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CLINICAL REPORT

Adequacy of control of preoperative hypertension can affect landiolol-induced hemodynamic changes in elderly patients during emergence from anesthesia

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Abstract We examined the dose-related effects of landiolol on hemodynamics during emergence from anesthesia of elderly patients with uncontrolled hypertension. Thirty-three normotensive, 34 controlled hypertensive, and 31 uncontrolled hypertensive elderly patients were divided into three groups: control (saline infusion), 0.125 landiolol group, and 0.25 landiolol group. Landiolol or saline infusion was administered at 0.125 (0.125 landiolol group) or 0.25 (0.25 landiolol group) mg/kg/min for 1 min and thereafter decreased to 0.04 or 0.08 mg/kg/min, respectively, until extubation, under regular heart rate and blood pressure monitoring. In normotensive patients, the 0.125 mg/kg/min landiolol infusion was suitable for stabilization of systolic blood pressure and heart rate during tracheal extubation. Controlled hypertensive patients required a 0.25 mg/kg/min landiolol infusion for stabilization of systolic blood pressure and heart rate during tracheal extubation. In uncontrolled hypertensive patients the 0.25 mg/kg/min landiolol infusion could stabilize heart rate, but not systolic blood pressure. In conclusion, the adequacy of preoperative hypertensive control could affect landiolol infusion-induced hemodynamic stability during emergence of elderly patients from anesthesia.

Keywords Emergence period · Landiolol · Heart rate · Elderly · Hypertension

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Introduction

Tracheal extubation and emergence from anesthesia induce abrupt changes in hemodynamics and humoral responses [1]. Many reports have documented that tracheal extubation causes transient but abrupt increases in blood pressure and heart rate, lasting from 5 to 15 min [1–3]. These hemodynamic changes during emergence from anesthesia may cause dangerous increases in myocardial oxygen demand in patients with coronary artery disease [2].

Beta-blockers are among the most effective drugs available for attenuation of the physiological changes associated with tracheal extubation and the emergence period [1–4]. Recent studies [5–8] show that the short-acting beta-1 blocker landiolol is effective in preventing the abrupt hemodynamic changes associated with tracheal extubation and the emergence period.

Exaggerated hypertensive responses to awakening and tracheal extubation are observed for hypertensive patients compared with those seen for normotensive patients [9–11]. In a previous study [12] we demonstrated that the effects of landiolol in preventing abrupt hemodynamic changes associated with tracheal extubation depended on patient demographics, for example age or the presence of preoperative hypertension. However, uncontrolled hypertensive patients were excluded from our previous study [12] because of the possibility that these patients were more prone to abrupt hemodynamic changes. We hypothesized that altering the infusion dosage of landiolol could have different effects on hemodynamics during tracheal extubation in uncontrolled hypertensive patients.

The purpose of this study was to examine the dose-related hemodynamic effects of landiolol on hemodynamics during the emergence period for elderly patients with uncontrolled hypertension.

Case presentation

This study was approved by the Ethics Committee of our institute and written informed consent was obtained from all patients. Elderly patients were defined as those above 70 years of age. Patients who were ASA physical status 3, 4, or 5, or who had an atrioventricular conduction block greater than first degree or a history of drug allergy were excluded from the study. Additional exclusion criteria were history of asthma, bronchospasm, chronic obstructive pulmonary disease, coronary artery disease, heart rate <50 beats/min, and systolic blood pressure <80 mmHg 1 min before the administration of landiolol.

Normotensive patients were defined as those who had never been diagnosed as being hypertensive on medical examination. Patients with hypertension were defined as those taking oral anti-hypertensive medication on first arrival at the hospital. The controlled hypertensive patients selected were those with normal blood pressure (systolic blood pressure <139 mmHg) as a result of treatment with anti-hypertensive drugs at the time of hospital admission, this being confirmed by at least three blood pressure measurements at different times during the day and night during the patients' hospital stay. Patients with uncontrolled hypertension were those with high blood pressure (systolic blood pressure >160 mmHg) despite treatment with anti-hypertensive drugs [13], as was confirmed by at least three blood pressure measurements both at night and in the daytime during the patients' hospital stay. These groups of patients were re-confirmed by cardiologists.

