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ORIGINAL ARTICLE

Does intravenous landiolol, a β_1-adrenergic blocker, affect stroke volume variation?

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Abstract
Purpose There are no reports about the effect of bradycardia on stroke volume variation (SVV), and we hypothesized that induced bradycardia alters the value of SVV. Landiolol, an ultra-short-acting adrenergic β_1-receptor blocking agent, was reported to induce bradycardia without decreasing blood pressure. The initial aim of this prospective study was to investigate changes in SVV values by induced bradycardia in patients with good cardiac function.
Methods At 30 min after anesthesia induction, if heart rate (HR) was >80 bpm, the patient was chosen as a subject. Ten ASA physical status I–II patients aged 38–75 years who were scheduled for elective abdominal surgery were included in this study. Baseline values were recorded, and then administration of landiolol was started at 125 μg/kg/min for 1 min and then continued at 40 μg/kg/min. SVV and other parameters were recorded at baseline and 3 min after continuous landiolol injection.
Results Landiolol significantly decreased systolic arterial pressure, and diastolic arterial pressure, contrary to our expectations, and also HR, SVV, cardiac output, stroke volume index, and pressure of end-tidal CO_2, whereas systemic vascular resistance values increased significantly.
Conclusions SVV decreased after continuous administration of a β_1-adrenergic blocker, probably because of a decrease in the difference of maximum stroke volume (SV) and minimum SV, or the downward shift of the Frank–Starling curve that occurred after landiolol administration. We believe that SVV values might be overestimated or misinterpreted when HR is decreased by landiolol and might not necessarily indicate that the patient is hypervolemic or normovolemic.

Keywords Stroke volume variation · Landiolol · Frank–Starling curve · Stroke volume

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Introduction

In an attempt to predict fluid responsiveness, many clinical studies have emphasized a lack of values for static indicators of cardiac preload such as central venous pressure (CVP), pulmonary artery occlusion pressure, and left ventricular end-diastolic area [1]. These studies have also emphasized the value of dynamic indices such as systolic pressure variation, pulse pressure variation (PPV), and echo-Doppler or pulse contour stroke volume variation (SVV) [1].

We recently reported that the rapid infusion of fluid may significantly influence these different parameters [2]. SVV

is affected by various factors such as intravascular volume status [3], depth of airway pressure and tidal volume [3–5], and intraabdominal pressure [6, 7], and we recently reported that SVV can be affected by induced hypertension (pressor test by bolus of phenylephrine) and hypotension (depressor test by bolus of nitroglycerine) [8–11] and by induced hypotensive anesthesia [11].

There are no reports, to our knowledge, about the effect of bradycardia on SVV, and we hypothesized that induced bradycardia alters the SVV value. We suspected that SVV values are changed by bradycardia induced by β_1-adrenergic blocker administration, and if so, SVV values might be overestimated or misinterpreted. Landiolol [12, 13], an ultra-short-acting adrenergic β_1-receptor blocking agent, induces bradycardia without decreasing blood pressure [14]. The initial aim of this prospective study was to investigate changes in SVV values by induced bradycardia in patients with good cardiac function.

Materials and methods

Approval for this study was obtained from the institutional review board of the International University of Health and Welfare Hospital, and written informed consent was obtained from all subjects. We registered this study in the "UMIN Clinical Trial Registry" (ID: UMIN000007474). The subjects of this study were patients scheduled to undergo elective abdominal surgery. All patients were ASA physical status 1 and 2, and none had known diabetes mellitus; hypertension; cardiovascular (including non-sinus rhythm and 2° or 3° A-V block), pulmonary, endocrinological, neurological, or autonomic diseases; or diseases that affect intravascular fluid volume or balance, such as gastrointestinal obstructive or inflammatory diseases. All patients underwent a preoperative fast for at least 8 h, and no premedication was given to any of the patients.

