Experimental Studies

Reduction of Thrombogenicity with Argon Laser Angioplasty

Comparison with Balloon Angioplasty

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SUMMARY

Direct argon or thermal laser angioplasty (LA) was evaluated for thrombogenicity using angioscopy, and compared with balloon angioplasty (BA). In each of 8 dogs, 4 segments (both proximal and distal iliac arteries) were treated by laser-thermal and/or balloon angioplasty. One segment was treated by balloon angioplasty and 3 other segments were treated with either thermal LA with 7 W using a “Hot-Tip” laser probe (2.0 mm), or BA and thermal LA, or a special optical probe which emits a 3 W argon laser beam. Mean percent area stenosis by thrombus was 44±23 in balloon-dilated, 23±21 in thermally-treated and balloon-dilated, 3±3 in thermally-treated, and 1±4 in directly-lased segments at 30 min. It was 62±28 in balloon dilated, 31±29 in thermally-treated and balloon-dilated, and 5±6 in thermally-treated, and 1±2 in directly-lased segments at 60 min. Balloon-inflated segments had the highest percent area stenosis which was significantly higher than that of either the direct laser or thermally-treated segments (p<0.0005). Histology showed thermal necrosis in laser-treated sites, and wall tears in BA sites. Thus, LA can provide a less thrombogenic arterial surface than BA. (Jpn Heart J 34: 79-90, 1993.)

Key Words:
Thrombogenicity Argon laser Angioscopy

PERCUTANEOUS transluminal balloon angioplasty (PTA) is a widely accepted treatment of obstructive artery disease in humans.1,2 How-
ever, despite the high primary success rate, restenosis occurs in up to 30–40% of reopened lesions following PTA.\(^2\) Endothelial denudation, dissection and platelet adhesion have been observed after balloon-induced arterial damage.\(^3\)–\(^8\) Platelet adhesion and thrombus formation may be responsible for occurrence of thrombosis, vasospasm, and release of platelet-derived growth factor.\(^5\),\(^7\)

Transluminal laser angioplasty is one of the potential alternatives to PTA. These energy sources are capable of removing atherosclerotic plaques,\(^9\)–\(^13\) whereas PTA remodels the artery by disruption of the intima and media.\(^3\),\(^4\) Laser irradiation has been shown to result in a lack of plaque progression for up to 6 months in atherosclerotic models.\(^13\),\(^14\) In a study evaluating the effects of laser thermal angioplasty and balloon angioplasty, restenosis was noted to be lower for laser thermal effects.\(^15\) Although current clinical data suggest that laser-assisted balloon angioplasty has a restenosis rate similar to that of PTA when the procedure was applied in totally occluded vessels,\(^13\),\(^16\) laser treatment as a sole therapy without PTA has been shown to provide a distinct benefit related to restenosis.

Several reports have attempted to evaluate the effect of laser irradiation and/or laser thermal angioplasty on surface thrombogenicity in vessels using morphologic and radioisotope (RI) labelling techniques.\(^17\)–\(^20\) Platelet deposition is one of the important factors for thrombosis, however, other factors including fibrinolytic or coagulative agents produced by the endothelial surface may influence development of thrombosis. To evaluate thrombus formation, angioscopy has been shown to be an acceptable and useful technique.\(^21\),\(^22\) This study was undertaken using angioscopy to evaluate thrombus formation following interventional treatments in normal dog arteries. The effects of both direct laser irradiation by continuous argon wavelength and laser thermal energy were compared to the effects of PTA. The effects of balloon dilatation following laser thermal treatment were also compared with laser thermal treatment or balloon dilatation alone.

**MATERIALS AND METHODS**

Eight mongrel dogs weighing a mean of 10 kg were used in this study. The dogs were sedated with sodium pentobarbital (30 mg/kg) intravenously, intubated and ventilated with air using a Harvard respirator.

**Experimental set up**

After a median abdominal incision, the aorta and both iliac arteries were isolated. A 7F catheter sheath was introduced into both external iliac
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REDUCTION OF THROMBOGENICITY WITH LASER

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Fig. 1. A: Schematic representation of experiment. Four iliac segments are treated using laser and/or balloon angioplasty. HT=hot-tip thermal angioplasty; B=balloon angioplasty; D=direct laser irradiation.

