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Novel Short-duration Heating Balloon Dilatation with Uniform Temperature Distribution: the Heating Conditions to Suppress Neo-intimal Hyperplasia

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***Abstract*— We investigate the relation between the influences on smooth muscle cells and the chronic performances of our novel short-duration heating balloon dilatation to reveal the heating conditions which can suppress the neo-intimal hyperplasia after our heating dilatations. The temperature of prototype balloon catheter surface was measured during short-duration heating balloon dilatation *ex vivo*. There existed 2°C temperature variations in the long direction of prototype balloon catheter at a maximum. The neo-intimal hyperplasia occupancy rate after our short-duration heating dilatations were measured *in vivo* porcine study. The neo-intimal hyperplasia was suppressed most at 75°C in balloon peak temperature *in vivo*. The estimated dead rate of smooth muscle cells at this condition was about 13% by the Arrhenius equation. We think that the suppression of neo-intimal hyperplasia was obtained after our short-duration heating dilatation due to the proper decrease of smooth muscle cells by heating and no thermal damages to the adventitia and surrounding tissues.**

I. Introduction

PERIPHERAL arterial disease (PAD) is one of the concern in vascular disease recently because the number of patients is forecasted to increase due to the increase of diabetes and dialysis patients [1]. PAD is caused by femoral artery stenosis and percutaneous transluminal angioplasty (PTA) is the conventional treatment method to get revascularization at femoral artery region [1]. However, the chronic performances of PTA were not so good because of vascular injuries during balloon dilatation, so new methods are needed to improve chronic performances.

In late 1980s, thermal angioplasties were proposed to reduce the vascular injuries during the arterial dilatation. With these methods, the vessel wall became softened with collagen thermal denaturation by vascular heating. There are two thermal angioplasties have proposed in the past. The first one is Laser Balloon Angioplasty (LBA) [2] and the second one is Radiofrequency Thermal Balloon Angioplasty (RFBA) [3]. However, serious thermal damages were unavoidable after these two thermal angioplasties because of the long penetration depth of Nd:YAG laser and long-duration heating to get uniform temperature distribution in the balloon, respectively [4, 5]. Although these thermal angioplasties could reduce vascular injuries to the vessel wall, the chronic performances were terrible due to the thermal damages.

We have developed new thermal angioplasty, Photo-thermo Dynamic Balloon Angioplasty (PTDBA), as a new treatment for PAD [6, 7]. PTDBA can realize short-duration heating (< 75°C, ≤ 15 s) and low dilatation pressure (< 0.4 MPa) by the combination of fluid flow inside the balloon and laser light irradiation [8]. We obtained the sufficient arterial dilatation with our short-duration heating balloon in our previous *in vivo* study [6], however the conditions which can suppress neo-intimal hyperplasia after heating dilatation have been unknown. To obtain these conditions, we need to investigate the relation between the influences on the smooth muscle cells and the chronic performances after our short-duration heating dilatation. We measured the surface temperature of the prototype PTDBA balloon catheter. The dead cell rate of the smooth muscle cells was estimated with Arrhenius equation, of which parameters were obtained in our previous *in vitro* study [9], and the occupancy rate of the neo-intimal hyperplasia after our short-duration heating dilatation was measured *in vivo* to investigate the chronic performances.

II. Materials and Methods

A. Measurement: temperature distribution of prototype PTDBA balloon catheter surface (ex vivo)

The prototype balloon catheter for PTDBA (diameter = 4.0mm, effective length = 20mm) was used. The temperature of prototype catheter surface was measured in the air during short-duration heating balloon dilatation with the infrared thermography (TVS-500EX, NECAvio, Tokyo, Japan). The experimental set-up is shown in Fig. 1. The heating conditions were as follows; 65°C (N=5), 75°C (N=5) in the peak temperature in the balloon, 15 s in the laser irradiation time (i. e. heating time), and about 0.35 MPa in the balloon pressure.

