Differential microcirculation dynamics during deliberate hypotension induced by nicardipine, PGE₁ and trimethaphan in rat mesentery

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The purpose of this study was to determine the arteriolar changes that occur in the microcirculation during deliberate hypotension and general anaesthesia and whether the changes depended on the drugs used to induce vasodilatation or on the degree of systemic blood pressure decrease. Changes in the vessel diameter and the velocity of red blood cells in the mesenteric arterioles of pentobarbitone-anaesthetized rats were observed using continuous biomicroscopy. Observations were made during deliberate moderate (BP 70 mmHg) or deep (BP 50 mmHg) hypotension by titration with nicardipine, prostaglandin E₁ (PGE₁) or trimethaphan. Then, the responses of arterioles to locally applied noradrenaline (1 µg) were assessed. During moderate hypotension PGE₁ decreased the arteriole diameter slightly (16.7 ± 1.6 to 14.7 ± 1.3 µm, $P < 0.05$), reduced the velocity of red blood cells considerably (1.98 ± 0.2 to 1.03 ± 0.4 mm·sec⁻¹, $P < 0.05$) and increased the contractile response of arterioles to locally-applied noradrenaline. Nicardipine and trimethaphan had no effect on the microcirculation. During deep hypotension, all drugs decreased the diameter of the arterioles slightly but reduced the velocity of red blood cells considerably ($P < 0.05$). We conclude that the major change in the mesenteric arterioles during deliberate

hypotension during general anaesthesia is a decrease in red blood cell velocity that is dependent on the drug used and the degree of blood pressure decrease.

Cette étude vise à déterminer les changements artériolaires qui surviennent au niveau de la microcirculation pendant l'hypotension délibérée; si ces changements dépendent de l'agent utilisé pour induire la vasodilatation ou s'ils dépendent du degré d'abaissement de la pression systémique. Les changements de diamètre vasculaire et la vélocité des hématies ont été observés chez des rats au niveau des artérioles mésentériques à l'aide de la biomicroscopie continue. Les observations ont été effectuées pendant l'hypotension délibérée modérée (PA 70 mmHg) et profonde (PA 50 mmHg) produite avec de la nicardipine, de la prostaglandine E₁ (PGE₁) ou du triméthaphan. Par la suite, la réponse des artérioles à l'application locale d'adrénaline (1 µg) a été évaluée. Pendant l'hypotension modérée, la PGE₁ raccourcit légèrement le diamètre artériolaire ($16,7 \pm 1,6$ à $14,7 \pm 1,3$ µm, $P < 0,005$) et augmente la contractilité des artérioles lors de l'application locale d'adrénaline. La nicardipine et le triméthaphan n'ont pas d'effet sur la microcirculation. Pendant l'hypotension profonde, tous les agents utilisés diminuent légèrement le diamètre artériolaire mais réduisent aussi la vélocité des hématies ($P < 0,05$). Les auteurs concluent que le changement le plus important produit au niveau artériolaire mésentérique pendant l'hypotension sous l'anesthésie générale consiste en une diminution de la vélocité des hématies et dépend de la drogue utilisée et du niveau de la pression artérielle.

Key words

ANAESTHETICS, INTRAVENOUS: pentobarbitone;
ARTERIOLES, MICROCIRCULATION: mesentery;
DELIBERATE HYPOTENSION: nicardipine; prostaglandin E₁;
trimethaphan;
TECHNIQUES: biomicroscopy; high-speed video.

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Deliberate hypotension, as an adjunct to general anaesthesia, provides a relatively bloodless surgical field, decreases operative blood loss, and diminishes the need for and the dangers associated with blood transfusion.^{1,2} Many laboratory or clinical studies have examined the haemodynamic and the hormonal changes during deliberate hypotension caused by several vasodilators. However, there is little information concerning microcircula-

tory changes that may affect oxygen delivery to tissues during deliberate hypotension.