None of the hypertensive patients was receiving beta-blockers. For all the hypertensive patients, anti-hypertensive drug therapy was administered on the morning of surgery.

A total of 98 elderly patients were studied, including 33 normotensive, 34 controlled hypertensive, and 31 uncontrolled hypertensive patients scheduled for orthopedic or gynecological surgery.

A 3-lead electrocardiography monitor was attached to all patients (Nihon Koden, Tokyo, Japan). Anesthetic induction with 2 mg/kg propofol, 0.6 mg/kg rocuronium, and 0.2–0.5 μg/kg/min remifentanil was followed by endotracheal intubation. Muscular relaxation was achieved by intermittent administration of rocuronium. All patients' lungs were ventilated with 40% oxygen and 60% N_2 with continuous monitoring of end-tidal carbon dioxide (Pet-CO_2) (Nihon Koden). Anesthesia was maintained with remifentanil, 0.2–0.4 μg/kg/min, and 0.8–1.5% sevoflurane in 40% oxygen and 60% N_2.

A bispectral index monitor (A-2000; Aspect Medical Systems, Natick, MA, USA) was used to assess anesthetic depth in all patients. After anesthetic induction, administration of the anesthetic agents remifentanil and sevoflurane was adjusted to maintain intraoperative BIS levels between 45 and 50 in all patients.

Normotensive, controlled and uncontrolled hypertensive groups were randomly divided into three groups each: control (saline infusion), 0.125 landiolol group, and 0.25 landiolol group. Immediately after the end of the surgery, administration of all anesthetics, including sedative agents, was discontinued. All patients were then ventilated with 100% oxygen until emergence from anesthesia and landiolol or a similar dose of saline infusion was started.

Landiolol (50 mg/vial) was dissolved in 20 ml saline. The landiolol infusion was administered at 0.125 (0.125 landiolol group) or 0.25 (0.25 landiolol group) mg/kg/min for 1 min and thereafter reduced to 0.04 (0.125 landiolol group) or 0.08 (0.25 landiolol group) mg/kg/min until extubation. When spontaneous respiration was observed after surgery, 0.04 mg/kg neostigmine and 0.02 mg/kg atropine sulfate were given over a 1-min period. Patients were extubated when they could breathe spontaneously and could open their eyes on command. Landiolol infusion was stopped after extubation.

Heart rate and blood pressure were recorded every minute from before administration of the landiolol infusion until discontinuation of the infusion, and every 5 min thereafter, for 30 min after termination of the infusion. After extubation, patients were moved to the post-anesthesia care unit (PACU) where they remained for 30–60 min.

All patients received patient-controlled analgesia with an intravenous infusion of 100 μg fentanyl from approximately 60 min before the end of the surgery, and then 20 μg fentanyl per hour was started for each patient. A rescue dose of 20 μg fentanyl was prepared, to be administered in the PACU if necessary.

Data were analyzed by an individual who was unaware of the treatment regimens.

All data are expressed as mean ± standard deviation (SD). After confirmation of equal variance among the groups by the Bartlett test, changes in mean values of heart rate and mean blood pressure (baseline and between groups) were compared by use of one-way factorial measure or two-way repeated measures ANOVA. When the F value was significant, the Bonferroni method was used for multiple comparisons. All calculations were performed on a Windows computer with SPSS (SPSS, Chicago, IL, USA) and StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Figure 1 shows a schematic diagram of the study procedure.

Table 1a–c shows the demographic data of the three groups of elderly patients. There were no significant differences in anesthetic time, surgical time, blood loss, urine output, landiolol infusion time, reversal agent time (time from the start of landiolol infusion to the time of

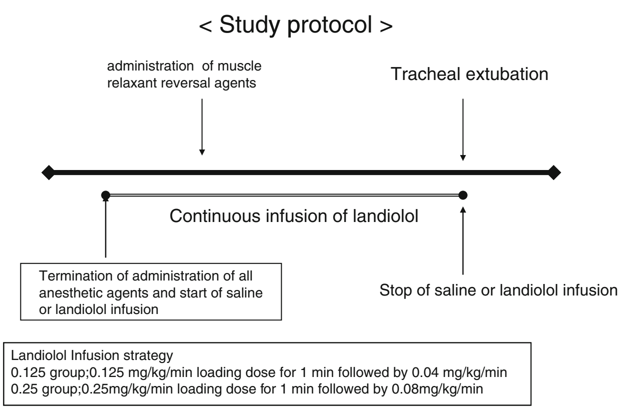

Fig. 1 Schematic diagram of the study procedure

administration of reversal agents), opiate dosage, and mean sevoflurane concentration during anesthesia among groups.