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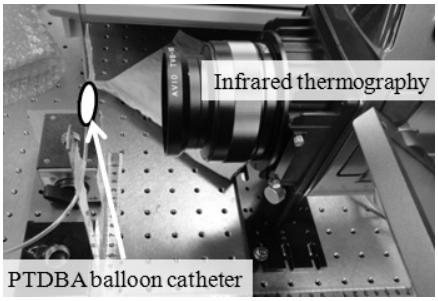

Fig. 1. The experimental set-up for measuring the temperature of prototype PTDBA balloon catheter surface

B. Estimation: the smooth muscle cells' dead rate after the short-duration heating dilatation in long direction of prototype balloon catheter

To estimate the dead rate of the smooth muscle cells, we used the Arrhenius equation showing in Eq. (1).

$$\Omega(t) = -\ln\frac{C(t)}{C(0)} = A\int_0^t \exp\left(-\frac{E_a}{RT}\right)dt \qquad (1)$$

where $\Omega(t)$ is accumulated cell damage (i.e. the smooth muscle cells' death), $C(0)$ is initial concentration of living cells, $C(t)$ is concentration of remaining living cells at time t, A [1/s] is frequency factor, E_a [J/mol] is activation energy of the reaction, R [J/(mol•K)] is gas constant, and T [K] is absolute temperature. The values of A and E_a (Arrhenius parameters) for the smooth muscle cells' death were obtained as 2.5×10^{16} /s and 1.17×10^{5} J/(mol•K), respectively, in our previous *in vitro* study [9]. After obtaining $\Omega(t)$ with Eq. (1) and the temperature history of the media, the smooth muscle cells' dead rate F_d [%] was estimated with the Eq. (2) as follows;

$$F_d = \frac{C(0)-C(t)}{C(0)} = 1-\exp\left[-\Omega(t)\right] \qquad (2)$$

To obtain the temperature histories of the media for the dead cell rate estimation, the measured temperature histories of the balloon, which were obtained *in vivo* porcine study, were used. The temperature histories of the media were estimated by the thermal conduction calculator, QuickTherm Bio® (Institute of Computational Fluid Dynamics, Japan).

C. Investigation: the neo-intimal hyperplasia occupancy rate after the short-duration heating dilatation (in vivo)

in vivo porcine study was performed according to the principles of the Declaration and Helsinki and was approved by the ethical committee of Keio University, Japan. Three male pigs (weight: 30-35kg) were anesthetized by isoflurane and ketamine. A 7 Fr. guiding catheter and 0.018" guide wire were inserted through a 7 Fr. vascular sheath in the left carotid artery. After 2 mg nitrol administration, X-ray fluoroscopic image was taken to measure the control diameter of both iliac arteries. The prototype PTDBA balloon catheter (diameter = 5.0-7.5mm, effective length = 20mm) was selected, of which diameter was 1.3 fold of the artery diameter, and delivered to the target region using X-ray fluoroscopic image guiding. The employed PTDBA conditions were as follows; 65°C (N=3), and 75°C (N=3) in the peak temperature of PTDBA balloon, about 15 s in the laser irradiation time (i. e. heating time), and about 0.35 MPa in the balloon pressure. Immediately after our heating dilatations, the X-ray fluoroscopic images were taken to ensure the acute arterial dilatation effect. Four week after the dilatations, the X-ray fluoroscopic images were taken again to check the chronic arterial patency. The three pigs were sacrificed by the overdose of isoflurane.

The HE stained specimens were made from each dilatation sites. The observations of these specimens were performed under bright-field and fluorescence microscopy (BX-51, Olympus, Japan). The areas of the neo-intimal hyperplasia S_{NI} and the inside area of internal-elastic-lamina S_{IEL} were measured and calculated the occupancy rate $R_{NI/IEL}$ [%] with the Eq. (3).

$$R_{NI/IEL} = \frac{S_{NI}}{S_{IEL}}\times 100 \qquad (3)$$

III. Results and Discussions

A. Measurement: temperature distribution of prototype PTDBA balloon catheter surface (ex vivo)

Fig. 2 shows the typical temperature history. The measurement points (T1, T2, T3) are shown in Fig. 3. We found that 2°C temperature variations in the long direction of prototype balloon catheter at a maximum in 15 s heating. Uniform temperature distribution was established within 5 s from the laser light irradiation kick-off.

According to the previous report about the dilatations with RFBA, 60-180 s heating time was necessary to make the balloon peak temperature 60-70°C [10]. The vessel wall softening with collagen thermal denaturation was used in the thermal angioplasties, and this thermal denaturation occurs over 60°C heating for several seconds. The electrode(s) was used in the heating mechanism of the RFBA balloon catheter and this/these electrode(s) placed on the center axis of the balloon [3, 5, 10] and the temperature distribution in the radial direction was suspected to be established. Thus, it expects that the longer time is needed to get uniform temperature distribution without fluid flow inside the balloon.

