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Effect of Prostaglandin E_1 on Cutaneous Microcirculation of Flap or Replantation

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— Abstract —

Recently prostaglandin E_1(PGE_1) has been shown to ensure flap survival by producing vasodilation of the peripheral vessels and platelet disaggreation. However, direct observation and detailed quantitative studies of the effects of PGE_1 on the cutaneous microcirculation have not been reported. In the present study, we investigated cutaneous microcirculatory changes in the rabbit ear chamber (REC) with an intravital microscope following intravenous administration of PGE_1. The results obtained in this study indicate that PGE_1 administered intravenously at a rate of 200ng/kg/min might act directly on the vessels and cause dilatation of metarterioles and capillaries without affecting vasomotion and systemic blood pressure.

Clinically in order to evaluate the effect of an intravenous administration of PGE_1 on the cutaneous microcirculation, cutaneous blood flow, skin temperature and transcutaneous Po_2 in the pedicle or free flap of operated patients were evaluated by the combination of several measurements following the administration of PGE_1.

The present study suggests that improvement of cutaneous microcirculation by PGE_1 may enhance the survival rate of flap or replantation.

Both vessel arterial ischemia and venous congestion are main factors of tissue necrosis in the flap surgery. Vasodilatory or antithrombotic agents have been used in salvage of flap necrosis. However, the therapeutic effects of those drugs are still not well elucidated.

Recently prostaglandin E_1(PGE_1) has been shown to ensure flap survival by producing vasodilatation of the peripheral vessels and platelet disaggregation [1-3]. Emerson and sykes[4] have obtained significant improvement in the flap survival in the rat using PGI_2. Suzuki et al.[5] have reported prolonged flap survival length by using PGE_1 in the rabbit and concluded that PGE_1 improved the microcircuration in the flap. However, direct observation and detailed quantitative studies of the effects of PGE_1 on the cutaneous microcirculation have not been reported. In the present study, we investigated microcirculatory changes in the rabbit ear chamber [6,7] with an intravital microscope following intravenous administration of PGE_1.

MATERIALS AND METHODS

1. Rabbit ear chamber(REC)

This REC is a transparent round-table chamber consisting of three parts : a basal disk having an observing round-table and three pillars for supporting the chamber, a mica cover-slip, and a holding ring(Fig. 1, 2).

The REC[6, 7] is implanted in the distal portion of ear adjacent to the central vessels. Four holes are made simultaneously using a specially devised steel punch. Both skins surrounding the central hole are removed by using an artificially blunted surgical knife and small forceps preserving blood vessels on the cartilage. The cover-slip and round-table are installed and fixed with dental resin.

Six weeks following the implantation, the microvascular network of the vessels had completely matured in the chamber. The microvascular network could be easily observed and arterioles, metarterioles, capillaries, and venules clearly distinguished under the microscope.

Experimental studies were performed using this model. Vital-microscopic observation was conducted by using a binocular microscope(Nikon, Japan) equipped with camera (Nikon, Japan) and a TV monitor (Toshiba, Japan). Microcirculatory changes were recorded and played-back with the VTR for repeated the observation (Fig. 3).