Figures 2a, b show the time course of changes in systolic blood pressure (sBP) and heart rate, respectively, in patients without hypertension in each group. sBP remained unchanged during emergence and tracheal extubation in the control and 0.125 landiolol groups, and decreased during emergence and tracheal extubation in the 0.25 landiolol group. Heart rate increased in the control group, remained unchanged in the 0.125 landiolol group and decreased during emergence and tracheal extubation in the 0.25 landiolol group.

Figures 3a, b show the time course of changes in sBP and heart rate in controlled hypertensive patients in each group. sBP increased during emergence and tracheal extubation in the control and 0.125 landiolol groups and remained unchanged during emergence and tracheal extubation in the 0.25 landiolol group. Heart rate increased during emergence and tracheal extubation in the control group and remained unchanged during emergence and tracheal extubation in the 0.125 and 0.25 landiolol groups.

Figures 4a, b show the time course of changes in sBP and heart rate in uncontrolled hypertensive patients in each group. sBP increased during emergence and tracheal extubation in all three groups of uncontrolled hypertensive patients, there being a significant difference in sBP 10 and 15 min after administration and at the time of termination of landiolol between the control, 0.125, and 0.25 landiolol groups. Heart rate increased during emergence and tracheal extubation in the control and 0.125 landiolol groups and remained unchanged in the 0.25 landiolol group. There was a significant difference in heart rate among the three groups of uncontrolled hypertensives during emergence and tracheal extubation.

One patient in the normotensive control group and one patient in the control group of controlled hypertensives required a rescue dose of 20 μg fentanyl in the PACU.

Discussion

This study shows that the adequacy of control of preoperative hypertension could affect the efficacy of landiolol infusion-induced hemodynamic stability during emergence of elderly patients from anesthesia. In addition, high doses of landiolol could stabilize hemodynamics in elderly patients with uncontrolled hypertension.

Recent studies have shown the efficacy of landiolol on inducing hemodynamic stability during extubation and emergence from anesthesia [5–8, 12]. Nonaka et al. [5] examined the effects of administration of 0.125 mg/kg/min landiolol for 1 min on hemodynamic changes after injection of neostigmine–atropine, and observed that the maximum increase in heart rate was 29.6 ± 12.3 beats/min in the control group whereas it was 14.1 ± 11.9 beats/min in the landiolol group. Other workers [6–8, 12] obtained similar results. Our study is the first of its kind to examine the effects of landiolol on hemodynamic changes in elderly patients with uncontrolled hypertension. It showed that the preoperative hypertensive state can greatly affect hemodynamic stability during the emergence period and that higher doses of landiolol can prevent abrupt hemodynamic changes during this period.

Some work has demonstrated that more abrupt hemodynamic changes are observed in hypertensive than in normotensive patients [9–11]. Prys-Roberts et al. [9] showed that hypertensive patients, whether treated or untreated, exhibit greater increases in blood pressure (compared with baseline pre-induction values) during endotracheal intubation, emergence, and extubation compared with normotensive patients. Stone et al. [11] examined the incidence of myocardial ischemia during anesthesia and surgery and found that myocardial ischemia was detected in 11 of 39 untreated hypertensive patients. They concluded that myocardial ischemia is prevalent during anesthesia in untreated hypertensive patients. These reports strongly indicate the clinical importance of hemodynamic stabilization during tracheal extubation to prevent myocardial ischemia. Sugiura et al. [14] showed that in hypertensive patients, 0.2 mg/kg landiolol was needed to suppress tachycardia after intubation, whereas 0.1 mg/kg was effective in normotensive patients. This demonstrates that a larger dose of landiolol is required to prevent hemodynamic changes in hypertensive patients, especially uncontrolled hypertensive patients, compared with normotensive patients. Our results showed that a larger dose of landiolol was required even in elderly uncontrolled hypertensive patients.

