Local Delivery Infusion Pressure is a Key Determinant of Vascular Damage and Intimal Thickening

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Local drug delivery following percutaneous transluminal coronary angioplasty (PTCA) may prevent restenosis by achieving higher local tissue concentrations of drugs than systemic administration. However, it remains unknown whether vascular damage and the ensuing intimal thickening is associated with the degree of infusion pressure achieved by local delivery. Therefore, local delivery of normal saline was performed using a channeled balloon catheter (Transport™) to the rabbit iliac artery with different infusion pressures of 0, 3, 5, 7, and 12 atm (n=4 for each). The extent of vascular damage and the development of intimal thickening were determined histopathologically 14 days after the procedure. In 10 additional rabbits, to assess the degree of vessel penetration, local delivery of indocyanine green dye solution was performed in a similar fashion. After 1 h, the green dye penetrated deeply at the higher infusion pressures of 7 and 12 atm. The incidence of internal elastic lamina laceration and occurrence of total occlusion as a result of thrombus formation demonstrated an increase proportional to the degree of local infusion pressure. When the vascular injury score in each arterial section was plotted against the infusion pressure, a significant relation was observed ($r=0.717$, $p<0.0001$). At 0, 3, 5, 7, and 12 atm, neointimal areas of 0.160 ± 0.005 , 0.163 ± 0.008 , 0.189 ± 0.017 , 0.260 ± 0.027 , and 0.329 ± 0.033 mm², respectively, were observed. Smooth muscle cell (SMC) proliferative activity also increased in proportion to the local infusion pressure. We have demonstrated for the first time that local delivery infusion pressure itself is related to the severity of vascular damage, resulting in the development of intimal thickening and an associated increase in SMC proliferative activity. Therefore, we suggest that infusion pressure is a key determinant of vascular injury during local drug delivery, with lower pressure causing the least neointimal response. (*Jpn Circ J* 1998; 62: 299–304)

Key Words: Local delivery; Pressure; Injury; Neointima; Channeled balloon catheter

Percutaneous transluminal coronary angioplasty (PTCA) is a potent therapeutic strategy for patients with coronary artery stenosis. However, restenosis remains a major long-term problem in 30–40% of all patients up to 6 months after successful angioplasty^{1–4}. Post-angioplastic restenosis is characterized by fibrocellular intimal thickening, which consists largely of proliferating smooth muscle cells (SMCs) and extracellular matrix in human pathologic studies^{5–8}. This excessive neointimal response may be triggered by platelet aggregation and growth factor release following vascular injury^{9–12}. Although several studies in experimental animal models have reported that therapeutic agents have reduced these vascular responses and decreased the restenosis rate, no pharmacologic therapy has been demonstrated to be effective in clinical trials^{13–16}. Local drug delivery has been proposed to achieve higher local tissue concentrations than those obtainable by systemic administration, thereby avoiding serious side-effects^{17,18}. However, high delivery pressures and large volumes of infusates may cause severe vascular damage and augment intimal thickening¹⁹. Previous investigations examining this problem using the porous balloon^{19,20} or double-

balloon²¹ technique have demonstrated a positive correlation between the infusion pressure, infusate volume, and the degree of vascular damage. However, it has been difficult to distinguish local delivery pressure from infusion pressure because the infusion pressure equals the angioplasty dilating pressure in these balloons. Recently, a new local delivery catheter (Transport™ dilation – infusion catheter) that is able to separate the effects of pure pressure from those of the phenomenon of stretch-elicited pressure has been developed²².

Accordingly, using this infusion catheter in a rabbit iliac injury, we investigated whether local delivery infusion pressure is related to the severity of vascular damage, with the subsequent vascular response consisting of thrombus formation and intimal thickening associated with an increase in SMC proliferative activity.

