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Right ventricular performance during hypotension induced by prostaglandin E_1, nicardipine HCl, glycerine trinitrate, and isosorbide dinitrate

YUKIHIRO WATOH and AKIRA TANAKA

Department of Anesthesiology, Tottori University, Faculty of Medicine, 36-1 Nishi-machi, Yonago-shi, Tottori 683, Japan

Abstract: This study investigated right ventricular (RV) performance during hypotensive anesthesia and compared the effect of the vasodilators prostaglandin E_1 (PGE_1), nicardipine HCl (Nic), glycerin trinitrate (GTN), and isosorbide dinitrate (ISDN) on RV function. Fifty patients were allocated into four groups [PGE_1 (n = 20), Nic (n = 10), GTN (n = 10), and ISDN (n = 10)] in random order. Pulmonary and RV hemodynamics were measured using a rapid-response thermodilution catheter before and during induced hypotension, when systolic arterial pressure was maintained at 80 mmHg. In the PGE_1, GTN, and ISDN groups, RV end-diastolic volume (RVEDV) and pulmonary vascular resistance were reduced in a similar manner. However, RV ejection fraction increased only in the PGE_1 group, and as a consequence, RV stroke volume (RVSV) was maintained. Nic did not change the RV parameters observed, but reduced only systemic vascular resistance (SVR). PGE_1 enhanced RV function during induced hypotension. Nic was a useful alternative agent for hypotensive anesthesia. GTN and ISDN reduced RV preload and RVSV; however, cardiac output was maintained by increasing heart rate (HR). Therefore, such nitrates should be used under an adequate RV preload.

Key words: Right ventricular performance, Prostaglandin E_1, Nicardipine HCl, Glycerin trinitrate, Isosorbide dinitrate

Introduction

There has been a great deal of research on left ventricular (LV) performance from various aspects. However, clinical studies on right ventricular (RV) function have had to await the development of new technology which made information on RV volume changes available. The development of the thermodilution technique using a rapid-response thermistor has opened a new era and made the evaluation of RV volume possible at bedside [1–5]. The reliability of this technique was confirmed by comparing the results with those of radionuclide angiography, two-dimensional echocardiography, and cineangiography [1,2,4,6,7].

Studies have indicated that RV function decreases in acute respiratory distress syndrome (ARDS), septic shock, and critically ill patients [8,9]. However, there are no precise reports on RV function during hypotensive anesthesia. The aim of this study was to investigate RV performance during hypotensive anesthesia induced by prostaglandin E_1 (PGE_1), nicardipine HCl (Nic), glycerin trinitrate (GTN), and isosorbide dinitrate (ISDN) using a rapid-response thermistor thermodilution catheter.

Subjects and methods

Fifty patients undergoing total cystectomy or radical hysterectomy were enrolled in the study. Informed consent was obtained from each patient. They were under 65 years of age and had no history of arteriosclerotic, cardiovascular, pulmonary, or severe systemic diseases. Each patient was randomly assigned to one of the four groups (PGE_1 group, n = 20; Nic group, n = 10; GTN group, n = 10; and ISDN group, n = 10).

All patients were anesthetized with intravenous administration of thiamylal sodium (6 mg·kg^{-1}) and succinyl choline chloride (1 mg·kg^{-1}), and maintained by balanced anesthesia with bolus IV injection of fentanyl (0.012–0.02 mg·kg^{-1}), droperidol (0.15–0.2 mg·kg^{-1}), diazepam (10 mg), pancuronium bromide, and inhalation of 60% N_2O.

Arterial pressure was monitored by a radial artery catheter. For thermodilution measurements, a pulmonary artery catheter equipped with a rapid-response (100 ms) thermistor (93A-431H7.5F, Ameri-

Address correspondence to: Y. Watoh
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can Edwards Laboratories, Santa Anna, CA, USA) was inserted via the right internal jugular vein. The opening of the proximal injectate lumen was placed right above the tricuspid valve by monitoring the pressure waveform obtained through the lumen [10]. RV ejection fraction (RVEF) and cardiac output (CO) were determined by injections of 5 ml ice-cold 5% dextrose solution and expressed as the mean value of three consecutive measurements. Pulmonary artery pressure (PAP) and pulmonary artery occlusive pressure (PAOP) were measured simultaneously at the end-expiration phase. Measurements of RVEF and CO, and computation of RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), and RV stroke volume (RVSV) were performed by an ejection fraction cardiac output computer (REF-1, American Edwards).