Landiolol reportedly has a predominant chronotropic, rather than an inotropic, effect, and thus causes neither excessive hypotension nor cardiac decompression [15]. The findings of this study are consistent with these

Table 1 Demographic data for the patients

	Control group	0.125 landiolol group	0.25 landiolol group	*P* value
(a) Normotensive patients				
Number of patients	11	11	11	
Age (years)	75 ± 3	76 ± 2	76 ± 2	0.66
Height (cm)	159 ± 7	156 ± 6	157 ± 7	0.81
Weight (kg)	52 ± 7	53 ± 6	52 ± 6	0.88
Anesthetic time (min)	278 ± 87	309 ± 106	311 ± 111	0.65
Type of operation: orthopedic/gynecological	6/5	7/4	7/4	
Operation time (min)	225 ± 56	249 ± 85	255 ± 78	0.67
Blood loss (ml)	209 ± 176	254 ± 169	256 ± 181	0.53
Urine output (ml)	304 ± 122	332 ± 109	299 ± 131	0.49
Landiolol infusion time (min)	21.5 ± 2.1	20.4 ± 3.2	20.3 ± 2.7	0.56
Remifentanil dosage (mg)	3.5 ± 0.4	3.5 ± 0.7	3.6 ± 0.7	0.84
Mean sevoflurane concentration (%)	1.4 ± 0.9	1.5 ± 0.9	1.6 ± 1.0	0.41
(b) Controlled hypertensive patients				
Number of patients	11	12	11	
Age (years)	73 ± 4	72 ± 2	73 ± 2	0.89
Height (cm)	158 ± 8	157 ± 7	158 ± 9	0.93
Weight (kg)	53 ± 6	53 ± 7	54 ± 7	0.83
Anesthetic time (min)	299 ± 108	321 ± 118	308 ± 131	0.49
Type of operation: orthopedic/gynecological	7/4	7/5	7/4	
Operation time (min)	248 ± 67	279 ± 69	278 ± 55	0.55
Blood loss (ml)	222 ± 155	269 ± 121	289 ± 138	0.61
Anti-hypertensive agents				
ACE inhibitor	7	8	7	
Ca channel blocker	5	4	4	
Urine output (ml)	289 ± 168	351 ± 190	321 ± 166	0.39
Landiolol infusion time (min)	22.2 ± 2.4	21.8 ± 2.5	20.9 ± 2.0	0.31
Remifentanil dosage (mg)	3.1 ± 0.6	3.3 ± 0.8	3.4 ± 0.9	0.56
Mean sevoflurane concentration (%)	1.3 ± 0.8	1.4 ± 1.0	1.4 ± 1.1	0.80
(c) Uncontrolled hypertensive patients				
Number of patients	10	10	11	
Age (years)	74 ± 4	75 ± 3	74 ± 3	0.71
Height (cm)	155 ± 8	157 ± 7	158 ± 8	0.44
Weight (kg)	50 ± 6	51 ± 7	53 ± 8	0.67
Anesthetic time (min)	321 ± 97	347 ± 116	360 ± 130	0.48
Operation time (min)	252 ± 66	289 ± 84	301 ± 97	0.43
Type of operation: orthopedic/gynecological	7/3	6/4	7/4	
Blood loss (ml)	245 ± 137	263 ± 151	286 ± 147	0.46
Urine output (ml)	345 ± 157	389 ± 121	305 ± 120	0.53
Anti-hypertensive agents				
ACE inhibitor	6	7	7	
Ca channel blocker	4	4	5	
Landiolol infusion time (min)	21.0 ± 2.3	21.9 ± 3.0	20.9 ± 2.9	0.50
Remifentanil dosage (mg)	3.7 ± 0.6	3.8 ± 0.8	3.8 ± 0.9	0.80
Mean sevoflurane concentration (%)	1.1 ± 0.8	1.1 ± 0.5	1.3 ± 0.9	0.65

pharmacological effects. A large dose of landiolol was required to stabilize sBP compared with heart rate in normotensive and controlled hypertensive patients.