Methods

Local Delivery Infusion Catheter

The local delivery infusion catheter used in this study was a 3.0-mm Transport™ coronary dilation – infusion catheter (CardioVascular Dynamics, Irvine, CA, USA) (Fig 1). This infusion catheter is a triple-lumen catheter with dual balloons. One lumen each is used for inflation of the inner angioplasty balloon, infusion of therapeutic agents through the outer balloon, and for passing the guide wire through the central lumen of the catheter shaft. The balloons are located one within the other. The inner high-pressure angioplasty balloon is fed by a

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Fig 1. Top: channeled balloon (Transport™) that is leaking solution through the microholes. Bottom: scheme depicting the structure of dual balloons, the inner angioplasty balloon located within the outer infusion balloon. The outer balloon is designed to be porous for 10 mm of its middle section with 48 small surface "channels" of 250 μ m diameter circumferentially.

separate inflation port and the outer balloon is designed to be porous for 10 mm of its middle section with 48 small surface "channels" of 250 μ m diameter circumferentially. Thus, a distinctive feature of this channeled balloon catheter is that local delivery infusion can be achieved using a separate port during simultaneous angioplasty.

Local Delivery at Different Degrees of Infusion Pressure

A total of 30 male New Zealand White rabbits, weighing 3.0–3.5 kg, were used in this study. All surgical procedures were performed by 2 skilled operators. Rabbits were positioned in the supine position and anesthetized with an intravenous injection of pentobarbital (30 mg/kg) via the marginal ear vein. A 1.5-cm skin incision was made at the right femoral region after local anesthesia with subcutaneous injection of 2% xylocaine (0.5 ml). After the right femoral artery had been carefully exposed, a Fogarty 2F balloon catheter (Baxter Healthcare, McGaw Park, IL, USA) was inserted backward into the abdominal aorta through the right common iliac artery by cut-down. The inflated balloon filled with 0.2 ml of air was pulled back 3 times from the aortic bifurcation to the right common iliac artery. After deflation and removal of the balloon catheter, under fluoroscopic guidance, a 0.014-inch guide wire was inserted into the abdominal aorta, and the Transport™ channeled balloon catheter was then introduced over the guide wire and advanced to the injured common iliac artery. The central marker of this catheter was placed 1.5 cm distal to the aortic bifurcation. The inner angioplasty balloon was inflated and maintained at a dilating pressure of 3 atm for 1 min using a hand inflator. Animals were randomly assigned to 5 different infusion pressure groups. Local delivery of 3 ml of normal saline was performed twice at different infusion pressures: 0 atm (dilating angioplasty balloon only), 3 atm, 5 atm, 7 atm, and 12 atm. Each delivery site was approximately 3 cm distal to the initial site. After local delivery, the Transport™ channeled balloon catheter was removed, the femoral artery was ligated, and the incision was then closed. No anticoagulant or antiplatelet therapy was given throughout the experiments.

After surgery, rabbits were returned to their cages and fed with standard rabbit chow. During the experiment animals were housed individually in metal cages and fed a pellet diet (Oriental Cobe MF, Tokyo, Japan) and tap water ad libitum for 14 days to acclimatize them [tem-

perature, $25 \pm 1^\circ\text{C}$; humidity, 45–60%; lighting time, 12 h/day (08.00–20.00 h)]. All experimentation and animal handling were conducted so as to minimize stress and discomfort to the animals. Rabbits were killed 1 h ($n=10$) after local delivery for the evaluation of vessel penetration and 14 days ($n=20$) for the other analysis. The iliac arteries were removed and processed following sacrifice as described below. All animal experiments conformed to the guidelines of the animal research committee of Juntendo University.

Evaluation of the Degree of Vessel Penetration

To assess the degree of vessel penetration, local delivery of 3 ml of 50% indocyanine green dye solution was performed in a similar fashion in an additional 10 rabbits. One hour after the infusion of dye solution, the arteries were removed, fixed in 95% ethanol and 1% acetate in phosphate-buffered saline (PBS), embedded in paraffin, and serially cross-sectioned at 4 μ m thickness. The extent of the penetration was then assessed in unstained cross-sections.

