Arterial Wall Strength After Endovascular Photodynamic Therapy

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Background and Objectives: Vascular photodynamic therapy (PDT) inhibits intimal hyperplasia (IH) induced by angioplasty in rat iliac arteries by eradicating the proliferating smooth muscle cells. This process may jeopardise the structure and strength of the arterial wall, reflected by a decreased bursting pressure.
Study design/Materials and Methods: Thirty male Wistar rats of 250–300 g were subdivided into 3 groups (n = 10). In all groups, IH was induced by balloon injury (BI). One experimental group received PDT at 50 J/cm diffuser length, the other group at 100 J/cm diffuser length. The third group served as control group and received no PDT. In half of each group the bursting pressure was analyzed after 2 hours (n = 5),in the other half after 1 year.
Results: Two hours after the procedure the bursting pressure was 3.37 ± 0.58 (±SEM) bar in the BI + PDT 50 and 3.96 ± 0.43 bar in the BI + PDT 100 group, compared to 2.20 ± 0.27 bar in the BI group ($P < 0.05$). After 1 year these values were 3.18 ± 0.87 bar in the BI + PDT 50 ($P < 0.05$) and 2.02 ± 0.31 bar in the BI + PDT 100 group, compared to 2.10 ± 0.30 bar in the BI group (NS). In the BI + PDT 100 group, 3 out of 5 rats appeared to have aneurysmal dilatation after 1 year.
Conclusions: Endovascular PDT increases the arterial wall strength as measured by the bursting pressure at short-term. After 1 year, wall strength is not diminished as measured by bursting pressure, but aneurysmal dilatation nevertheless developed with 100 J/cm · dl. This may limit the use of high energy PDT. Lasers Surg. Med. 33:8–15, 2003. © 2003 Wiley-Liss, Inc.

Key words: ALA; arteries; bursting pressure; photodynamic therapy; remodeling; restenosis

INTRODUCTION

Restenosis due to IH and constrictive remodelling decreases the long-term success rates of therapeutic vascular interventions for recanalisation of stenotic or occluded arteries. The incidence of this complication varies between 30% and 50% within 6 months [1], which is still an unfavourable therapeutical outcome that needs to be improved.

In the patho-etiology of restenosis, an excessive proliferation of smooth muscle cells (SMC) after arterial injury leading to IH plays a major role [2]. Remodelling is another important factor [3,4]. The exact contribution of SMCs in the development of constrictive remodelling remains to be elucidated, but various preventive studies showed that the elimination of these SMCs prevent or inhibit restenosis [5–10].

An adjuvant strategy to prevent restenosis may be the use of photodynamic therapy (PDT), a modality based on the light induced cytotoxicity of a light sensitive substrate (photosensitizer) that accumulates in the SMCs of the arterial wall after oral or intravenous administration (photosensitization) [11,12].

Since the first unsuccessful PDT based dose-finding study with Photofrin reported in 1985 [13], the search to find the optimal protocol in PDT studies to prevent restenosis was initiated [14]. Despite the following successful inhibition of IH using this first generation photosensitizer, its use was limited by systemic side effects of photocytotoxicity. This led to the development of second generation photosensitizers like phtalocyanines [15–17]. These photosensitizers are easily absorbed in arterial tissue but with less systemic side effects. However, lipophilic photosensitizers are only activated at high energy levels and are not really tissue specific.

In 1995 the first reports with the pro-drug aminolaevulinic acid (ALA) proved to be successful in the prevention of IH without systemic side effects [18–20] and therefore

Abbreviations: ALA, amino laevulinic acid; BI, balloon injury; HR, heart rate; IH, intima hyperplasia; J/cm · dl, Joule per cm · diffuser length; MAP, mean arterial pressure; AD, arterial diameter; PDT, photodynamic therapy; SEM, standard error of the mean; SMC, smooth muscle cell.

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resulted in the first clinical application. [21]. ALA is a naturally occurring intermediate of the heme biosynthetic pathway, which is artery type- and tissue-dependently metabolized to the photosensitizer protoporphyrin IX [22].

It became clear that the dose of the photosensitizer, the timing of illumination, the energy level and the type of artery are important parameters to determine the therapeutical outcome.

However, the direct and long-term effect of PDT induced SMC elimination on the structure of the arterial wall as a safety measure for this strategy is unknown. In this study, the bursting pressure of BI and PDT treated arteries was determined to study the strength of the arterial wall directly after the procedure and one year later.

