Changes in Venous Capacitance during Prostaglandin E_1-induced Hypotension; Comparisons with Trinitroglycerin

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The purpose of this study was to examine the effects of prostaglandin E_1 (PGE_1) on venous capacitance during controlled hypotension. Trinitroglycerin (TNG) was used as a control agent. In rats anesthetized with ketamine, mean arterial pressure was lowered to 70 mmHg and subsequently 50 mmHg by intravenous infusion of PGE_1 or TNG. Venous capacitance was assessed before and during induced hypotension by measuring the mean circulatory filling pressure (MCFP). MCFP was measured after briefly arresting the circulation by inflating an indwelling balloon in the right atrium. MCFP was significantly decreased by PGE_1 from 7.9 ± 0.3 to 6.9 ± 0.3 mmHg at mean arterial pressure of 70 mmHg and to 6.9 ± 0.2 mmHg at mean arterial pressure of 50 mmHg. The decrease in MCFP by PGE_1 at mean arterial pressure of 70 mmHg was not significantly different from TNG. However, the decrease in MCFP by PGE_1 at mean arterial pressure of 50 mmHg was significantly less than that by TNG. The results suggest that the venous capacitance may be increased by PGE_1 to a similar degree with TNG at doses to produce a comparable level of moderate hypotension, but the increase in venous capacitance may be less in PGE_1 than TNG at doses to produce deep hypotension. (Key words: induced hypotension, mean circulatory filling pressure, prostaglandin E_1, trinitroglycerin, vein)

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Prostaglandin E_1 (PGE_1) is used for controlled hypotension during anesthesia due to its potent vasodilating action[1,2]. Several studies have examined the hemodynamic changes during controlled hypotension caused by PGE_1 as compared with other vasodilators, such as nitroprusside, nitroglycerin, or adenosine triphosphate[3,4]. However, the effect of PGE_1 on venous system during hypotensive anesthesia is not clearly elucidated. The venous system plays a role in circulation not solely as a conduit of blood stream but as a reservoir of the circulating blood[5]. Since a change in venous capacitance significantly alters venous return and thus affects cardiac output, it is important to know the effect of PGE_1 on

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venous capacitance particularly during the hypotensive anesthesia.

The effect of drugs on venous capacitance can be assessed by measuring mean circulatory filling pressure (MCFP)[6,7]. In this study, we examined the effect of PGE_1-induced hypotension on MCFP, and compared it with that of trinitroglycerin (TNG)-induced hypotension. The study was performed under ketamine anesthesia, because it has been previously shown that ketamine has little effect on venous capacitance[8].

Methods

Surgical preparaton

Male Wistar rats (n=8), weighing 300–490g, were used in this study. Rats were anesthetized with ketamine 125 $mg \cdot kg^{-1}$ given intraperitoneally, and a supplemental dose of 10 $mg \cdot kg^{-1}$ was added every 30 min. The femoral artery and vein were cannulated. The arterial catheter was advanced up to the iliac bifurcation, and the venous catheter was positioned in the thoracic inferior vena cava. The catheters were connected to pressure transducers for recording arterial and central venous pressure, respectively. The proper position of the venous catheter was confirmed by a synchronous change of the pressure with respiration. The left external jugular vein was cannulated for the route of drug infusion. A balloon-tipped catheter was placed in the right atrium through the right external jugular vein, and the proper location was tested by injection of air (0.3 ml) into the balloon to stop the circulation completely. If a smooth increase in venous pressure and a simultaneous decrease in arterial pressure to less than 30 mmHg were not observed, the balloon was repositioned. Tracheostomy was done and the rats were allowed to breathe air with oxygen.

Measurements of MCFP

The mean circulatory filling pressure (MCFP) was measured using the technique reported by Yamamoto et al.[9]. Immediately after the balloon was inflated, arterial pressure decreased and venous pressure increased and reached a plateau within 4–5 seconds. Since in this method, arterial and venous pressure during circulatory arrest were not in complete equilibrium, MCFP was calculated according to the following equation:

$$MCFP = VPP + K(FAP - VPP),$$

where VPP is the venous plateau pressure, and FAP is the final arterial pressure during circulatory arrest, and K is the arterial-to-venous compliance ratio. According to the report by Yamamoto et al.[9] a K value of 1/60 was used in this study.