RV end-diastolic pressure (RVEDP) was also measured in 10 patients of the PGE_1 group and all Nic group patients by temporarily placing the proximal injectate lumen on the RV inflow tract.

The control values were measured and recorded during surgery when the patients were in stable condition. Each vasodilator was infused via the catheter injection port using a syringe pump (STC-521, Terumo, Tokyo, Japan). Systolic arterial pressure was maintained at 80 mmHg during induced hypotension. Measurements for the hypotensive phase were done after hypotension had been maintained for 15 min. Arterial and mixed venous blood samples were drawn and analyzed by an IL 1302 blood gas analyzer and an IL CO-Oximeter 282 (Instrumentation Laboratory, Lexington, MA, USA). Pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and pulmo-

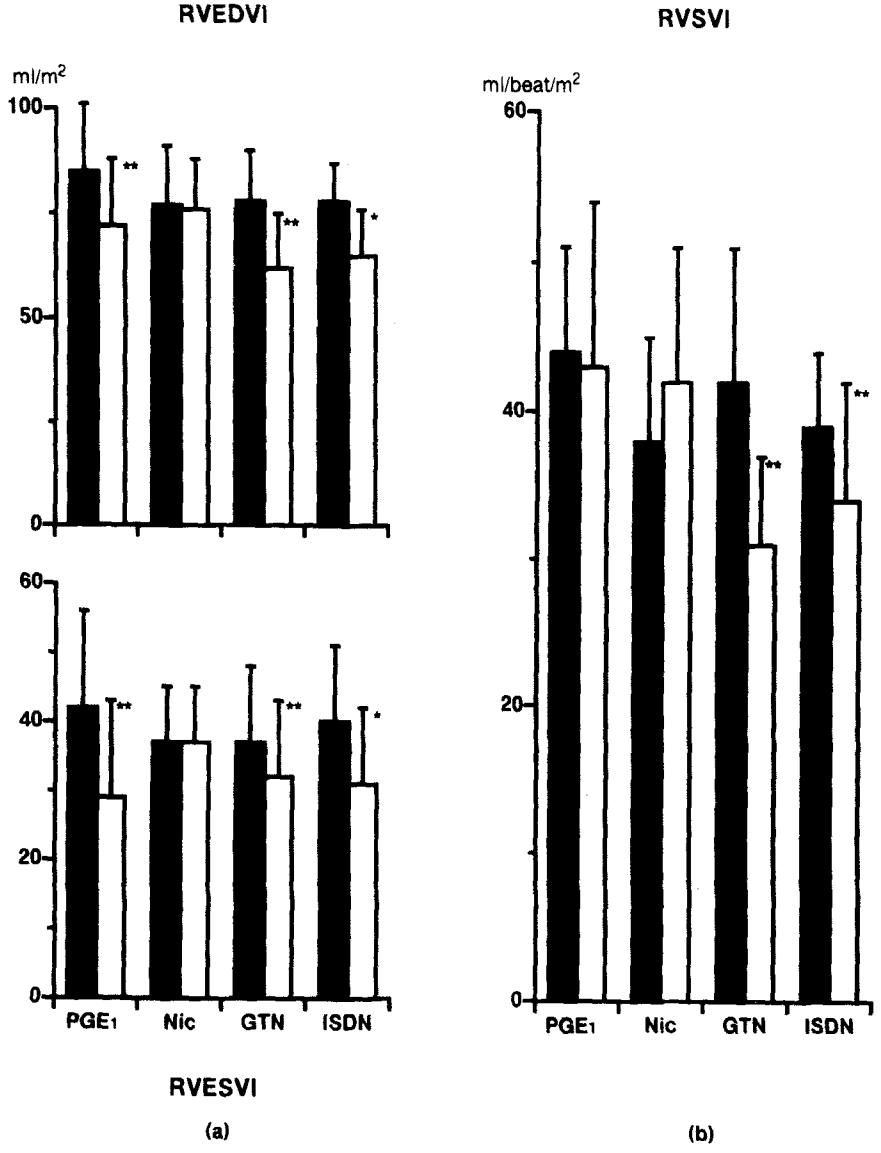