MATERIALS AND METHODS

The experimental protocol was approved by The Committee on Animal Research of the Erasmus University of Rotterdam and complied with "Principles of Good Laboratory Practice." Male inbred Wistar rats (Harlan CPB, Austerlitz, The Netherlands) weighing 200–300 g were used. The animals had free access to rat chow (AM II, Hope Farms, Woerden, The Netherlands) and tap water, while maintained in a standard 12-hour light/dark cycle.

Study Design

Thirty male Wistar rats of 250–300 g were subdivided into three groups (n = 10). In all groups, IH was induced by balloon injury (BI) in the right common iliac artery. One experimental group received PDT at 50 J/cm · diffuser length, using endovascular laser illumination at 2½ hour after the administration of ALA, the other group at 100 J/cm · diffuser length. The third group served as control group and received no PDT. In half of each group the bursting pressure was analyzed after 2 hours (n = 5), in the other half after 1 year.

Photosensitization

The PDT groups received 200 mg/kg ALA (Sigma-Aldrich Chemie, Zwijndrecht, The Netherlands) intravenously dissolved in phosphate buffered saline at 40 mg/ml. The solution was freshly made for each animal and kept from light exposure. The photosensitised rats were kept in the dark during 2½ hour prior to treatment and 12 hour afterwards to prevent skin reactions from photosensitivity. The time interval after ALA administration is based on a previous study, where we found that at that time point the accumulation of the photosensitive compound protoporphyrin IX became maximal.

Laser

A dye laser (600 Series Dye Module, Laserscope, Surgical Systems, San Jose, CA), pumped by a 532/KTP surgical laser (Laserscope, Surgical Systems, San Jose, CA), was used to generate monochromatic light of 633 nm. The power emitted from the cylindrical diffusing tip (core diameter 200 μm, outer diameter 1.0 mm, tip length 20 mm: Lightstic™, Cardiofocus, West Yarmouth, MA) [23] was calibrated with a built-in power meter, and verified with an external linear diffuser in an integrating cylindrical sphere (Optometer Model 370, Graseby Optronics, Orlando, FL). A spectroscope (WaveMate, Coherent, Auburn, CA) was used to verify the accuracy of the wavelength.

Temperature. The real-time temperature during endovascular PDT was checked at 100 mW/cm · dl for 16 minutes and 40 seconds (100 J/cm · dl) to exclude high-energy induced hyperthermal effects instead of low-energy induced phototoxicity. Two fibre-optic thermosensors with a diameter of 0.5 mm were coupled to a Luxtron thermometry unit (Luxtron Corp., Santa Clara, CA). One was approximated parallel to the laser fibre along the artery at an axial distance of 10 mm in the fibre tip and the other next to the rat. The temperature was determined every second.

Linear fluence calibration with an isotropic probe. The linear fluence of 100 J/cm · dl from the cylindrical diffuser in the arterial wall was measured at an irradiance of 100 mW/cm · dl (illumination time of 1,000 seconds). An isotropic probe was approximated parallel to the laser fibre outside the artery at axial distances of 10 mm from and 0, 10, and 20 mm in the fibre tip.

Surgical Technique

A median laparotomy was performed under general anaesthesia with intramuscular injection of ketamine (Ketalar, Parke Davis and Co., Inc., 40 mg/kg) and xylazin (Rompun Bayer Ag, Leverkusen, Germany; 5 mg/kg). Subdued light using a yellow filter (620–650 nm Kodak) was applied during the procedure to prevent a photodynamic reaction caused by the operating lamp [24]. The right common iliac artery was cranially and caudally temporarily occluded with vascular clamps (Haemostat B1, Stöpler, Utrecht, The Netherlands). To create a blood free lumen, the arteries were flushed with 1 ml heparin (50 IU/ml 0.9% NaCl) infusion solution (Baxter) through an arteriotomy 5 mm proximal to the abdominal aortic bifurcation. The artery was then only balloon injured in the control group and BI + PDT was performed in the experimental groups (see Balloon injury and Endovascular Photodynamic Therapy). Hereafter, the clamps were removed. Reperfusion of the dilated section was observed directly after flushing with heparin and closing the arteriotomy (interrupted 9-0 prolene sutures). The abdominal wall was closed in two layers (continuous 2-0 prolene sutures). The animals recovered in subdued light after treatment.