2. Experiment

Twenty two Adult male white Japanese domestic rabbits weighing 3.0-3.2kg were

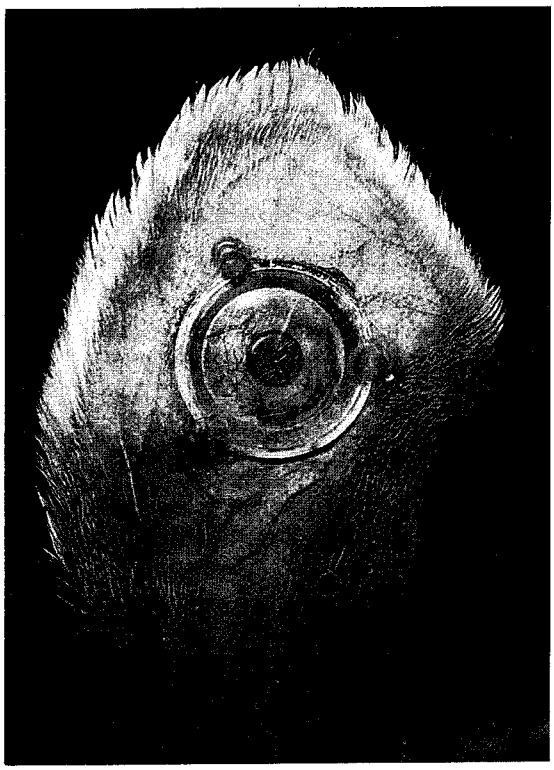

Fig. 1. Six week following implantation

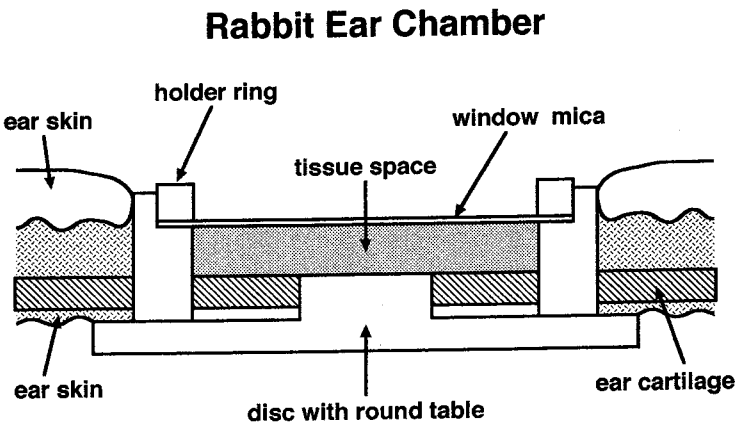

Fig. 2. The space between round table and window mica has a diameter of 6.4mm and a height of 50μm

used in these experiments. Because the blood pressure was stable after administration of PGE_1 at a rate of less than 200ng/kg/min but dropped by 10mm Hg at a rate of 500ng/kg/min, it was decided to use PGE_1 at a rate of either 50 or 200ng/kg/min.

The conscious animal was placed in a standard rabbit box(metal drum). A catheter was introduced into the vein of the opposite ear lobe as to that which drugs were applied. The systemic blood pressure was also monitored at the central artery of the ear lobe. PGE_1 was dissolved in the physiological saline solution at the concentration of 5000ng/ml and continuously infused at a rate of either 50 or 200ng/kg/min to the animals through the catheter using an intravenous drip pump. In the control group, physiological saline solution was infused at a rate of 10ml/kg/hr. The microcirculation in the REC was recorded and the diameter of vessels as visualized on the TV monitor was measured with a slide caliper. The diameter of arteriole(30-50μm), metarteriole(15-30μm), venule(20-50μm) before and after PGE_1 administration was measured every ten minutes(Fig. 4).

