19

Mean $\pm$ standard deviation

MAC: minimum alveolar concentration

TABLE II Hemodynamics, nicardipine concentration, and renin angiotensin aldosterone system

Time (min)		0	1	3	5	10	20	30
BP (mmHg)	Iso	127±17	111±14)*	113±15*	115±16*	118±17*	120±16*	116±18*
	Sev	120±15	106±15*	100±17*†	105±18*†	110±19*	114±18	110±19*
HR (beats·min ⁻¹)	Iso	82±13	87±15	89±15	95±17*	88±14	83±12	82±13
	Sev	86±14	89±18	92±17	96±19	89±16	85±13	83±11
Nic (mg·mL ⁻¹)	Iso	0	N/A	N/A	47±13	26±7	15±4	7±3)
	Sev	0	N/A	N/A	39±10	20±5	12±2	8±2
Renin (ng·mL ⁻¹ ·h ⁻¹)	Iso	0.33±0.19	N/A	N/A	0.4±0.23	0.45±0.27	0.46±0.25	0.47±0.26
	Sev	0.37±0.23	N/A	N/A	0.39±0.26	0.44±0.3	0.4±0.26	0.42±0.26
AngI (pg·mL ⁻¹)	Iso	225±132	N/A	N/A	270±124	275±124	410±165*	421±130*
	Sev	232±151	N/A	N/A	259±116	263±154	316±205	269±154
AngII (pg·mL ⁻¹)	Iso	16±6	N/A	N/A	18±7	16±5	17±6	16±7
	Sev	19±12	N/A	N/A	23±12	16±11	18±11	16±8
Ald (pg·mL ⁻¹)	Iso	6.8±2.9	N/A	N/A	6.7±2.8	6.8±3.4	6.7±3.3	6.5±3
	Sev	5.6±2.5	N/A	N/A	5.9±2.5	6.3±3.7	6.3±3.5	6±2.9

(*s*): standard deviation, N/A: not available, BP: systolic blood pressure, HR: heart rate, Nic: nicardipine concentration, Renin: renin activity, AngI: angiotensin I, AngII: angiotensin II, Ald: aldosterone, Iso: isoflurane, Sev: sevoflurane, *: $P < 0.05$ vs the control value, †: $P < 0.05$ vs the isoflurane group

ences in blood pressure between these two studies which might influence the hepatic circulation.

Plasma epinephrine and norepinephrine concentrations did not change during sevoflurane anesthesia while both increased during isoflurane anesthesia after nicardipine administration.³ Catecholamine released by nicardipine stimulates juxtaglomerular cells in kidney to activate renin release. Increased renin stimulates production of angiotensin II which increases catecholamine secretion.⁴ Therefore, we expected that the renin-angiotensin-aldosterone system would be activated in isoflurane anesthesia. However, only angiotensin I increased significantly with increasing tendency of renin activity in isoflurane anesthesia. The 30 min observation time might be too short to detect the changes in renin-angiotensin-aldosterone system. We preferred to complete the study during stable surgical conditions. Thus, 30 min was the limit as in the previous study.³ In addition, renin activity might increase significantly if the number of patients was larger.

Rapid increase in concentrations of isoflurane increases plasma renin activity,¹ perhaps as a result of reduction of blood pressure. The renin-angiotensin system is stimulated by decreased renal perfusion pressure and increased renal sympathetic outflow.⁵ Reduction of renal perfusion pressure was the main determinant of renin-angiotensin activation during isoflurane anesthesia.⁶ In contrast, the importance of plasma renin activity in the maintenance of blood pressure during isoflurane anesthesia has been demonstrated in humans.⁷

Calcium may inhibit renin secretion by a direct action on the juxtaglomerular cell.⁸ Calcium antago-

nist can block this inhibition and may facilitate the activation of renin-angiotensin-aldosterone system by hypotensive stimulation. In awake hypertensive patients, nicardipine increases plasma renin activity which is associated with the increase of heart rate.⁹ However, plasma aldosterone concentration decreases or does not change.⁹ Nicardipine affects various renal parameters related to the release mechanism of renin; vasodilation and stimulation of the afferent baroreceptor and also the macula densa, which may respond to changes in sodium and chloride delivery.¹⁰ However, in the present study, renin-angiotensin-aldosterone system was not activated by nicardipine during isoflurane or sevoflurane anesthesia except for angiotensin I in isoflurane anesthesia. These results suggest that activation of the renin-angiotensin-aldosterone system by nicardipine might be inhibited during isoflurane and sevoflurane anesthesia with more completely inhibited in sevoflurane anesthesia. These interactions may be beneficial in patients with renal disease or hypertension.

In conclusion, the activity of renin-angiotensin-aldosterone system was not increased by a single dose of nicardipine during isoflurane or sevoflurane anesthesia.

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