Balloon Injury

A 2F Fogarty embolectomy catheter (Baxter Health Care Corp., Edward's Div., Irvin, CA) was inserted to denude the arterial wall at a pressure of 2 bar (manometer, Baxter) by pulling and rotating the insufflated balloon from distally to proximally over a 15-mm long segment for three successive times [25]. The balloon was desufflated proximally and insufflated distally. Then, the arteries were flushed with 1ml heparin solution, closed with Prolene 8-0 and marked halfway the denuded segment with a suture.

Endovascular Photodynamic Therapy (PDT)

In the PDT group, a 400 μm fibre (Lightstic 360, Rare Earth Medical Inc., West Yarmouth, MA) with a 20-mm long cylindrical diffusing tip was applied. The fibre tip was centred endovascularly in the denuded area to illuminate 10 mm of the balloon damaged arterial wall and 5 mm of the untreated arterial wall both cranially and caudally. Because of the cylindrical illumination, the fluence was expressed in Joule per cm · diffuser length (J/cm · dl). The target area was illuminated at random with 50 (n = 5) or 100 J/cm · dl (n = 5), applied with a fluence rate of 100 mW/cm · dl. After treatment, the lumen was thoroughly flushed with 1 ml heparin solution. Abdominal organs were protected from light exposure with a light absorbing plastic folium during illumination.

Bursting Pressure

The bursting pressure was determined in situ. A 2F cannula was fixed proximally in the iliac artery with Vicryl 6-0. At 15 mm distally, the segment was occluded with Vicryl 4-0. The cannula was connected with a T-piece to an analog pressure transducer (WIKA type Ecotronic) coupled to a converter module matrix. The intra-luminal pressure was gradually increased by pushing a glycol solution (Sigma-Aldrich 5000 MW, 5 g/ml 0.9% NaCl) into the sealed arterial segment via the cannula using a syringe with pressure manometer. Simultaneously, the intra-luminal pressure was digitally displayed on the video screen. The pressures at which the tunica media became transparent due to compression, and at which the tunica adventitia bursted were recorded on S-VHS for analysis (Fig. 1). Just before bursting, the arterial diameter (AD) expressed in mm was determined from the digital images using a scale bar as reference.

Histopathology

After the measurement of the bursting pressure the iliac artery was removed and processed for histopathological analysis. The arteries were fixed in formalin, cross-sectioned and embedded in paraffin. Sections (4 μm) were cut and stained with H & E and Elastic von Gieson.

Statistical Analysis

The presence of aneurysmal dilatation after treatment was analysed using a Fisher's exact test. The bursting pressure was expressed as mean ± standard error of the mean (SEM).