RESULTS

The cutaneous microcirculation showed spon-

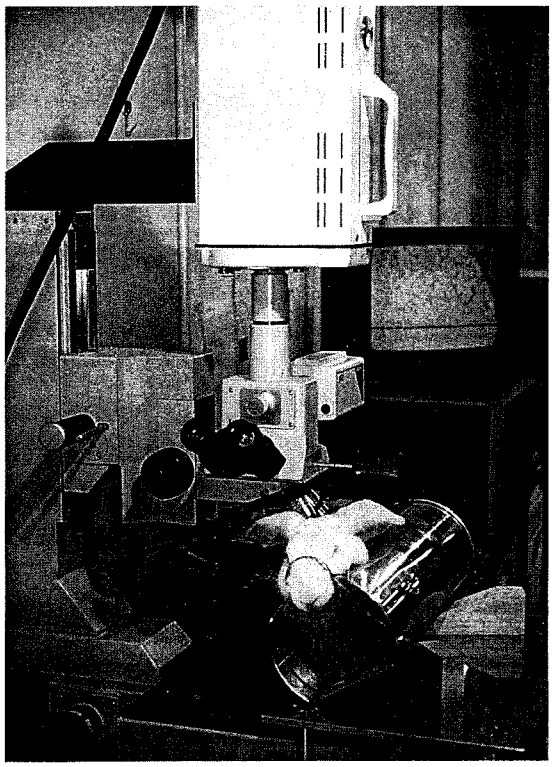

Fig. 3. The Vital-microscopic equipment for observation

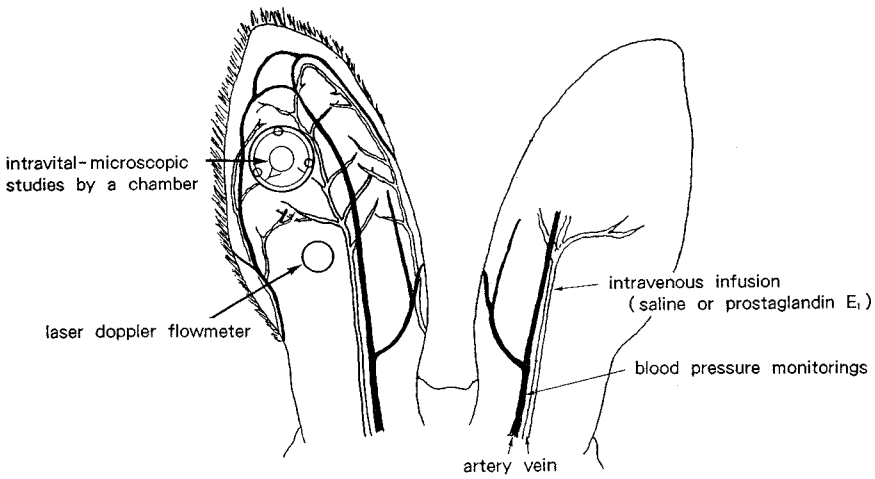

Fig. 4. Drug administration method

taneously rhythmic changes consisting of both an increase and decrease in the diameter of vessels as well as the volume and velocity of blood flow, this suggesting the vasomotion.

Vessel diameter was measured at the full dilation phase of vasomotion before, during and after PGE_1 administration. Before PGE_1 administration, physiological saline solution was infused through the catheter for 30 minutes.

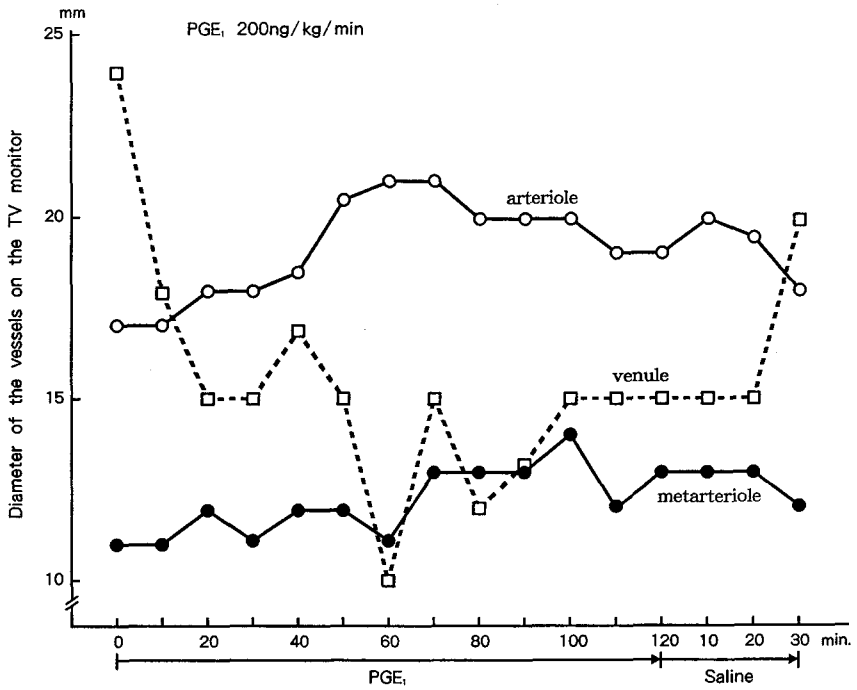

Fig. 5. Typical time courses of the diameter change produced by PGE_1 (200ng/kg/min) in various vessels