The clinical implication of our study is that the adequacy of preoperative hypertensive control could affect landiolol infusion-induced hemodynamic stability during

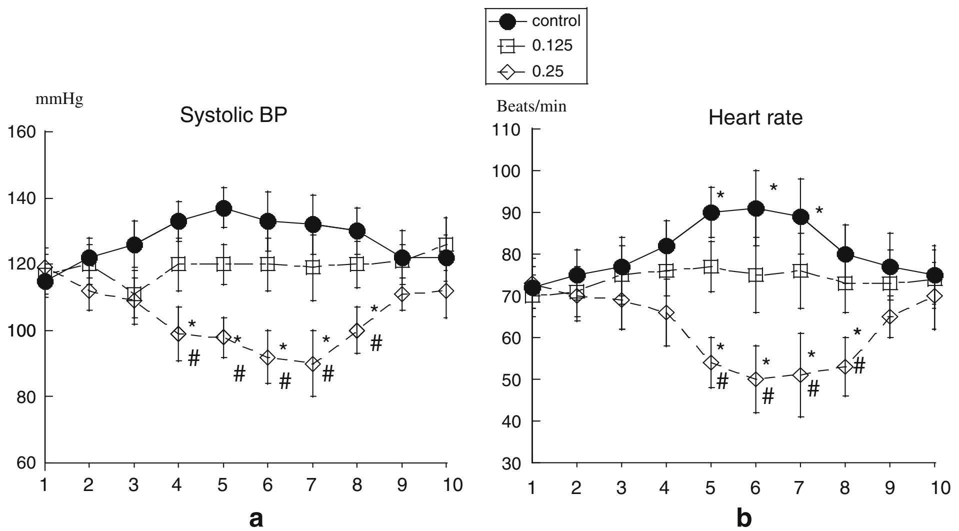

Fig. 2 Time course of changes in systolic blood pressure (**a**) and heart rate (**b**) in the three groups of normotensive patients. *$p < 0.05$ compared with time point 1, $^{\#}p < 0.05$ compared with the other groups. *1*, pre-infusion; *2*, 1 min after administration of landiolol; *3*, 2 min after administration of landiolol; *4*, 5 min after administration of landiolol; *5*, 10 min after administration of landiolol; *6*, 15 min after administration of landiolol; *7*, at the time of termination of landiolol; *8*, 5 min after termination of landiolol; *9*, 10 min after termination of landiolol; *10*, 15 min after termination of landiolol

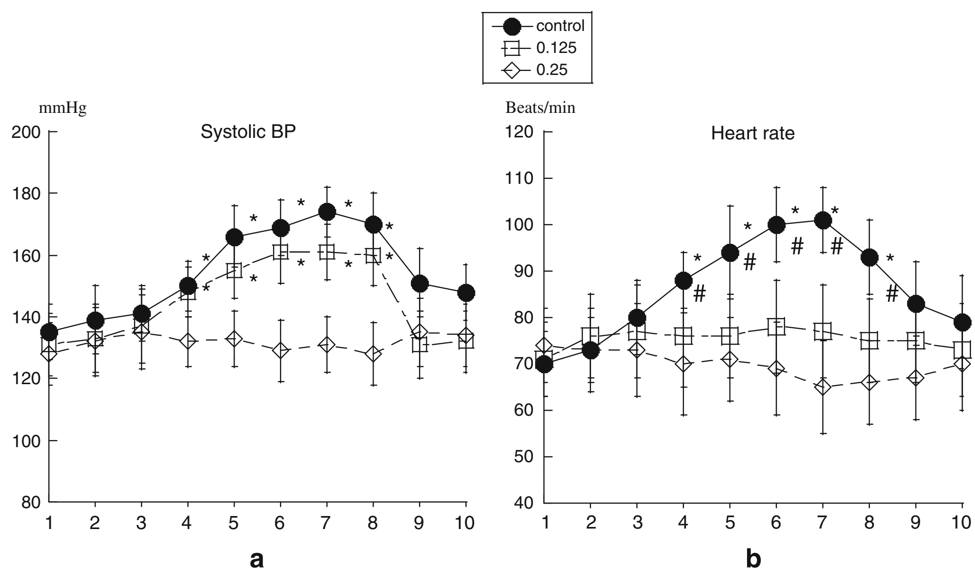

Fig. 3 Time course of changes in systolic blood pressure (**a**) and heart rate (**b**) in the three groups of controlled hypertensive patients. *$p < 0.05$ compared with time point 1, $^{\#}p < 0.05$ compared with the other groups. *1*, pre-infusion; *2*, 1 min after administration of landiolol; *3*, 2 min after administration of landiolol; *4*, 5 min after administration of landiolol; *5*, 10 min after administration of landiolol; *6*, 15 min after administration of landiolol; *7*, at the time of termination of landiolol; *8*, 5 min after termination of landiolol; *9*, 10 min after termination of landiolol; *10*, 15 min after termination of landiolol

emergence of elderly patients from anesthesia. In addition, continuous infusion of landiolol should be used to stabilize hemodynamics during emergence from anesthesia of elderly patients with uncontrolled hypertension.