Vascular Injury Scoring and Quantification of Intimal Thickening

On the 14th postoperative day rabbits were generally reanesthetized with an intravenous injection of pentobarbital (30 mg/kg). After longitudinal abdominal skin incision, the abdominal aorta and both iliac arteries were surgically exposed. A cannula was inserted into the aorta for exsanguination to perfuse 0.01 mol/L PBS into the aortic lumen at physiologic pressures for 5 min. After removal of the abdominal aorta and both iliac arteries en bloc, fixative fluid including 95% ethanol and 1% acetate in PBS was perfused into the lumen of the vessel for 10 min at physiologic pressure. Perfusion-fixed specimens were fixed in the same solution for 24 h. The injured arterial segment was divided at intervals of 4 mm. The mid-portion of these subsegmental arteries was embedded in paraffin and serially cross-sectioned at 4 μ m thickness.

The cross-sections were deparaffined and stained with van Gieson's solution. The extent of vascular damage was evaluated by: (1) the percent laceration of the internal elastic lamina (IEL); (2) total occlusion as a result of thrombus formation; and (3) the use of vascular injury scoring²³ (which was described as follows: 0, intact IEL; 1, IEL lacerated; 2, media visibly lacerated; 3, external elastic lamina (EEL) lacerated). The mean injury score was assessed for each subsegment and averaged for the number of subsegments. For evaluation of intimal thickening, neointimal area (IA, mm^2), medial area (MA, mm^2), and intima/media (I/M) ratio were determined. Intimal and medial area were measured by carefully tracing the margin of the lumen, IEL, and EEL using a computerized image analyzer (IBAS 2000, Kontron, Munich, Germany). The cross-sectional area was calculated by subtracting the lumen area from the IEL area. The medial area was also calculated by subtracting the IEL area from the EEL area. Evaluation of both vascular damage and intimal thickening was performed by a blinded observer for the infusion pressure allocation.

Immunohistochemistry for Evaluation of SMC Proliferative Activity

SMC proliferative activity was evaluated by immunohistochemical analysis for proliferating cell nuclear antigen

Fig 2. Representative arterial cross-sections with different degrees of infusion pressure of 0, 3, 5, 7, and 12 atm in rabbit iliac arteries 14 days after local delivery. The neointimal area increases proportionally with the degree of infusion pressure. Control indicates a representative cross-section from a control rabbit. Original magnification $\times 16$.

Fig 3. Bar graph showing the influence of different degrees of infusion pressure on the percent frequency of internal elastic lamina (IEL) laceration and total occlusion. There was a significant increase in the frequency of IEL laceration and thrombus formation proportional with the degree of infusion pressure.

(PCNA). The sections were deparaffined and rehydrated, and microwaved pretreatment was added for amplification of PCNA in 0.01 mol/L citrate buffer (pH 6.0) for 10 min. Endogenous peroxide activity was blocked with 0.3% hydrogen peroxide in 100% methanol at room temperature for 30 min. The sections were preincubated with 10% normal goat serum for 30 min to block non-specific protein binding, and were then incubated overnight at 4°C with monoclonal antibodies against PCNA (PC-10, Novocastra Laboratories, Newcastle upon Tyne, UK) at a dilution of 1:100 in 1% bovine serum albumin/PBS to identify proliferating cells. A monoclonal antibody against HHF35 (Dako, Denmark) was used to detect smooth muscle cells at a dilution of 1:500. Negative controls were incubated with normal mouse IgG (Dako) or with PBS alone in a similar fashion. After rinsing in PBS, biotinylated goat anti-mouse Igs (Dako) was added for 30 min. The sections were then rinsed in PBS and incubated with horseradish peroxidase-conjugated streptavidin (Dako) at a dilution of 1:300 for 30 min. Sections were repeatedly rinsed in PBS and incubated with 3, 3'-diaminobenzidine as a substrate for the peroxidase, resulting in a brown product. The sections were counterstained

Table 1 The Number of Each Injury Score and Mean Injury Score Measured 14 Days After Local Delivery With Different Degrees of Infusion Pressure