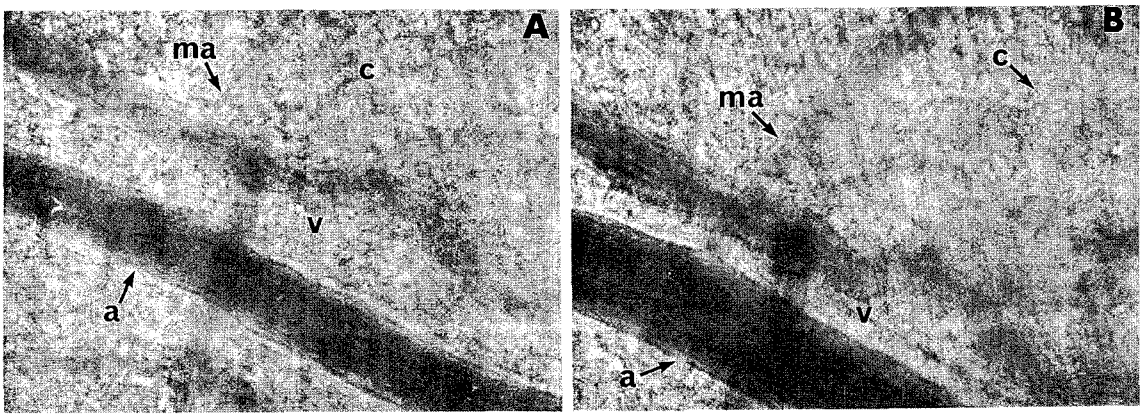

Fig. 6. Representive photograph

A. Before administration of PGE_1 (200ng/kg/min)

B. After administration of PGE_1 (200ng/kg/min)

a : arteriole, ma : metarteriole, c : capillary, v : venule

Typical time courses of the diameter change produced by PGE_1 (200ng/kg/min) in various vessels are presented in Fig. 5, 6. In these experiments, PGE_1 induced appreciable vasodilatation not only of arterioles and metarterioles but also of capillaries and increased the velocity of blood flow in the capillaries and venules. Successive measurements of metarteriolar diameter for 2 hours of continuous PGE_1 (200ng/kg/min) infusion are illustrated in Fig. 7. PGE_1 produced statistically significant dilatation of metarterioles throughout the observation period whereas physiological saline solution did not affect the microcirculatory state. Changes in arteriolar diameter were also shown (Fig. 8). The dilatation of arterioles was observed but the vasodilator responses to equal dose of PGE_1 differed from one animal to another. However, in the venules, dilatation of vessels were not observed as had been expected. The diameter of venules slightly decreased, but there was no statistical significant difference (Fig. 9).

PGE_1 at low dose of 50ng/kg/min did not influence the microcirculatory vasculature in REC. PGE_1 also augumented the amplitude of vasomotion. However, frequency characteristics and phasic proportion of vasomotion were not influenced.