Although it is generally accepted that angiotensin-converting enzyme (ACE) inhibitors should be withheld on the day before surgery, because of increased episodes of hypotension during anesthesia, we did not stop this agent in patients who were being treated with it, because of the potential for an increased incidence of hypertension on admission to the operation room.

Hypertensive patients treated with beta-blockers were excluded in this study because of the potential of dangerous

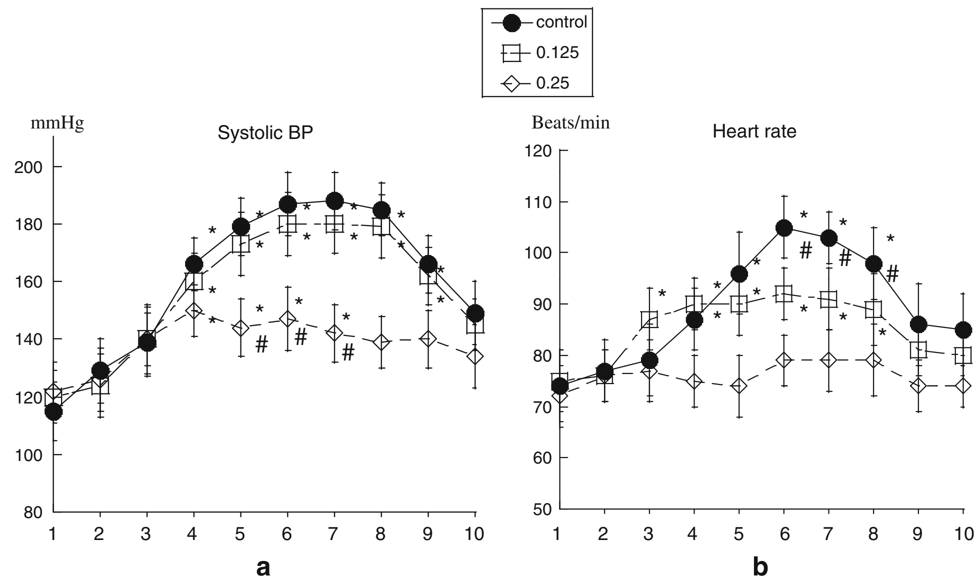

Fig. 4 Time course of changes in systolic blood pressure (**a**) and heart rate (**b**) in the three groups of uncontrolled hypertensive patients. $^{*}p < 0.05$ compared with time point 1, $^{\#}p < 0.05$ compared with other groups. *1*, pre-infusion; *2*, 1 min after administration of landiolol; *3*, 2 min after administration of landiolol; *4*, 5 min after administration of landiolol; *5*, 10 min after administration of landiolol; *6*, 15 min after administration of landiolol; *7*, at the time of termination of landiolol; *8*, 5 min after termination of landiolol; *9*, 10 min after termination of landiolol; *10*, 15 min after termination of landiolol

hypotension and bradycardia during anesthesia in patients receiving these drugs. It is clinically important to examine whether beta-blockers have different effects on hemodynamic variables during anesthesia in hypertensive patients treated with them. Further study is necessary to address this question.

We selected continuous infusion of landiolol for stabilizing hemodynamic changes during emergence from anesthesia. The most easily available and simple method of use of landiolol is administration of a single dose of landiolol if tachycardia occurs. However, because the purpose of this study was to examine the preventive effects of landiolol on hemodynamic changes during emergence from anesthesia, we opted to use a continuous infusion of landiolol.

In conclusion, the adequacy of control of hypertension preoperatively could affect the efficacy of landiolol-induced hemodynamic stability during emergence of elderly patients from anesthesia.

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Conflict of interest None.

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