Group (n=vessels)	The number of injury score				Mean injury score
	0	1	2	3	
Control (12)	12	0	0	0	0
0 atm (4)	4	0	0	0	0
3 atm (6)	6	0	0	0	0
5 atm (11)	8	2	1	0	0.36 $\pm$ 0.20
7 atm (17)	4	5	5	3	1.10 $\pm$ 0.35*
12 atm (16)	0	5	5	6	2.25 $\pm$ 0.31**

* $p < 0.05$ vs 0, 3, 5 atm, ** $p < 0.005$ vs 0, 3, 5, 7 atm.

with hematoxylin. Photomicrographs were taken $\times 16$ or $\times 50$ magnification.

The extent of SMC proliferative activity in each cross-section was measured as the percent of PCNA-positive cells on total SMCs. PCNA-positive cells were scored by an independent analyst who was blinded for the infusion pressure allocation.

Statistical Analysis

All results were expressed as means $\pm$ SEM. Differences among groups were evaluated by one-way ANOVA and Fisher's protected least significant difference. The comparison between the degree of neointimal formation (and intima/media ratio) and infusion pressure was performed by linear regression analysis. Differences were considered significant at $p < 0.05$.

Results

Evaluation of the Degree of Vessel Penetration

Green dye was seen surrounding the vessels throughout the adventitia at high infusion pressures. Full penetration was demonstrated in all of the unstained cross-sections at 5, 7, and 12 atm but not at 0 or 3 atm.

Vascular Damage With Different Degrees of Infusion Pressure

The extent of vascular damage after local delivery was evaluated by the percentage of segments with IEL laceration, by the frequency of total occlusion as a result of thrombus formation, and by the mean injury score in a total of 54 arterial cross-sections [0 atm (n=4), 3 atm (n=6), 5 atm (n=11), 7 atm (n=17), and 12 atm (n=16)]

Table 2 Intimal Area (IA), Medial Area (MA) and Intima/Media (I/M) Ratio Measured 14 Days After Local Delivery With Increasing Infusion Pressure

Group (n=vessels)	IA (mm ²)	MA (mm ²)	I/M ratio
Control (12)	0	0.348±0.011	0
0 atm (4)	0.160±0.005	0.341±0.007	0.50±0.01
3 atm (6)	0.163±0.008	0.336±0.012	0.52±0.02
5 atm (11)	0.189±0.017	0.352±0.027	0.55±0.02
7 atm (17)	0.260±0.027*	0.397±0.025	0.62±0.06
12 atm (16)	0.329±0.033**	0.428±0.031	0.76±0.05*

* $p<0.05$ vs 0, 3, 5 atm, ** $p<0.005$ vs 0, 3, 5, 7 atm.

Table 3 SMC Proliferative Activity Measured 14 Days After Local Delivery With Increasing Infusion Pressure

Group (n=vessels)	PCNA positive cells (%)
Control (12)	0
0 atm (4)	11.3±1.0
3 atm (6)	11.2±0.8
5 atm (11)	12.1±2.1
7 atm (17)	17.1±0.6*
12 atm (16)	22.0±1.0**

* $p<0.05$ vs 0, 3, 5 atm, ** $p<0.005$ vs 0, 3, 5, 7 atm.

Fig 4. Photomicrograph showing representative arterial cross-sections with the infusion pressure of 3 (left) and 7 atm (right) with van Gieson's staining (VG) and immunohistochemical staining. Middle: α -smooth muscle actin (α -SMA). Bottom: proliferative cell nuclear antigen (PCNA). Proliferative SMCs with expression of PCNA were increased in the arterial section of 7 atm with larger neointimal formation. Original magnification $\times 50$.

examined at 14 days. Fig 2 shows representative cross-sections from rabbit iliac arteries at infusion pressures of 0, 3, 5, 7, and 12 atm. At 7 atm infusion pressure, IEL laceration can be observed. Expressed as a percentage of segments with IEL laceration, there was no evidence of IEL laceration in arterial cross-sections at 3 atm infusion pressure, which was similar to 0 atm infusion pressure (3 atm dilating pressure of angioplasty only). At 5 atm infusion pressure, the percentage of IEL laceration was 27%, and at the higher pressure of 7 atm it reached 63%. At 12 atm, IEL laceration was detected in all segments. The frequency of total occlusion caused by thrombus formation showed (Fig 3).