As nicardipine (dihydropyridine calcium channel blocker),^{3,4} PGE₁ (prostaglandin E₁)⁵ and trimethaphan (ganglionic blocker)^{6,7} are potent vasoactive agents with predictable, brief and easily reversible effects, they are used frequently during anaesthesia. Nicardipine and PGE₁ have protective actions against tissue ischaemia,⁸⁻¹⁰ and, thus, may be suitable to produce deliberate hypotension.

As nicardipine, PGE₁ and trimethaphan have different vasodilating mechanisms and sites of action, each may have a different effect on the distribution of cardiac output.¹¹ Therefore, changes of regional blood flow may occur during deliberate hypotension that is dependent on the drugs used and/or on the degree of systemic blood pressure decrease.

This study was designed to compare nicardipine-, PGE₁-, and trimethaphan-induced hypotension. In order to investigate the changes that may occur on arterioles that affect oxygen delivery during deliberate hypotension and whether the changes depend on drugs used and/or the degree of systemic blood pressure decrease, changes in the diameters of and red blood cell velocity in rat mesenteric arterioles were observed using continuous biomicroscopy^{10,12-14} during deliberate hypotension. Then, the effects of locally applied noradrenaline to the arterioles were assessed.

Methods

Thirty male Wistar rats, weighing about 170 g, were used as experimental animals. During anaesthesia produced with pentobarbitone (30 mg · kg⁻¹ *im*), a patent airway was established and maintained with tracheostomy and spontaneous ventilation. The internal carotid artery and femoral vein were cannulated to measure arterial pressure and heart rate, and as a route for infusion, respectively. Warm physiological saline, mixed with pentobarbitone 3.4 mg · ml⁻¹ for anaesthetic maintenance was infused at a rate of 2.0 ml · kg⁻¹ · hr⁻¹. The rectal temperature was kept stable by the infusion and by covering the rat with aluminium foil.

For the experiment, the rat was placed in the lateral position on a stage (equipped with a perfusion device) remoulded for biomicroscopy and after laparotomy the mesentery was spread over an optically clear lucid block. The intestine was covered with wet cotton, and was continuously superfused with buffered Ringer's solution at 37°C and at a rate of 100 ml · hr⁻¹. The Ringer's solution contained gelatin (10 g · L⁻¹) and the pH was adjusted to 7.4 with sodium bicarbonate. This preparation maintains stable conditions for about 150 min without microcirculatory changes.¹⁰ A video image of the mesenteric

microcirculation was projected on a television monitor and recorded on a high-speed video system (HSV400: nacinc. Tokyo, Japan). This system produces 400 frames per second and can reproduce the shapes of red blood cells in the arterioles. The arteriole diameter and red blood cell velocity were analyzed from slow-motion pictures (accuracy: <0.1 μm, reproducibility: <0.01 μm).^{10,14}

After control observation, the microcirculatory changes were first observed during moderate hypotension at a mean arterial pressure of approximately 70 mmHg, and then during deep hypotension at a mean arterial pressure of approximately 50 mmHg induced by nicardipine, PGE₁ or trimethaphan. Ten rats were used in each group and only one drug, diluted in physiological saline was infused in each rat. The microcirculatory observations were made after each decrease in blood pressure, that was maintained stable for >20 min. Doses of nicardipine were 5.7 ± 2.5 and 11.2 ± 4.0 μg · kg · min⁻¹, of PGE₁ were 5.3 ± 2.0 and 10.7 ± 2.1 μg · kg · min⁻¹ and of trimethaphan were 60 ± 13 and 117 ± 13 μg · kg · min⁻¹ to produce mean arterial pressures of 70 mmHg and 50 mmHg, respectively. Total infusion volumes were <4.0 ml · kg · hr⁻¹ and were the same for each rat receiving each drug. Noradrenaline (1 μg in 0.1 ml 37°C Ringer's solution) was applied locally during control and moderate hypotension. The solution was dripped over the arteriole using a glass micropipette alongside the biomicroscope. All experimental procedures for each rat were completed within 120 min after spreading the mesentery.

The results of experiments were expressed as mean ± SD. Group differences in the absolute values and group differences in the numbers were analyzed by ANOVA-factorial (Scheffe F-test) and contingency table analysis, respectively, at a significance level of 0.05.