Protocol

MCFP was measured at a control state as well as during hypotension produced by PGE_1 or TNG. Each rat received two drugs. The order of the drugs was randomized. At least 20 min was allowed between two drugs. MCFP was determined during moderate hypotension at the mean arterial pressure of about 70 mmHg and during deep hypotension at about 50 mmHg. The drugs were diluted in physiological saline. Doses of PGE_1 were 5.4 ± 2.0 and 10.8 ± 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the mean arterial pressure of 70 mmHg and 50 mmHg, respectively. Doses of TNG were 30 ± 20 and 67 ± 53 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the mean arterial pressure of 70 mmHg and 50 mmHg, respectively. Total volumes of infusion were less than 300 μl and same between rats receiving PGE_1 and TNG.

Statistical analysis

Data are expressed as mean ± SEM. Student's unpaired t-test was used for comparisons of results between PGE_1

Table 1. MAP, HR, CVP and MCFP at control and during moderate and deep hypotension by PGE_1 or TNG

	MAP (mmHg)	HR (beats·min^{-1})	CVP (mmHg)	MCFP (mmHg)
Control				
PGE_1	102 ± 4	346 ± 20	1.7 ± 0.4	7.9 ± 0.3
TNG	106 ± 5	345 ± 22	1.6 ± 0.5	8.1 ± 0.2
Moderate hypotension				
PGE_1	68 ± 2[a]	350 ± 16	1.4 ± 0.4	6.9 ± 0.3[a]
TNG	70 ± 2[a]	354 ± 16	1.4 ± 0.6	6.8 ± 0.4[a]
Deep hypotension				
PGE_1	52 ± 2[a,b]	332 ± 18	1.6 ± 0.5	6.9 ± 0.2[a]
TNG	54 ± 2[a,b]	350 ± 15	1.5 ± 0.5	6.5 ± 0.2[a,b]

PGE_1, prostaglandin E_1; TNG, trinitroglycerin; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; MCFP, mean circulatory filling presure.

[a] $P < 0.05$ vs. control

[b] $P < 0.05$ vs. moderate hypotension

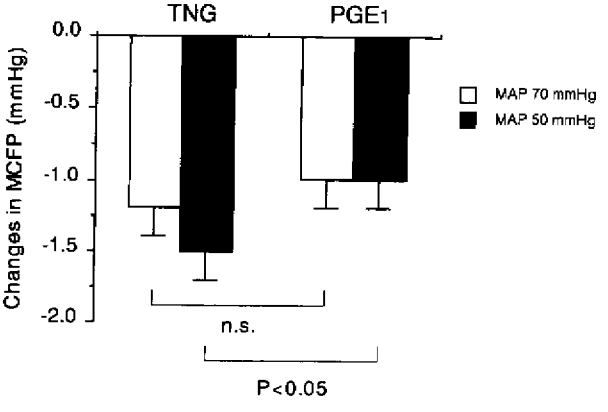

Fig. 1. Changes in MCFP during moderate hypotension at MAP 70 mmHg and during deep hypotension at MAP 50 mmHg by TNG and PGE_1. The decrease in MCFP by PGE_1 was not significantly different from that by TNG at MAP 70 mmHg, but the decrease was significantly less in PGE_1 than TNG at MAP 50 mmHg. MCFP, mean circulatory filling pressure; MAP, mean arterial pressure; TNG, trinitroglycerin; PGE_1, prostaglandin E_1.

and TNG. A paired t-test was used for comparisons between the control state and during drug-induced hypotension. $P < 0.05$ was considered to be significant.