PATIENTS, MATERIALS AND METHODS

In order to evaluate the clinical effects of

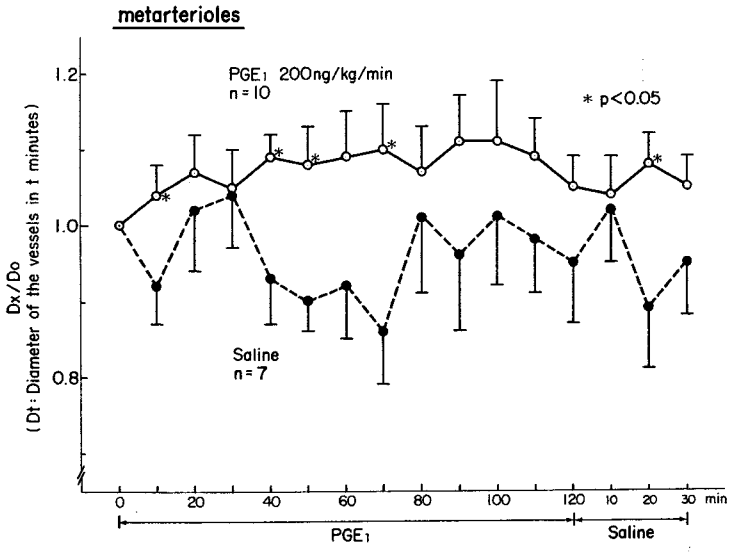

Fig. 7. Successive measurements of metarteriolar diameter following administration of PGE_1 (200ng/kg/min)

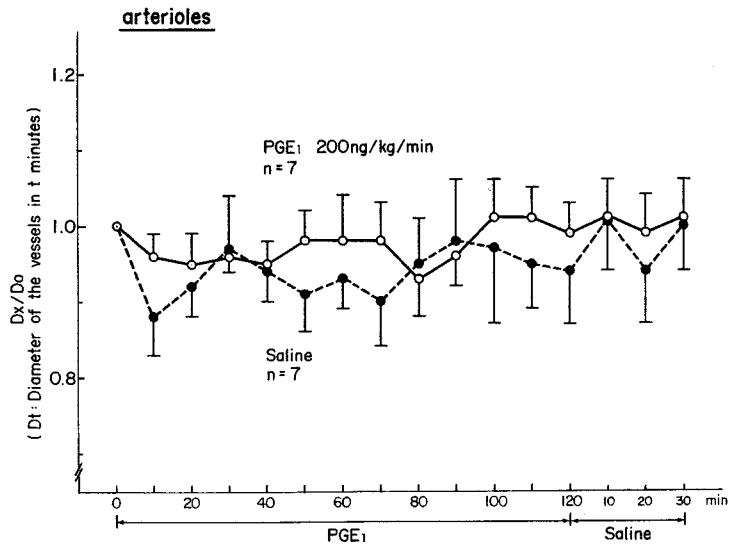

Fig. 8. Successive measurements of arteriolar diameter following administration of PGE_1 (200ng/kg/min)

an intravenous infusion of PGE_1 (10ng/kg/min, 2 hours) in three patients after flap (free or pedicle) transfer, we applied laser Doppler velocimetry (ALF, Advance Co., Tokyo Japan) at proximal, middle, distal area of flap and Cutaneous Po_2, Pco_2 Monitor(Koken Medical Co., Tokyo Japan) at the distal area of flap.

Case 1. This patient was a 69 year old man with a contracted burn scar on the right palm. A groin flap was transferred to the lesion with a skin pedicle. Postoperative course was uneventful(Fig. 10).

Case 2. This patient was a 34 year old woman with a skin defect on the right foot due to a road traffic accident. The ulcer was covered with a free rectus abdominis musculocutaneous flap. Postoperative course was uneventful(Fig. 11).

Case 3. This patient was a 73 year old woman with a chronic radiation ulcer on the chest. The irradiated skin and costal cartilage were removed and the defect was covered with a rectus abdominis musculocutaneous flap. Postoperative course was uneventful(Fig. 12).

Systematic blood pressure was stable after administration of PGE_1 at a rate of 10ng/kg/min. The PGE_1 infusion increased the value of $TcPo_2$ and decreased the value of $TcPco_2$ at the distal area of the flap. The raised blood flow was seen at the center or distal area of the flap. The effect of PGE_1 began at the end of the infusion and were continued thereafter for a least 3 hours.