Fig. 1. Changes in right ventricular end-diastolic volume index (RVEDVI), right ventricular end-systolic volume index (RVESVI) (**a**), and right ventricular stroke volume index (RVSVI) (**b**). In the three groups other than the nicardipine HCl (*Nic*) group, both RVEDVI and RVESVI decreased significantly. In the GTN and ISDN groups, RVSVI decreased significantly. Values represent the mean ± SD; $^{**}P < 0.01$; $^{*}P < 0.05$ *vs* control. *Solid bars*, control; *open bars*, hypotension. *PGE_1*, prostaglandin E_1; *GTN*, glycerine trinitrate; *ISDN*, isosorbide dinitrate

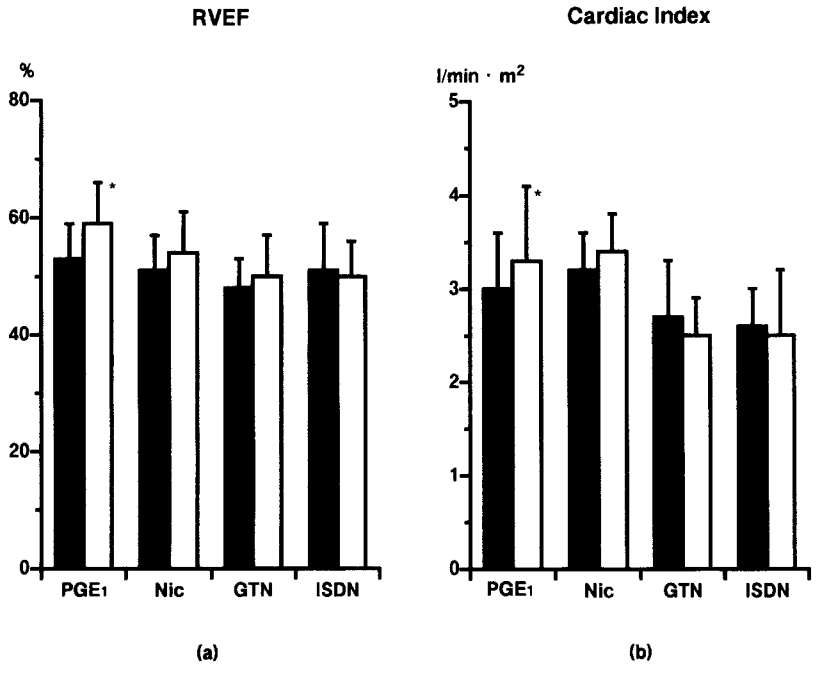

Fig. 2. Changes in right ventricular ejection fraction (*RVEF*) (**a**) and cardiac index (CI) (**b**). In the PGE_1 group, RVEF and CI increased significantly. Values represent the mean ± SD; $*P < 0.05$ *vs* control. *Solid bars*, control; *open bars*, hypotension