Induction of anesthesia was performed with propofol (initial effect-site concentration 4 μg/ml) and 1 μg/kg remifentanil intravenously (IV) in total, and rocuronium 0.6 mg/kg IV. After induction of anesthesia, a 23-gauge catheter was inserted in the left or right radial artery for direct arterial pressure monitoring, and the patient's lungs were mechanically ventilated by means of a semiclosed circle system at a fresh gas flow of 6 l/min (O_2, 2 l/min and air, 4 l/min). Controlled ventilation was set at 10 breaths/min, with a tidal volume of 8 ml/kg and an inspiratory:expiratory ratio of 1:2. Later, the effect-site concentration of propofol was adjusted to achieve a target bispectral index (BIS) between 40 and 60 and stable circulatory variables (propofol was administered by a plasma target-controlled infusion method).

Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR), cardiac output (CO), and SVV, stroke volume index (SVI), systemic vascular resistance (SVR), and pressure of end-tidal CO_2 ($P_{ET}CO_2$) were continuously monitored with a standard monitor (S/5 Anesthesia Monitor; GE Healthcare, Helsinki, Finland) and the FloTrac/Vigileo system (software version 01.14) (Edwards Lifesciences, Irvine, CA, USA). We did not insert central venous catheters into the patients to directly measure CVP. We obtained the data for SVR using a fixed CVP (= 0 mmHg) by inputting the pressure into the FloTrac/Vigileo system. CVP is not changed by continuous administration of landiolol [15].

Thirty minutes after induction of general anesthesia, if the patient's HR was >80 bpm, the patient was chosen as a subject, and the baseline values of SAP, DAP, HR, $P_{ET}CO_2$, CO, SVV, SVI, and SVR were recorded. Then, the patients received landiolol 125 μg/kg/min IV for 1 min followed by administration at 40 μg/kg/min [13, 14]. CO, SVV, SVI, and SVR were recorded 20 s after SAP, DAP, HR, and $P_{ET}CO_2$ were recorded because the Vigileo samples the pressure waveform at 100 Hertz over 20 s, capturing 2,000 data points for analysis, and parameter calculations are provided at the end of every 20-s timeframe [2, 16]. Three minutes after landiolol injection was started, these values were recorded again. All these studies were conducted before the surgery began, and just 100 ml normal saline was administered to the patients to maintain minimal change in SVV values for general anesthesia induction and during this study.

Sample size was estimated from preliminary data obtained from four patients, and an assumption was made that a three-point change in SVV between baseline and 3 min after landiolol start would be clinically relevant. Power analysis suggested that a minimum of nine patients would be needed for a $\beta = 0.1$ and $\alpha = 0.05$. To compensate for potential dropouts, we enrolled ten patients in this study. This analysis was performed using GraphPad StatMate 2.00 (GraphPad Software, La Jolla, CA, USA).

Statistical analysis

Values are expressed as mean ± standard deviation (SD). Comparisons of SAP, MAP, DAP, HR, SVV, CO, SVI, $P_{ET}CO_2$, and SVR were performed with paired Student's *t* test to determine whether there were significant differences between the parameters ($P < 0.05$). A P value < 0.05 was required to reject the null hypothesis. All analyses were performed with GraphPad Prism 5.04 (GraphPad Software).

Results

Patient characteristics are shown in Table 1. Values after intravenous landiolol are shown in Table 2. At 3 min after

Table 1 Demographic data of the study group

Patients (M/F)	10 (8/2)
Age (years)	55.5 ± 11.2 (38–75)
Weight (kg)	64.7 ± 7.0
Height (cm)	166.8 ± 6.4
Body surface area (m^2)	1.73 ± 0.12

Values are mean ± SD (range) or number

Table 2 Values after intravenous landiolol

	Baseline	After landiolol	*P* value
SAP (mmHg)	126.7 ± 27	116.1 ± 19.2	0.012
DAP (mmHg)	68.2 ± 13.8	64.1 ± 10.7	0.049
HR (bpm)	88.7 ± 9.4	82.9 ± 8.7	0.004
SVV (%)	17.2 ± 6.0	14.1 ± 4.2	0.038
CO (l/min)	6.0 ± 1.7	4.8 ± 1.2	0.0001
SVI (ml/beat/m^2)	39.3 ± 9.8	33.1 ± 6.2	0.0019
$P_{ET}CO_2$ (mmHg)	37.3 ± 3.7	36.1 ± 3.3	0.0026
SVR (dynes s/cm^5)	1197 ± 157	1375 ± 220	<0.0001