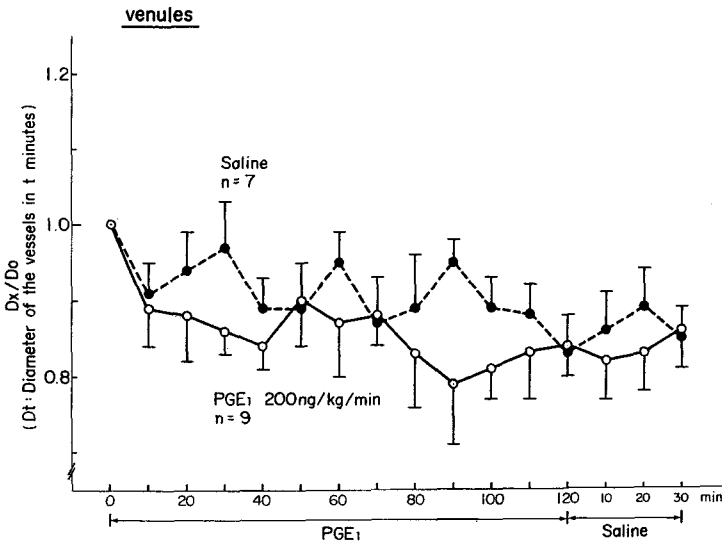

Fig. 9. Successive measurements of venular diameter following administration of PGE_1 (200ng/kg/min)

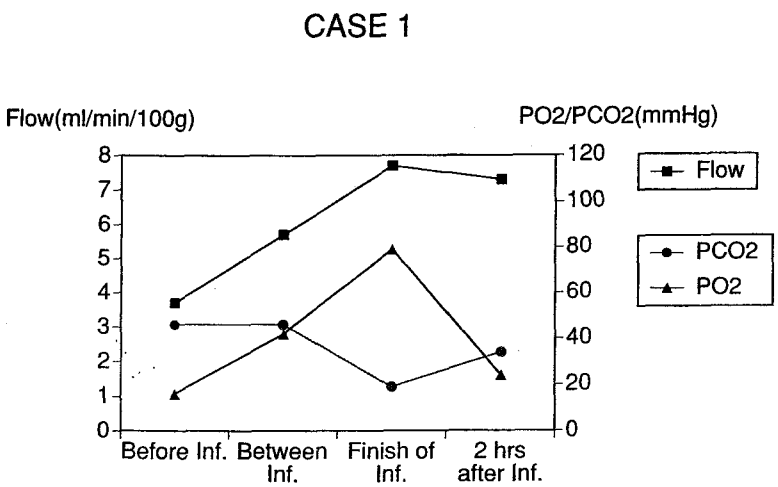

Fig. 10. The effects of PGE_1 (10ng/kg/min) in operated patient. A pedicle groin flap was transfered.