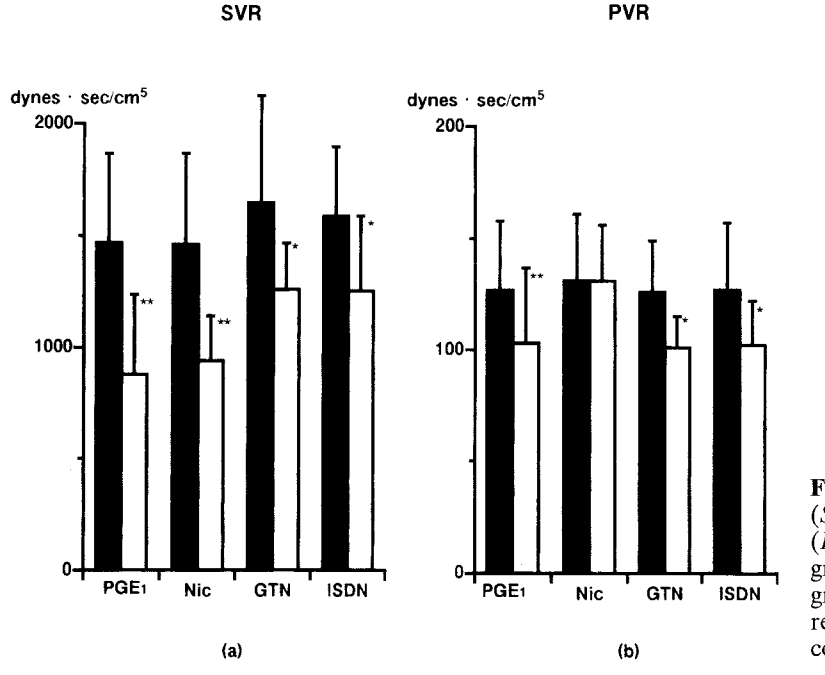

Fig. 3. Changes in systemic vascular resistance (*SVR*) (**a**) and pulmonary vascular resistance (*PVR*) (**b**). SVR decreased significantly in all groups (**a**). In the three groups other than the Nic group, PVR decreased significantly (**b**). Values represent the mean ± SD; $**P < 0.01$; $*P < 0.05$ *vs* control. *Solid bars*, control; *open bars*, hypotension

nary shunt ratio (QS/Qt) were calculated by standard formulae [11].

Statistical analysis

Student's *t*-test was used for data analysis. Correlation analysis, i.e., linear regression between each variable, was also performed. A *P* value less than 0.05 was used to accept or reject statistical hypotheses. Data were presented as mean ± SD.

Results

There were no significant differences among the four groups in the patients' characteristics and surgical profiles (Table 1).

The doses required to maintain hypotension (systolic arterial pressure = 80 mmHg) were as follows: PGE_1 0.4 ± 0.2; Nic 5.2 ± 2.4; GTN 4.0 ± 0.2; and ISDN 4.5 ± 2.5 ($mcg \cdot kg^{-1} \cdot min^{-1}$, mean ± SD). Hemodynamic data are presented in Table 2 and Figs. 1, 2, and 3.

Table 1. Characteristics of 50 patients in the four groups

	Number of patients	Age	Male	Female	Radical hysterectomy	Total cystectomy
PGE_1	20	59 ± 6	8	12	9	11
Nic	10	57 ± 9	3	7	5	5
GTN	10	60 ± 6	5	5	5	5
ISDN	10	61 ± 5	5	5	5	5

PGE_1, prostaglandin E_1; Nic, nicardipine HCl; GTN, glycerine trinitrate; ISDN, isosorbide dinitrate.

Table 2. Hemodynamic changes in the four groups

		PGE_1	Nic	GTN	ISDN
sAP (mmHg)	Control	125 ± 10	123 ± 11	121 ± 10	117 ± 10
	Hypotension	81 ± 1*	80 ± 0*	81 ± 1*	80 ± 1*
dAP (mmHg)	Control	66 ± 11	68 ± 11	75 ± 16	66 ± 9
	Hypotension	47 ± 7*	47 ± 6*	50 ± 7*	49 ± 5*
HR (beats·min^{-1})	Control	71 ± 12	79 ± 6	67 ± 9	68 ± 9
	Hypotension	81 ± 16*	80 ± 12	80 ± 15*	78 ± 15*
sPAP (mmHg)	Control	25 ± 5	24 ± 3	21 ± 3	21 ± 3
	Hypotension	19 ± 4*	23 ± 3	14 ± 3*	15 ± 2**
PAOP (mmHg)	Control	9 ± 2	8 ± 1	8 ± 2	8 ± 2
	Hypotension	6 ± 2*	7 ± 2	5 ± 2*	6 ± 3**
CVP (mmHg)	Control	8 ± 3	7 ± 1	7 ± 2	8 ± 3
	Hypotension	6 ± 2*	7 ± 2	5 ± 2*	6 ± 3**
RVEDP (mmHg)	Control	11 ± 2	10 ± 2	No data	No data
	Hypotension	8 ± 2*	9 ± 4		
SVR (dynes·s·cm^{-5})	Control	1470 ± 396	1462 ± 407	1647 ± 477	1589 ± 311
	Hypotension	877 ± 359*	938 ± 202*	1259 ± 209**	1254 ± 337**
PVR (dynes·s·cm^{-5})	Control	127 ± 31	131 ± 30	126 ± 23	127 ± 30
	Hypotension	103 ± 34*	131 ± 25	101 ± 14*	102 ± 20*
Qs/Qt (%)	Control	7.6 ± 3.9	8.5 ± 4.2	8.2 ± 4.6	5.2 ± 2.2
	Hypotension	12.7 ± 5.6*	9.4 ± 3.9	14.1 ± 4.8*	7.3 ± 4.5