When the injury score in each cross-section was plotted against infusion pressure, a significant linear relation was observed ($r=0.717$, $p<0.0001$), with a significant corresponding increase in the severity of vascular damage; the mean injury scores were: 0 for 0 and 3 atm; 0.36 ± 0.20 for 5 atm; 1.10 ± 0.35 for 7 atm; and 2.25 ± 0.31 for 12 atm (Table 1).

Intimal Thickening and SMC Proliferative Activity

There was no neointimal formation in the sham artery which did not undergo the local delivery procedure. As also shown in Fig 2, the development of intimal thickening

increased in proportion to the infusion pressure. At a low infusion pressure of 3 atm, mild intimal thickening was detected with an area of 0.163 ± 0.008 mm². An infusion pressure of 0 atm also resulted in mild intimal thickening, with an area of 0.160 ± 0.005 mm² as a result of the dilating angioplasty balloon alone. In contrast, at the higher infusion pressures of 5, 7, and 12 atm, the neointimal area increased proportionally: to 0.189 ± 0.017 , 0.260 ± 0.027 , and 0.329 ± 0.033 mm², respectively (Table 2). Thus, a significant linear increase in intimal thickening occurred at infusion pressures of 3, 5, 7, and 12 atm ($r=0.550$, $p<0.0001$). We also found a similar relationship between infusion pressure and intima/media (I/M) ratio ($r=0.489$, $p<0.0005$). There was no significant change in the medial area at any infusion pressure.

Fig 4 shows representative arterial cross-sections at higher magnification, which show an increased number of SMCs and PCNA-positive cells at 7 atm compared with 3 atm. The proliferative activity increased proportionally with increasing infusion pressure. PCNA-positive cells were identified more frequently at higher infusion pressure in both neointima and media, with a significant increase at 7 and 12 atm of $17\pm1\%$, $22\pm1\%$, respectively (Table 3).

Discussion

The present study was designed to address whether different degrees of infusion pressure of local delivery using the channeled balloon may influence vascular damage and the development of intimal thickening in a balloon-injured rabbit iliac artery. The principal finding of this study is that higher infusion pressures may not only extend delivery to the deep layers of vessel wall but also simultaneously lead to severe vascular damage, resulting in proportional development of intimal thickening associated with enhanced SMC proliferation.

The relationship between vascular damage and infusion pressure of local delivery has been reported in a few previous experimental studies^{20,24,25}. Santoian et al²⁰ established that medial disruption occurred more frequently at infusion pressures of 10 atm than of 5 atm using a porous balloon catheter in a swine coronary artery injury model. And other experimental angioplasty models have shown that medial and IEL disruption injury is frequently associated with mural thrombus formation and platelet deposition in porcine carotid arteries^{9,26}. However, the porous balloon used in these previous studies did not allow the effect of infusion pressure to be distinguished from infusate volume and/or angioplasty dilating pressure. The channeled balloon used in our study allowed this differential effect to be analyzed accurately for the first time.

Evaluation of the depth of vessel wall penetration by local dye delivery revealed that diffusion to the adventitia occurred at all pressures except 0 and 3 atm. Higher infusion pressures using the channeled balloon were also associated with deeper vessel wall penetration than lower pressures. In a report from Fram et al²⁴ the depth of penetration of horseradish peroxidase was directly related to pressure and duration of infusion. In a postmortem study, green dye marker infused at 8 atm using a perforated balloon entered deeper into the vessel wall than at 4 atm²⁷. Although normal arteries treated with balloon injury were selected in the present study, our data were consistent with the previous studies. High infusion pressures of 7 and 12 atm resulted in severe arterial damage in the present study. The mean injury score at these higher pressures reached 1.10 and 2.25, respectively. The majority of arterial cross-sections exhibiting IEL laceration were treated at the higher infusion pressures. We postulate a force translation concept whereby higher infusion pressures may transmit increased kinetic forces to fluids and accelerate the outward flow velocity from the balloon pores. Accordingly, higher infusion pressures might be critical to the development of severe vascular damage and additional thrombotic events despite the advantage that they extend delivery to deeper layers than do lower pressures, as the present data indicate.