B: Schema of laser or balloon treatment.

arteries in a retrograde fashion. Figure 1 shows the schematic representation. The common iliac arteries were separated into 4 segments (proximal right, distal right, proximal left and distal left iliac arteries). The first segment was treated with a thermal “Hot-Tip” (HT) probe (2.0 mm Laserprobe-PLRTM, Trime dyne Inc., Santa Ana, CA, USA) activated by an argon laser. This was performed in 6 consecutive rows covering a 2 cm long portion of the arterial segment. Additionally, the probe temperature was measured by a thermocouple attached to the probe tip in the last 5 dogs. Five
exposures of 7W for 1 sec each were delivered at each site. These parameters were similar to those used in patients. The second segment was treated using direct argon laser irradiation in 6 consecutive rows using a special ball-tipped 300 µm optical fiber with a cut edge, which emits a laser beam at a 45 degree angle to the long axis of the arterial segment. A single exposure of 3W for 1 sec was used for each spot (0.5 mm in diameter), and 4 spots each 90 degree apart were lased in each row. Six rows covered a 2 cm long portion of the arterial segment. These parameters were used since greater energy would have consistently perforated the artery. The third segment was dilated 3 times with a 3.5 mm balloon angioplasty catheter (USCI). Each inflation was done under constriction with tape threads using saline solution at 6 atmospheres and lasted for 60 sec. The fourth segment was treated by HT then followed by balloon dilatation. Following laser thermal treatment, balloon dilatation was performed at the laser treated site. Lasing and balloon dilatation were done under the same conditions as mentioned above. Figure 1B represents these treatments. For each of the 8 experiments, the treated segments were staggered so that different procedures were done on both iliac segments.

**Angioscopic evaluation**

Angioscopy was performed at 30 and 60 min after treatment by injection of 10–20 cc of saline from the sheath to clear the blood field under ligation of the aorta (Fig. 1A). Angioscopic color pictures were obtained by a Video Monitor System (Sony Co., Ltd., Tokyo). Percent luminal obstruction by thrombus on angioscopy was calculated from tracing of the angioscopic pictures using planimetry. All angioscopic pictures were read by 2 doctors independently and discrepancies resolved by subsequent simultaneous reading. The cross-sectional area of the normal vessel at the thrombosed site was traced and calculated (A), and the area of lumen occupied by thrombus was also calculated (B).\(^22\) \(\text{Percent area stenosis} = \frac{B}{A} \times 100\)\%

**Gross and microscopic examination**

Animals were sacrificed after final angioscopy at 60 min following treatment. To determine the status and thrombogenicity of treated sites, the perfusion-fixed arterial segments were examined using light microscopy. Arterial segments were embedded in paraffin, cut into 7 µm thick sections, and mounted on glass slides. The sections were stained with hematoxylin and eosin, and Elastica Van Gieson stains, and examined using a light microscope.
Statistical analysis

Groups were compared by means of a two-way analysis of variance (ANOVA), and Sheffe's F-test was used to test for the significance of difference between any 2 groups. Paired t-test was used for analysis of difference in percent area stenosis between 30 and 60 min following treatments. A $p$ value of less than 0.05 was considered significant for statistical comparison.

Results

Data from 8 dogs were available for this study. While arterial segments were treated by either argon laser irradiation or thermal probe, no severe spasm was observed in the treated control segments. However, browning of the vessel surface was seen during direct argon lasing, and a sizzling sound with occasional smoking could be seen. With the HT probe, both browning and mild contraction of the vessel were also seen, and these were permanent changes. HT probe sticking was present in all thermally treated segments.

Percent area stenosis of treated segments

Table I shows graded percent area stenosis of the treated segments. All vessels treated with laser showed less than 25% stenosis. Although some of the HT treated arteries showed mural thrombus, there was no thrombus in most of either the argon or HT treated segments by angioscopy (Fig. 2A

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HT = hot-tip treatment, underline indicates inclusion (25-50 means 25 $\leq$ and $<50$). * $P<0.05$, ** $P<0.01$, *** $P<0.005$ vs Balloon.
Fig. 2. Angioscopic images of treated segments at 60 min following the treatment. A: A directly lased spot shows a charred crater without mural thrombus (arrow). B: Laser thermal treatment by HT resulted in thermal charring (arrow), but no mural thrombus. C: Angioscopic image shows balloon-dilated segment. Intimal tear and occlusive thrombus (arrow) are visualized. D: Thermally-treated and balloon-dilated segment demonstrates both thermal charring and mural thrombus (arrow).