sAP, systolic arterial pressure; dAP, diastolic arterial pressure; HR, heart rate; sPAP, systolic pulmonary artery pressure; PAOP, pulmonary artery occlusive pressure; CVP, central venous pressure; RVEDP, right ventricular end-diastolic pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Qs/Qt, pulmonary shunt ratio.
All values are expressed as the mean ± SD.
*$P < 0.01$; **$P < 0.05$ compared to value at the control stage.

Both RVEDV index (RVEDVI) and RVESV index (RVESVI) decreased significantly in the PGE_1 ($P < 0.01$), GTN ($P < 0.01$), and ISDN groups ($P < 0.05$) (Fig. 1). In contrast, in the Nic group these parameters did not change.

During hypotension, RVSVI decreased significantly both in the GTN and ISDN groups ($P < 0.01$), while that in the PGE_1 and Nic groups did not change.

RVEF increased significantly during hypotension in the PGE_1 group ($P < 0.05$), and cardiac index (CI) also increased ($P < 0.05$). However, in the other three groups, RVEF and CI did not change (Fig. 2).

A significant decrease in RVEDP was observed in the PGE_1 group ($P < 0.01$) but there was no change in the Nic group.

In the PGE_1 and Nic groups, marked decreases in SVR were observed during hypotension ($P < 0.01$). The decreases in the SVR, GTN, and ISDN groups were also significant ($P < 0.05$). Pulmonary vascular resistance (PVR) decreased during hypotension in the PGE_1 ($P < 0.01$), GTN, and ISDN groups ($P < 0.05$). In the Nic group, however, no change was observed (Fig. 3).

No significant correlations were observed between each of REVDP, RVEDVI, PAOP, RVSV, or RVEF in any group.

Discussion

The left ventricle has been perceived as the cardiac structure of the greatest importance for pump function, whereas the RV has been considered as a low-pressure volume conduit that conveys venous blood into the

high-compliance and low-resistance pulmonary vascular bed [12]. However, the RV is anatomically bonded to the LV by cardiac muscle fibers that run from the free wall of the RV to the anterior wall of the LV. Even in disorders primarily affecting the LV, this conduit has been proven essential for maintenance of normal cardiac performance [13]. Therefore, left-side events may have marked clinical effects on right-side function; thus, a vicious cycle ending in severe global myocardial decompensation may occur [14]. Also, recent reports on RV function have stated that during right heart failure and RV ischemia, the dilated RV restricted LV filling and reduced the stroke volume of the LV, thereby causing a decrease in CO and insufficient oxygen delivery [15,16]. RV performance closely connects to LV function and affects the entire cardiac function. Thus, monitoring the performance of both ventricles is crucial to balance the whole cardiac performance precisely.

In recent research on LV, LVEDV has been reported to be a more accurate indicator of LV preload than LV end-diastolic pressure (LVEDP) [9]. However, due to difficulties in obtaining information on LV volume changes in the clinical setting, the monitoring of RV volume changes has been evaluated and proven clinically useful [8].