Schwartz et al²³ have shown that the degree of vessel injury is strongly correlated with development of intimal thickness in a coil wire implantation model in porcine coronary arteries. Data from the porcine coronary artery model using a porous balloon also indicate that higher infusion pressure induce greater intimal hyperplasia by overstretching the artery²⁰. In a similar fashion, our results show a positive correlation between injury score and the degree of intimal thickening ($r=0.550$, $p<0.0001$). Furthermore, SMC proliferative activity was also strongly correlated with the injury score. Interestingly, the rate of

SMC proliferation as determined by positive expression of PCNA, remained above quiescent levels 14 days after local delivery in our study. Previous studies have reported that bromodeoxyuridine staining reacts its quiescent levels 14 days after arterial injury²⁸. We suggest that this finding may be explained by the effect of infusates remaining within the media and the intermittent overstretching effect to the injured artery. The rupture of IEL exposes medial tissue to circulating blood, leading to platelet deposition and subsequent neointimal proliferation. Moreover, the fluid jets may directly stimulate the medial components, including SMCs, collagens, and extracellular matrix.

In our study, we were able to compare the relative effect of local delivery to angioplasty alone (0 atm infusion pressure). Neointimal formation was significantly greater at infusion pressures over 7 atm. As vascular damage increased, there was a linear increase in neointimal formation proportional to the degree of infusion pressure. In our study, 5 atm of infusion pressure resulted in greater vascular damage than that caused by 0 and 3 atm infusion pressure. Therefore, it is suggested that 5 atm infusion pressure may be a critical threshold pressure during local delivery, beyond which more severe vascular damage including medial or IEL laceration occurs. In contrast, 3 atm infusion pressure did not induce such severe vascular damage and may be a more feasible infusion pressure for local delivery using channeled balloon. Similar findings were found in a study by Hong et al²⁹ in which 2 atm local delivery infusion pressure after angioplasty at 6 atm using a channeled angioplasty balloon catheter caused stretching of the vessel but no evident medial disruption. Moreover, in a recent study of local delivery using anti-sense oligonucleotides³⁰ there was no vessel wall disruption or gross edema evident at infusion pressures between 1 and 6 atm.

Study Limitation

First, local drug delivery is a multifactorial process including location, depth of penetration, the degree of vascular damage, infusate volume, and infusate molecular sizes. Although this experimental model had sufficient reproducibility to evaluate whether infusion pressure during local delivery could act on the vessel wall as an independent factor for vessel wall injury, all experiments including our model have been performed in normal arteries. Accordingly, insufficient data exist to consider these vascular responses as being typical of a complex human atherosclerotic lesion containing cholesterol necrotic cell debris, fibrosis, and calcification. Therefore, more experimental studies in atherosclerotic arteries or clinical trials will be required. Secondly, PCNA immunostaining was evaluated once 14 days after local delivery, but assessment at the beginning of the first week when maximum SMC proliferation occurs may be preferable. Thirdly, it is suggested that vascular remodeling of injured arteries did not contribute to stenosis in the present study.

Conclusion

We have shown that the severity of vascular damage and the development of intimal thickening increased proportionally with the degree of local delivery infusion pressure. Local delivery infusion pressure is an independent determinant of vascular damage, resulting in the

neointimal formation associated with an increase in SMC proliferative activity. Therefore, we suggest that infusion pressure is carefully monitored as a factor causing vessel wall injury during local drug delivery.

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