Results

Table 1 shows values for mean arterial pressure, central venous pressure, heart rate, and MCFP at control state as well as during moderate and deep hypotension in rats treated with PGE_1 and TNG. Mean arterial pressure, central venous pressure and heart rate at control state were not different between the two drugs. The drugs were infused until the desired hypotension was achieved at the mean arterial pressure of about 70 mmHg and 50 mmHg, so that the mean arterial pressures during hypotension were not different between two groups. Central venous pressure and heart rate were not significantly altered by PGE_1 and TNG. During drug-induced hypotension, PGE_1 and TNG decreased MCFP as compared with the respective values at control ($P < 0.05$ for both drugs). Figure 1 shows changes in MCFP during moderate and deep hypotension by

TNG and PGE_1. At the mean arterial pressure of 70 mmHg, the decrease in MCFP by PGE_1 was not significantly different from that by TNG. However, at the mean arterial pressure of 50 mmHg, MCFP was significantly less decreased in PGE_1-induced hypotension as compared with TNG-induced hypotension ($P < 0.05$).

Discussion

The present study demonstrated that during moderate hypotension PGE_1 decreased MCFP to a similar level with TNG, but during deep hypotension the decrease in MCFP by PGE_1 was less than that by TNG. These results suggest that the venodilator effect of PGE_1 was similar to TNG at moderate hypotension, and less than TNG at deep hypotension.

We used MCFP as an index of venous capacitance. MCFP is an equilibrium pressure between veins and arteries during circulatory arrest. Thus, MCFP is a function of total vascular capacitance and blood volume. However, since arterial capacitance is quantitatively insignificant as compared with venous capacitance,[6,10] it is generally accepted that, at any given blood volume, MCFP is a reliable index of venous capacitance. The validity of this method for the measurements of MCFP has been discussed in the previous reports[8,9]. It has been shown that MCFP obtained by this method is not different from MCFP obtained by the classical method using blood transfer from the arterial to venous system after circulatory arrest[10]. It also has been used to examine the effect of various vasoactive drugs of anesthetic agents on veins and to examine venodilator effects of drugs during controlled hypotension[8,9,11].

The venodilator effect of PGE_1 is in agreement with the results of Weiner and Kaley[12], who showed that *in vivo* microcirculation studies, PGE_1 dilated venules as well as arterioles. Our previous report, in which PGE_1 decreased left ventricular end-diastolic dimension and pressure, supports the venodilator effect of PGE_1[3]. Nakano and McCurdy[4] also considered that a secondary fall of cardiac output following the initial increase observed after PGE_1 infusion was attributed to a diminished venous return as a consequence of a dilatation of capacitance vessels. However, there has been no study to compare the venodilator effect of PGE_1 with TNG. We used TNG as an agent for comparison, because TNG has been used as a hypotensive drug during anesthesia and the venodilating action of TNG is widely known[13,14]. In the present study, it was demonstrated that the venodilator effect was more potent by TNG than PGE_1 at the doses to produce a comparable level of deep hypotension, although the venodilator effect was similar at the doses to produce moderate hypotension.

The dose of PGE_1 to produce mean arterial pressure of 50 mmHg was approximately two-fold as compared with that to produce 70 mmHg. There were no significant change in MCFP at mean arterial pressure of 50 and 70 mmHg with PGE_1. Thus, the effect of PGE_1 on arterial pressure seems to be dose-dependent, but that on MCFP is not in dose-dependent fashion. In contrast, TNG decreased MCFP in dose-dependet fashion. Therefore, it is suggested that the decrease in arterial pressure from moderate to deep levels by PGE_1 may result primarily from dilatation of resistance vessels but the decrease by TNG may be due to dilatation of both resistance and capacitance vessels.

As arterial blood pressure decreases, arterial baroreceptor reflex is elicited, leading to an increase in sympathetic nerve discharges and a release of catecholamine. The reflex-induced sym-

pathetic augmentation can alter the effect of vasodilators on venous capacitance. In addition, it is reported that PGE_1 itself modulates the baroreceptor reflex[15]. Since the present study was undertaken in baroreceptor intact animals and under ketamine anesthesia which has been shown to maintain arterial baroreceptor reflex[8], it is likely that the result may differ if anesthesia was different and baroreceptor reflex was depressed.

In this study, we found that in ketamine-anesthetized rats PGE_1 produced an increase in venous capacitance to a similar degree by TNG at moderate hypotension, and the increase was less at deep hypotension. The less venodilatation may contribute to better maintenance of venous return and thus cardiac output with PGE_1-induced hypotension.

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