On the other hand, a goal of hypotensive anesthesia is to achieve appropriate hypotension and also to maintain adequate organ blood flow. Some vasodilators are known to dilate not only arterial resistance vessels, but also venous capacitance vessels, and to cause peripheral venous pooling. There are few reports describing the effects of hypotensive drugs on RV performance. This study aimed to evaluate RV performance during hypotensive anesthesia induced by vasodilators in clinical use.

RVEF is considered to reflect RV contractility. However, other factors such as changes in RV afterload or RV preload can also be a function in certain conditions and may affect RVEF as well.

From the results of this study, no significant correlation between RV preload and RVEF was found in any group. These findings may suggest that changes in RV preload do not affect RVEF or are at least negligible for the preload changes observed in the study. As a consequence, this study suggests that RVEF is a function of RV contractility, and the role of RV afterload and RV preload may be minimum in normal hearts. In this study, administration of PGE_1 decreased both RV preload (RVEDV) and afterload (PVR). However, RVSV was maintained well due to the increased RVEF.

Several studies have examined the effects of RV afterload on RV performance. Some studies on septic shock patients and patients with ischemic heart disease, in which the same method as in the present study was used, have revealed a clear negative linear correlation between RVEF and RV afterload (PVR or mPAP) [8,9]. On the basis of those observations and basic RV physiology, it is likely that the decrease in RV afterload observed in this study may account for the increase in RV function, and may result in some increase in RVEF. However, the reduction of RV afterload alone does not explain the different results obtained between the PGE_1 and nitrate groups, or the opposite directional change in RVEF against RV preload and afterload reduction. This may suggest other contributing factors, such as the increase in RV contractility observed in the PGE_1 group. These findings also suggest that the decreases in RVSV in the GTN and ISDN groups were mainly due to RV preload (RVEDV) reduction, and that RV contractility was not affected. Nakano and McCurdy found that intravenously injected PGE_1 increased dP/dt_{max} in the LV, and increased myocardial contractile force in both ventricles [17]. Another report provides evidence that PGE_1 enhances LV contractility [18]. It is therefore plausible that the positive inotropic effect of PGE_1 on the RV resulted in RV preload reduction, although the details of this mechanism are not clear and need further investigation. Comparing PGE_1 with GTN and ISDN, PGE_1 appears to be the better hypotensive anesthetic agent in terms of RV performance.

The administration of nitrates has reportedly enhanced cardiac contractility in patients with myocardial ischemia and heart failure [19], but did not affect or enhance RV ejection in intact hearts in this study. Therefore, we strongly recommend administering these drugs under an adequate preload.

Nic had a minimal effect on RV performance with the dose studied. Neither RV preload (RVEDVI) nor RV afterload (PVR) changed. RVSV was maintained well, and hypotension was induced safely. Nic is considered a safe and potent agent for hypotensive anesthesia. Furthermore, Nic does not dilate the pulmonary vessels, thus causing no increase in pulmonary shunting. In view of our results on RV volume measurements, we consider the effect of Nic to be highly selective with respect to the resistance vessels. Nic did not induce tachycardia, which often occurs following the administration of vasodilators. Direct suppression of sinoatrial (SA) node or atrioventricular (AV) node conduction by Nic is a desirable feature in clinical use [20].

RVEDP was evaluated in terms of whether it can be an accurate indicator of RV preload. However, there was no significant correlation observed between RVEDP and other parameters such as RVEDVI, PAOP, or RVSVI. The authors conclude that RVEDP does not indicate RV preload accurately, which may be explained in part by the fact that the RV is a high-compliance and low-pressure conduit.

Conclusions

PGE_1 decreased RV preload and afterload, and enhanced RV function. Nic did not affect RV performance. Nic was a useful alternative agent for hypotensive anesthesia. While GTN and ISDN did not affect RVEF, a reduction of RV preload causing a decrease in RVSV was found. Although the CI was maintained by increasing the HR, such nitrates should be used under an adequate preload. RV is a high-compliance and low-pressure conduit; thus, RVEDP does not indicate RV preload correctly.

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