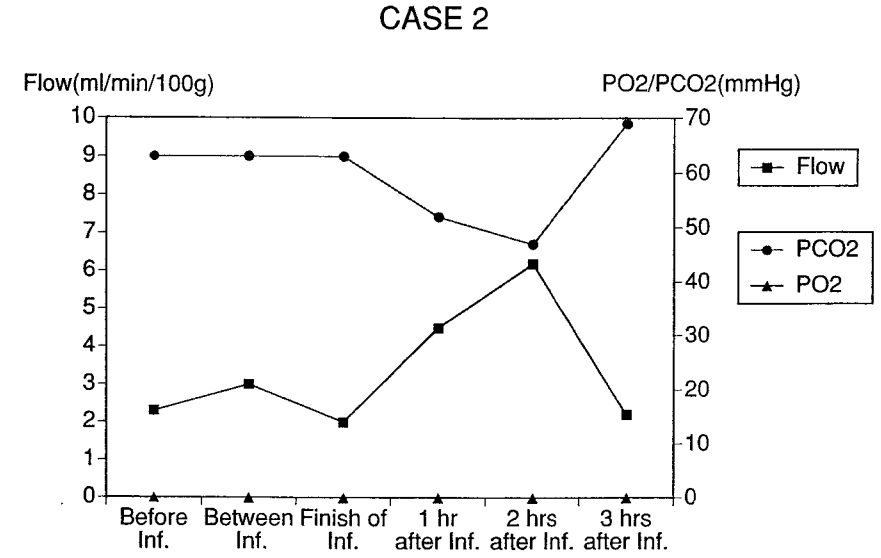

Fig. 11. The effects of PGE_1 (10ng/kg/min) in operated patient. A free rectus abdominis flap was transfered.

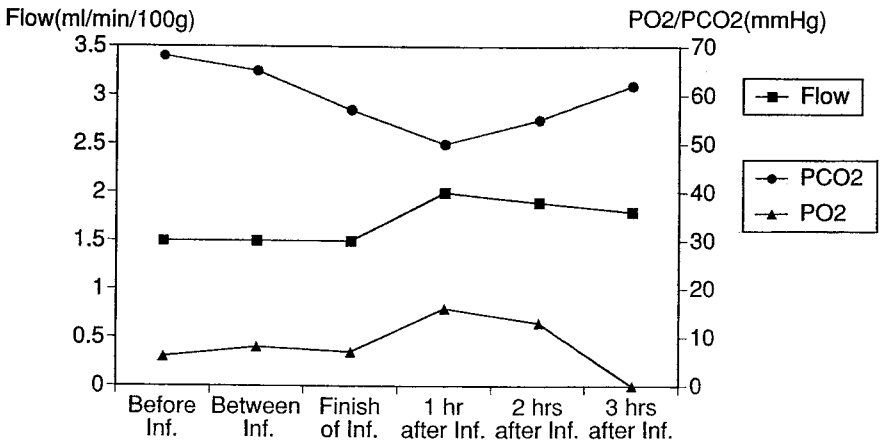

Fig. 12. The effects of PGE_1 (10ng/kg/min) in operated patient. A pedicle rectus abdominis flap was transfered.

DISCUSSION

There is no argument about the effects of Prostglandins on peripheral vascular disease[1-3]. Emerson and Syker[4] have demonstrated that intra-peritoneal administered PGI_2 can significantly increase flap survival in the rat. Recently, Suzuki et al.[5] have reported that intravenous administrated PGE_1 could also increase the blood flow and enhance the flap survival in the rabbit. On the contrary, Forrest and Pang[8] reported that intravenous infusion

of PGE_1 was not effective in augmentation of distal perfusion or length of skin viability in porcine skin flaps. In those flap experiments, the effects of vasoactive drugs were mainly estimated by dye distance, surviving flap length and radioactive methods. However, dye distance or surviving length in the control animals may vary with anesthesia. With those indirect methods to estimate blood flow, it is difficult to detect which microvasculature on the flap could be influenced by the administration of a vasoactive drug.

In the present study, cutaneous microcirculation within the REC was observed under vital-microscopy and the microcirculatory events were visualized with a microscope TV system. PGE_1 administered intravenously at a rate of 50ng/kg/min did not influence the microcirculatory vasculature in REC without affecting systematic blood pressure. This may be due to the partial destruction of PGE_1 by a single passage through the lung[9, 10]. PGE_1 administered intravenously at a rate of 200ng/kg/min produced dilatation of metarterioles and increased capillary flow without affecting systemic blood pressure. This helps to confirm that 200ng/kg/min was sufficient to affect the cutaneous microcirculation. The diameter of venules were not changed or were slightly decreased, but there was no congestion by compensation for increased velocity of venulous blood flow. These findings indicate that the intravenous administration of PGE_1 may cause a physiologically acceptable vasodilation accompained by vasomotion which would facilitate the oxygen diffusion. The present study suggests that improvement of cutaneous microcirculation by PGE_1 may enhance the survival rate of flap or replantation.

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