Values are mean ± standard deviation

SAP systolic arterial pressure, *DAP* diastolic arterial pressure, *HR* heart rate, *SVV* stroke volume variation, *CO* cardiac output, *SVI* stroke volume index, $P_{ET}CO_2$ pressure of end-tidal CO_2, *SVR* systemic vascular resistance

beginning administration of landiolol, values of SAP, DAP, HR, SVV, CO, SVI, and $P_{ET}CO_2$ had all decreased significantly, whereas SVR values had increased significantly.

Discussion

Although the main aim of this study was to investigate changes in SVV values after bradycardia induced by continuous administration of landiolol, a β_1-adrenergic blocker that is reported not to decrease arterial blood pressure [14], our results showed that continuous landiolol administration had decreased blood pressure, in contrast to our expectations. Therefore, we could not show the effect of bradycardia on SVV values. Goyagi et al. [14] concluded that continuous administration of landiolol did not affect blood pressure because they had many study points, and also they chose Scheffé's *F* test as the post hoc test for data analysis [both many study (measuring) points and the choice of Scheffé's *F* test as the post hoc test for data analysis are factors that reduce statistical power to detect differences]. The reason we chose the hemodynamic measurement point at 3 min after landiolol injection was that in our preliminary study, we found a statistically significant decrease in HR that started after 3 min of continuous landiolol administration, whereas Goyagi et al. [14] found that HR began to decrease significantly after 4 min of continuous landiolol administration.

We could, however, show the effect of continuous landiolol on various parameters, including SAP, DAP, HR, SVV, CO, SVI, $P_{ET}CO_2$, and SVR, and this is the first report, to our knowledge, to show the effect of an ultra-short-acting adrenergic β_1-receptor blocking agent, specifically landiolol, on these parameters. The present study showed that values of SAP, DAP, HR, SVV, CO, SVI, and $P_{ET}CO_2$ decreased significantly, whereas SVR values increased significantly. SVV is defined as $SVV\ (\%) = 100 \times (SV_{max} - SV_{min})/[(SV_{max} + SV_{min})/2]$, where stroke volume (SV) and maximal and minimal values for SV were determined as SV_{max} and SV_{min}, respectively, over a single respiratory cycle of paced breathing [2, 11]. Because SV decreased after landiolol, the denominator in this formula clearly decreased. Therefore, the reason for the decrease in SVV value was the decrease in the difference between maximum SV and minimum SV, and this phenomenon can be explained by the fact that the absolute SVV value decreased in this study (Table 2).

It is very important to note that PPV, the alternative to SVV [17], is not an indicator of volume status or a marker of cardiac preload but is an indicator of the position on the Frank–Starling curve (Fig. 1) [1, 18]. Also, a rapid decrease in myocardial contractility occurring after landiolol infusion might shift the Frank–Starling curve downward (Fig. 1) [18] and thus might decrease the SVV value, as was seen in the present study. However, the changes in SVV by landiolol might be affected by other factors. Because landiolol infusion decreased SVV, we therefore believe that the interpretation of SVV values during landiolol infusion should be undertaken with caution: in such a situation, the patient may not be entirely normovolemic or hypervolemic.

Landiolol increases SVR in acute decompensated heart failure in tachycardia patients [19], and esmolol, the first ultra-short-acting adrenergic β_1-receptor blocking agent, also increases SVR in humans with severe left ventricular dysfunction [20] and pigs with endotoxemic shock [21]. Iskandrian et al. [20] examined the effect of esmolol in patients with severe left ventricular dysfunction and commented that "esmolol appears to have no direct effect on the peripheral vasculature; SVR increased to compensate for the decrease in cardiac output. This rise in SVR was not great, allowing the central aortic pressure to decline which is important in successfully reducing myocardial oxygen demand even in patients with severe left ventricular dysfunction."