Results

Mean arterial pressure and heart rate

Control mean arterial pressures and heart rates did not differ among the three groups. The drugs were infused until the desired hypotension was achieved at the mean arterial pressure of approximately 70 mmHg or 50 mmHg, so that the mean arterial pressure during hypotension was not different among groups. Heart rates did not change with PGE₁ and trimethaphan, but after nicardipine it increased ($P < 0.05$) during both moderate and deep hypotension (Table I).

Diameters of the arterioles

Prostaglandin E₁ decreased the arteriole diameters during both moderate and deep hypotension ($P < 0.05$) (Figure 1). Trimethaphan decreased the diameters only during

TABLE I MBP and HR during control, moderate and deep hypotension induced by nicardipine, PGE₁ or trimethaphan

	mBP (mmHg)	HR (beats · min ⁻¹)
Control		
- Nicardipine	106.4 ± 14.2	337.4 ± 22.3
- PGE ₁	102.8 ± 8.5	343.4 ± 49.9
- Trimethaphan	106.6 ± 11.8	338.2 ± 35.7
Moderate hypotension		
- Nicardipine	71.2 ± 2.1	380.4 ± 11.7 ^a
- PGE ₁	70.7 ± 1.9	344.8 ± 47.1
- Trimethaphan	72.0 ± 1.0	312.8 ± 27.5
Deep hypotension		
- Nicardipine	54.0 ± 1.1	377.4 ± 16.2 ^a
- PGE ₁	50.1 ± 2.7	332.8 ± 34.8
- Trimethaphan	53.4 ± 0.9	310.8 ± 17.1

Values are mean ± SD of ten experiments. Moderate hypotension: mean arterial pressure of approximately 70 mmHg, deep hypotension: mean arterial pressure of approximately 50 mmHg, mBP: mean blood pressure, HR: heart rate. (a) Different from control ($P < 0.05$).

deep hypotension ($P < 0.05$) whilst no decrease was observed with nicardipine did not occur the decrease ($P > NS$).

Velocity of red blood cells

Red blood cells velocity decreased in a pressure-dependent fashion (Figure 2). During moderate hypotension PGE₁ decreased red blood cell velocity by about half (1.98 ± 0.24 to 1.03 ± 0.44 mm · sec⁻¹, $P < 0.05$), but no changes were seen with nicardipine or trimethaphan. During deep hypotension the velocity decreased considerably after each day but velocity was reduced less with nicardipine than with PGE₁ ($P < 0.05$).

Responses of arterioles to noradrenaline (Table II)

Preliminary dose-ranging studies had demonstrated that locally applied 1 µg noradrenaline decreased the arteriole diameters in the control state, by about 70%. Similar changes were seen during moderate hypotension with all drugs. The contraction continued for longer during PGE₁-than during nicardipine-induced hypotension. During moderate hypotension induced by any drug the abnormality of arteriole red blood cell flow did not change (Table II).

After deep hypotension, analysis of arterial blood gas was carried out ($n = 4$ on each drug). The pH, PaCO₂, PaO₂ and base excess were not different among the nicardipine, PGE₁ and trimethaphan groups. Hypoxaemia, and hyper- or hypocarbia did not occur. Microcirculatory abnormalities such as stasis, plasma skimming, sludge, dysoria, rolling phenomenon of white blood cells or flying thrombus were not observed in the 120 min of the study.

FIGURE 1 Arteriole diameters during deliberate hypotension induced by nicardipine (NIC), prostaglandin E₁ (PGE₁) or trimethaphan (TMP). Values are mean ± SD of ten experiments respectively. Moderate hypotension: mean arterial pressure of approximately 70 mmHg, Deep hypotension: mean arterial pressure of approximately 50 mmHg. (a) Different from control ($P < 0.05$).

FIGURE 2 Red blood cell velocity in arterioles during deliberate hypotension induced by nicardipine (NIC), prostaglandin E₁ (PGE₁) or trimethaphan (TMP). Values are mean ± SD of ten experiments respectively. Moderate hypotension: mean arterial pressure of approximately 50 mmHg. (a) Different from control ($P < 0.05$). (b) Different from PGE₁ ($P < 0.05$).