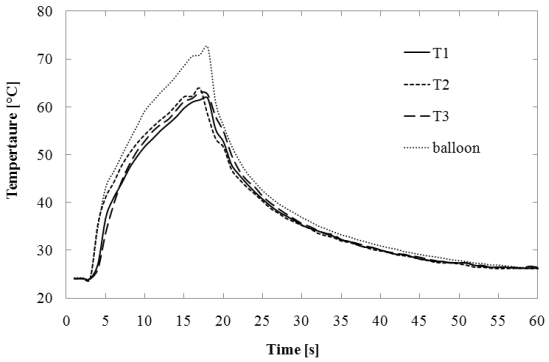

Fig. 2. The measured temperature history of prototype balloon catheter surface and inside the balloon

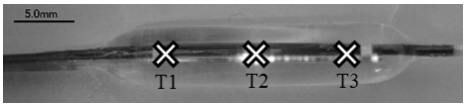

Fig. 3. The temeperature measurement points

B. Estimation: the smooth muscle cells' dead rate after the short-duration heating dilatation in long direction of prototype balloon catheter

From the results of III-A, we assumed that there is no temperature distribution in the long direction of our short-duration heating dilatation region. The estimated dead rate of smooth muscle cells after the heating dilatations was 4.5±0.2% at 65°C (N=4) in the balloon peak temperature and 13.1±1.9% at 75°C (N=4) in the balloon peak temperature.

According to the previous reports of the dilatations with LBA and RFBA, the peak temperature in the media was more than 80°C and 70°C, respectively; otherwise the peak temperature in the media was less than 70°C with our short-duration heating dilatation. In addition, the heating time was different; 10-30 s in the dilatations with LBA [2], 60-180 s in the dilatations with RFBA [10], and 15 s in our short-duration heating dilatation. The estimated results of smooth muscle cells' dead rates were 100% at these heating conditions of LBA and RFBA. It is well known that the vessel wall become thin and doesn't work well when all the smooth muscle cells in the media are dead. However, it is reported that there were serious thermal damages to the adventitia and surrounding tissues after the dilatations with LBA and RFBA [4, 5], and so that the neo-intimal hyperplasia was made on chronic phase (after one month or longer) [10, 11]. From these reports, the proper decrease of smooth muscle cells by heating and no thermal damages to the adventitia and surrounding tissues are needed to improve the chronic performances of thermal angioplasty. Our short-duration thermal angioplasty might solve these problems which were induced with other thermal angioplasties, such as LBA and RFBA.

C. Investigation: the neo-intimal hyperplasia occupancy rate after the short-duration heating dilatation (in vivo)

The measured neo-intimal hyperplasia occupancy rate had distribution in the long direction of our dilatation region. Typical results are described in Table. 1. All obtained results were less than 50% at 65°C in balloon peak temperature and less than 20% at 75°C in balloon peak temperature. Although there were the neo-intimal hyperplasia formations inside the internal-elastic-lamina area, the arterial dilatation were maintained and the lumen diameters were almost as same as the balloon diameters which were used to dilate arteries.

According to the previous report of the dilatations with LBA and RFBA, the restenosis rate (i. e. the neo-intimal hyperplasia occupancy rate in our results) in human coronary area was more than 50% [11] and 67% [10], respectively. The restenosis rate was much higher than after our short-duration heating dilatation *in vivo* porcine study. From this result, the long-term sufficient arterial dilatation might be obtained with our short-duration thermal angioplasty.

Table. 1. The distribution of measure neo-intimal hyperplasia occupancy rate [%] (75°C in balloon peak temperature)

control (distal)	PTDBA dilatation region			control (proximal)
	distal	center	proximal	
7.1	8.1	3.4	4.8	3.4

IV. CONCLUSION

We found that there was a little temperature distribution in the long direction of prototype PTDBA balloon catheter *ex vivo*. The uniform temperature distribution was obtained within 5 s from the laser light irradiation start due to the fluid flow inside the balloon. We found that the neo-intimal hyperplasia was suppressed most at 75°C in balloon peak temperature *in vivo* porcine study. The estimated smooth muscle cells dead rate was about 13% at this short-duration heating condition. We suspect that the proper decrease of smooth muscle cells by heating and no thermal damages to the adventitia and surrounding tissues are important to suppress the neo-intimal hyperplasia formation after thermal angioplasty.

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