In the present study, after landiolol infusion, both CO values and $P_{ET}CO_2$ values decreased significantly (Table 2). There was a significant linear correlation between percent change in $P_{ET}CO_2$ and percent change in

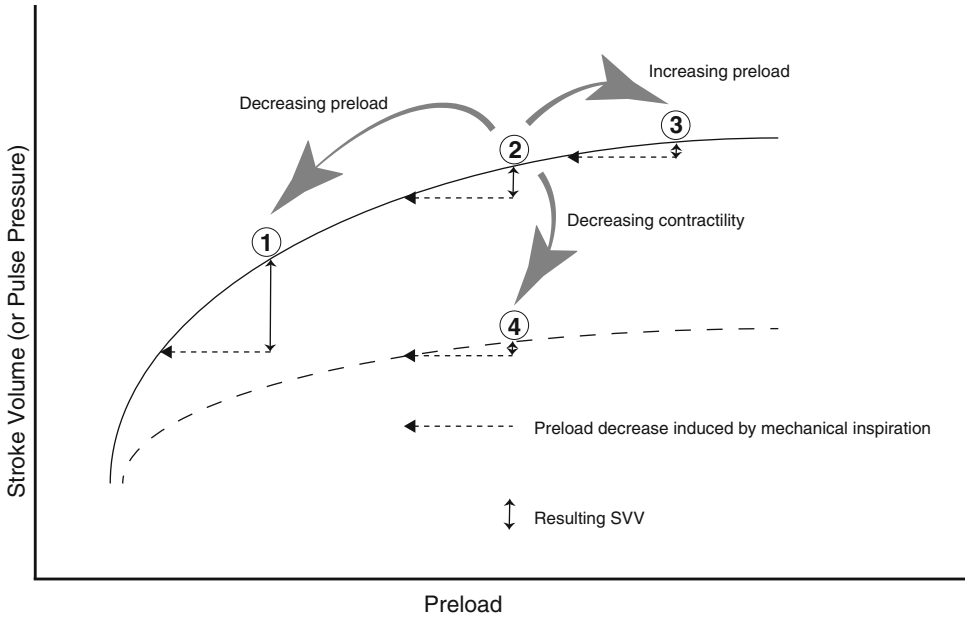

Fig. 1 Determinants of stroke volume variation (SVV). SVV is a marker of the position on the Frank–Starling curve, not an indicator of blood volume or a marker of cardiac preload. SVV is minimal when the heart is operating on the plateau of the Frank–Starling curve (③, ④). Decreasing contractility induces a decrease in SVV (from ② to ④), also increasing preload (from ② to ③). Decreasing preload induces an increase in SVV (from ② to ①)

CO [22, 23]. Our results are not inconsistent with those of previous studies [22, 23].

Other situations might also affect SVV values. de Wilde et al. [24] recently showed that a volume shift induced by a change in body position varies SVV values: a 30° head-up position increased SVV, and a 30° head-down position decreased the SVV. Furthermore, Fukuda [25] recently showed a negative correlation between blood volume and SVV: larger blood volume resulted in lower SVV values, and smaller blood volume resulted in higher SVV values. These situations might also affect SVV.

Our study had several limitations: first, the initial aim of this study was to investigate changes in SVV values by induced bradycardia in patients with good cardiac function, and we thought that we could achieve this aim at the preliminary study stage (by choosing an appropriate sample size based on the calculations made by the statistical analysis software), but we could not accomplish this aim because landiolol decreased SAP and DAP, in contrast to our expectation. Therefore, other methods should be considered to determine the effect of bradycardia on SVV values. Second, although we found that SVV decreased after 3 min of continuous administration of landiolol, we did not investigate the entire effect of landiolol on hemodynamic parameters such as CO, SVI, and SVR over a short time period (e.g., 5–10 min), and, therefore, we need to study this further in the future.

In summary, SVV decreased after continuous administration of landiolol, a β_1-adrenergic blocker, probably because of a decrease in the difference between maximum SV and minimum SV and/or a shift of the Frank–Starling curve that also occurred. We believe that SVV values might be overestimated or misinterpreted when HR is decreased by landiolol and might not necessarily indicate that the patient is hypervolemic or normovolemic.

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Conflict of interest None.

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