Fig. 3. Percent area stenosis with thrombus at 30 and 60 minutes following treatments.
and B). In the balloon-treated segments, thrombus was usually seen by angioscopy and occlusive thrombus was present in most of the segments. Angioscopy showed reddish thrombus developing from intimal and medial tears (Fig. 2C). Balloon-treated segments following HT treatment presented a lower percent area of stenosis due to thrombus (Fig. 2D).

Figure 3 shows percent area stenosis of the treated segments at 30 and 60 min, respectively, after the treatment. Mean percent area stenosis caused by thrombus was 44±23 in balloon-dilated, 23±21 in thermally-treated and balloon-dilated, 3±3 in thermally-treated, and 1±4 in directly-lased segments at 30 min. It was 62±28 in balloon-dilated, 31±29 in thermally-treated and balloon-dilated, 5±6 in thermally-treated, and 1±2 in directly-lased segments at 60 min. The percent area stenosis of balloon-dilated lesions and thermally-treated lesions was significantly higher at 60 min than 30 min (p<0.05).

Balloon-inflated segments had the highest percent area stenosis which was significantly higher than that in direct laser or thermally-treated segments (p<0.0005). Mean percent area stenosis was higher in balloon-treated segments than in balloon-dilated and thermally-treated segments, however, not significantly.

**Histologic findings**

Figure 4 shows photomicrographs of the laser or balloon treated segment. Direct laser-treated sites showed craters with tissue vaporization and thermal necrosis. The segments treated by direct argon laser showed craters with sharply cut edges. A platelet plug with fibrin and aggregated blood cells was seen filling the crater. Few platelets were seen beyond the crater edges. At thermally-treated sites, thermal coagulation necrosis and cell layer compression were seen, however, there was occasional intimal and/or medial dissection. Scattered cellular debris were adherent to the lumen, and a few platelets were seen adherent to the surface. The sites where the probe was stuck and pulled away showed extreme tears in the endothelial lining, however, mural thrombus developed only occasionally. In balloon-treated segments, medial dissection and stretching of the arterial wall were frequently present. Balloon-dilated segments showed irregular intimal surface tears and flaps with numerous platelets adherent to the arterial surface and occlusive thrombus developed from the intimal and medial tears. Laser-balloon treated sites had both thermal necrosis and medial dissection. Laser-balloon treated sites showed features of both balloon and thermally-treated sites. However, less platelet deposition and blood cell aggregation were observed in laser balloon-treated sites than sites treated with balloon only.
**Surface temperature of the vessels and probe temperature**

HT probe temperatures were measured in 5 animals. The maximal probe temperature ranged from 101 to 134°C and the mean temperature was 115±13°C.

**Discussion**

To evaluate the thrombogenicity of laser or balloon treatment in vivo or in vitro experiments have been conducted using various experimental designs. We have already shown that laser thermal treatment could reduce platelet deposition by thermal coagulation of collagen. However, thrombus is not only composed of platelet, but also fibrin and other blood cell components. Angioscopy has been shown to be a useful tech-
Technique for detection and evaluation of thrombotic stenosis. Thrombus can be clearly differentiated from vessel wall by angioscopy. In this study, angioscopy was used for serial evaluation of thrombus formation.