Discussion

Nicardipine, PGE₁ and trimethaphan are potent vasodilating agents. Each acts via a different mechanism, and causes a different redistribution of cardiac output.¹¹ Therefore, regional blood flow and microcirculatory reactions to catecholamines may vary amongst them and with the degree of induced systemic hypotension. We used the rat mesentery to investigate these possibilities. The mes-

TABLE II Arteriole changes by locally applied noradrenaline during moderate hypotension

	Control	Nicardipine	PGE ₁	Trimethaphan
Changes of diameters (%) ^b	71.5 ± 21.3	56.3 ± 19.0	62.8 ± 24.7	62.7 ± 10.0
Time by maximal contraction (sec)	19.4 ± 7.7	11.7 ± 3.0	9.7 ± 7.2	17.5 ± 8.0
Time by recovery (sec)	81.6 ± 8.5	77.5 ± 4.4	90.0 ± 13.1 ^a	80.1 ± 8.5
Change of RBCs flow up (no.) ^c				
- No change	7	6	3	5
- Slow down	2	2	4	3
- Stop	1	2	3	2

Values are mean ± SD of ten experiments. Moderate hypotension: mean arterial pressure of approximately 70 mmHg, RBCs: red blood cells. (a) Different from nicardipine ($P < 0.05$). (b) Diameters of the arterioles before administration of noradrenaline were taken as 100%. (c) No differences among groups.

entry of rat has few parenchymal cells that affect regional blood flow and has some visible vessels, which make it useful for microcirculation studies.^{10,12,14}

We showed that several changes of the microcirculation such as a decrease in the diameter of the arterioles, decrease in the velocity of red blood cells and hypersensitivity to locally applied noradrenaline occurred during hypotension. Some differences were observed among the three drugs and among the different degrees of systemic hypotension.

During moderate hypotension, nicardipine and trimethaphan maintained the velocity of red blood cells similar to control, but PGE₁ decreased it. Cardiac output and/or distribution of blood flow to the mesenteric vascular bed may be maintained by nicardipine¹⁵ and trimethaphan¹⁶ but is reduced by PGE₁^{17,18} during moderate hypotension. Nicardipine increased heart rate, which might have been responsible for the maintenance of mesenteric blood flow. The velocity of red blood cells was not maintained during deep hypotension with nicardipine and trimethaphan. Thus, the velocity of red blood cells depends both on the vasodilating drug used and on the degree of mean blood pressure decrease.

However, not only nicardipine and PGE₁ but also trimethaphan relax vascular smooth muscle.¹⁹ All drugs slightly decreased the diameter of the arterioles in this study that may be the result of a decrease of blood flow.²⁰

It has been demonstrated that PGE₁ potentiates the vasoconstrictor responses to nerve stimulation and to noradrenaline in rat mesenteric arteries but not to noradrenaline in the cremaster muscle.^{13,21} Our results showed that PGE₁ extended the contractile response time induced by noradrenaline more than did nicardipine. This suggests sympathetic nerve stimulation during deliberate hypotension induced by PGE₁ may decrease regional blood flow. Various local effects of the three drugs such as direct vasodilatation and inhibition of platelet aggregation also differ.^{4,13,19,22} We could not confirm these effects as we applied the drugs systemically. The different

responses of arterioles among drugs to locally applied noradrenaline should be affected by their different systemic and local effects, and might affect the different distribution of blood flow induced by each drug.

Though our results showed that trimethaphan maintained blood flow in the mesenteric vascular bed during moderate induced hypotension, trimethaphan also decreased blood flow to the mesentery during mean arterial pressure 80 mmHg in dogs anaesthetized with pentobarbitone.²³ Thus, the effects of vasodilating drugs may change depending on the duration of hypotension, methods of anaesthesia, tissues or animals, and so it is very difficult to estimate the effects universally by only one experiment. However, we demonstrated clearly that under continuous biomicroscopy the change in the arterioles during deliberate hypotension and general anaesthesia is mainly the decrease in red blood cell velocity and depends on the vasodilating drug used and on the degree of hypotension.

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