Balloon inflation in vessels is reported to result in platelet deposition. However, there is controversy regarding the thrombogenicity of laser treatment and there have been only a few studies conducted to compare thrombogenicity of balloon angioplasty with direct laser irradiation or laser thermal effects. Ragimov et al evaluated thrombogenicity of direct laser irradiation using various laser sources and laser thermal treatment using canine vessels in an artificial circuit. In their study, direct laser irradiation using Nd-YAG, excimer or argon energy and laser thermal treatment by HT probe resulted in less thrombogenicity than balloon dilatation, and there was no significant difference in thrombogenicity between different laser sources. Alexopoulos et al reported that laser thermal coronary angioplasty with 1 sec pulses was associated with minimal platelet deposition which was comparable to control or wire-passed segments, and that longer pulses are accompanied by significant platelet deposition. There is a similar report that demonstrated less thrombogenicity in thermally-treated segments than excimer or control. On the contrary, excimer laser irradiation has been recently shown to result in less platelet deposition than laser thermal treatment. However, no temperature monitoring was done and it is assumed that extensive thermal injury might produce platelet deposition. In that report, laser treatments were not compared with balloon angioplasty. Whichever laser treatment is thrombogenic, comparison with balloon angioplasty is important. Our study revealed that balloon-inflated segments were much more thrombogenic than were segments treated by optical fiber or HT probe. Balloon dilated segments had a significantly higher percent stenosis due to thrombus than direct laser treated or thermally-treated segments. Thus balloon inflation resulted in constant thrombus formation in this study.

Although thermally-treated sites showed less thrombogenicity than balloon-dilated sites, PTA following laser thermal treatment could cancel the lower degree of thrombogenicity of laser thermal treatment. This may be the reason that almost the same restenosis rates are seen in laser-assisted balloon angioplasty as in balloon angioplasty. However, in clinical situations, the extent of mechanical or thermal damage to the vessel by laser balloon angioplasty varies with cases because there are differences in the degree of stenosis, length and composites of obstruction. Control of either laser thermal or mechanical energy is also difficult in the clinical situation. In this study, we used the same energy level under stable conditions. Slight
charring and probe sticking usually occurred, however, no extensive thermal injury was seen. The laser balloon-treated segments showed less percent area stenosis than balloon-dilated segments. These results clearly demonstrated that laser thermal treatment under temperature control could attenuate thrombus formation produced by balloon dilatation.

There have been few studies of laser thrombogenicity using temperature measurements. In our study, probe temperatures were monitored in several arteries treated by HT probe. Mean maximal probe temperature of 115°C obtained in saline medium using 5 pulses of 7W for each row was similar to that seen in our clinical experience. Recanalization of human occluded arteries has been achieved with a mean probe temperature of 136°C in our clinical study. Rapid motion of the probe was used to reduce tissue contact time. In this study, no probe motion was done and sufficient heat was transmitted to the arterial wall. Charring inside the vessel lumen was usually present in thermally treated segments. This indicates that luminal temperature was higher than the surface temperature which was measured using a thermocouple. Clearly there was sufficient energy as evidenced by the probe sticking to the artery and by the histological findings. Even with a higher probe temperature, surface thrombogenicity following laser thermal angioplasty has been shown to be less than in normal controls.

Laser thermal energy causes damage to the arterial wall including denaturation of surface proteins and coagulation necrosis, but not medial dissection. On the other hand, balloon angioplasty and to a much lesser extent direct laser radiation can result in severe medial damage and dissection. Histologic examination showed a relatively smooth arterial surface with minimal craters with minimal platelet deposition in HT treated segments, and rough and irregular craters with more platelet adherence in laser-irradiated segments. Balloon angioplasty induced medial tears and had greater thrombogenic effects. Because the mechanism of balloon dilation of stenosed arterial lumen involves disruption of intima and media, platelet deposition usually occurs on the exposed subendothelium and is considered to be an important cause of acute reclosure and restenosis after PTA. On the other hand, laser thermal angioplasty leaves a smooth surface with thermal changes including protein denaturation, thermal coagulation necrosis and/or charring. Thus, laser angioplasty may be less likely to elicit rethrombosis if laser power is applied under probe temperature control to prevent extensive thermal damage.

In conclusion, this study suggests that (1) thrombogenicity of laser-treated or balloon-inflated arterial segments can be assessed by angioscopy, (2) direct argon irradiation or laser thermal angioplasty by HT probe under
temperature monitoring results in less thrombus formation than balloon angioplasty, (3) balloon-inflated arterial segments are more thrombogenic than HT treated or direct laser-treated segments, (4) slight thermal injury of the lased artery does not induce thrombus formation probably due to thermal coagulation of collagens, and (5) laser angioplasty under temperature control as a sole therapy should be useful to prevent thrombotic reocclusion.

**References**