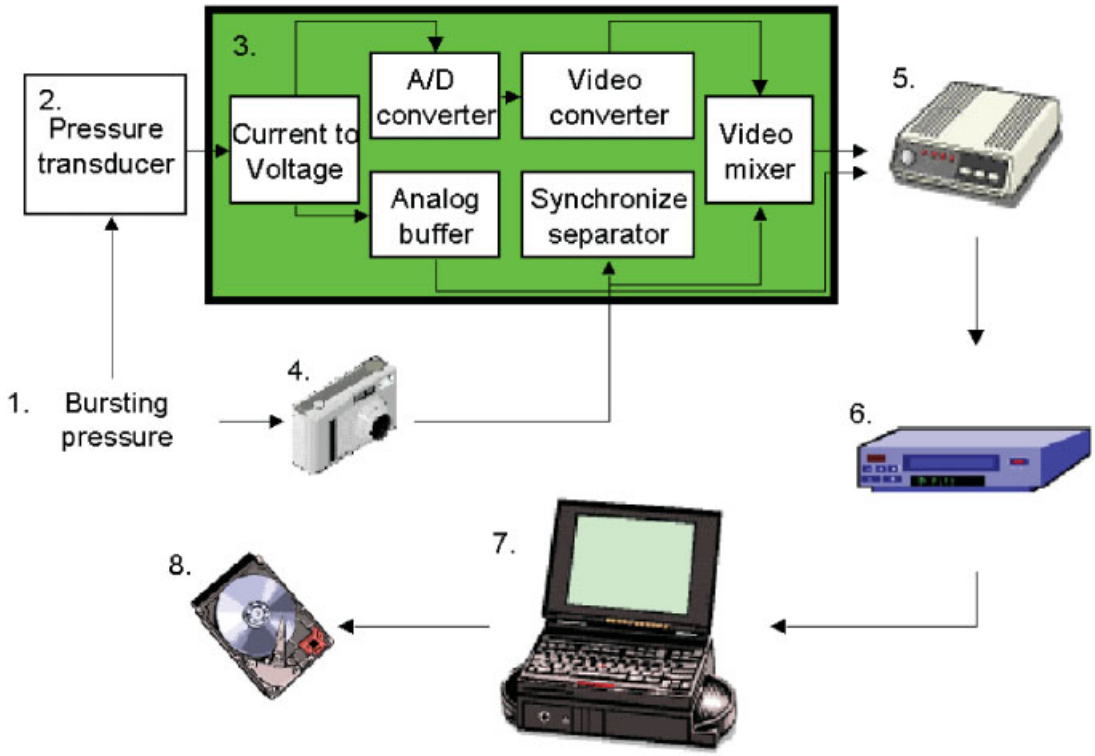

Fig. 1. A schedule representing the model to determine the bursting pressure of the treated right iliac artery as illustrated in the photograph (**1**). The 2F sheet is linked to a pressure manometer and a pressure transducer coupled (**2**) to a converter module matrix (**3**). The analog voltage signal evoked by the pressure is converted to digits in the video screen. These digits are integrated in the display of the bursting pressure analysis using an A/D converter and synchronize separator (1–**4**). This signal is incorporated using a video mixer and for tracing a second video mixer (**5**). For recording the output of the second video mixer is connected to a S-VHS system (**6**). The incorporated signal is displayed on a monitor and digitally converted using a computer (**7**) and CD (**8**).

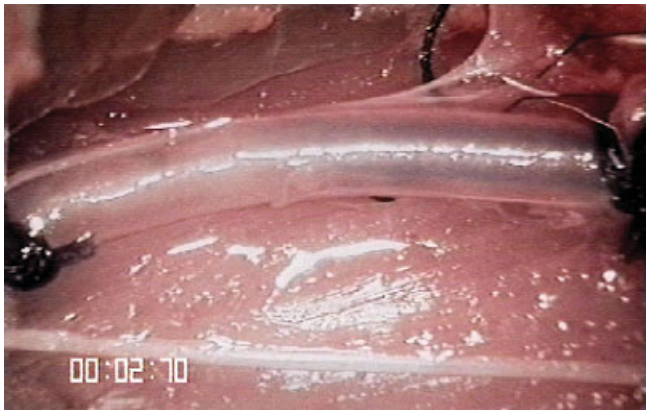

Fig. 1. (*Continued*)

ANOVA with a Dunnett's correction was used to compare the experimental means with the means of the control group. ANCOVA was used to study if the arterial diameter (AD) has a significant effect on the outcome of the bursting pressure. A difference was considered to be significant at P values less than 0.05.

RESULTS

Two rats of the BI + PDT 50 group died directly after the procedure and were excluded from further analysis. All other rats appeared healthy after treatment without significant weight loss or skin phototoxicity during the experiments. In all groups, after 52 weeks macroscopic neovascularization in the fascia covering the treated arterial area was seen in contrast to 0 weeks (Fig. 2). Strikingly, 3 out of 5 rats of the BI + PDT 100 group developed an aneurysmal dilatation at the proximal site of the PDT treated segment after 52 weeks of which one developed a distally occluded segment (Fig. 3). The fluence of 100 J/cm · dl had a significant effect on the development of the aneurysmal dilatation ($P < 0.03$). The temperature in the arterial wall did not increase during illumination and the light fluence was distributed homogenously in the arterial wall [20].

Bursting Pressure of the Tunica Adventitia

The bursting pressure of the tunica adventitia at 2 hours after the procedure was 2.20 ± 0.27 bar in the control group, compared to 3.37 ± 0.58 bar in the BI + PDT 50 group ($^{*}P < 0.05$) and compared to 3.96 ± 0.43 bar in the BI + PDT 100 group ($^{**}P < 0.05$). The bursting pressure of the tunica adventitia at 52 weeks was 2.10 ± 0.30 bar in the control group compared to 3.18 ± 0.57 bar in the BI + PDT 50 group ($^{\dagger}P < 0.05$) and to 2.02 ± 0.31 bar in the BI + PDT 100 group (NS) (Fig. 4). In general, the tunica media got compressed and became transparent in all groups at a pressure of between 0.22 and 0.46 bar.

Arterial Diameter (AD)

After 1 year, the AD just before the bursting pressure had increased significantly in the BI + PDT 50 (1.89 ± 0.04 mm) and 100 group (2.58 ± 0.14 mm) compared to the control group (1.42 ± 0.03 mm) ($P < 0.05$) (Table 1). The AD did not significantly correlate with the mean bursting pressure (c:−0.33, $P < 0.12$).

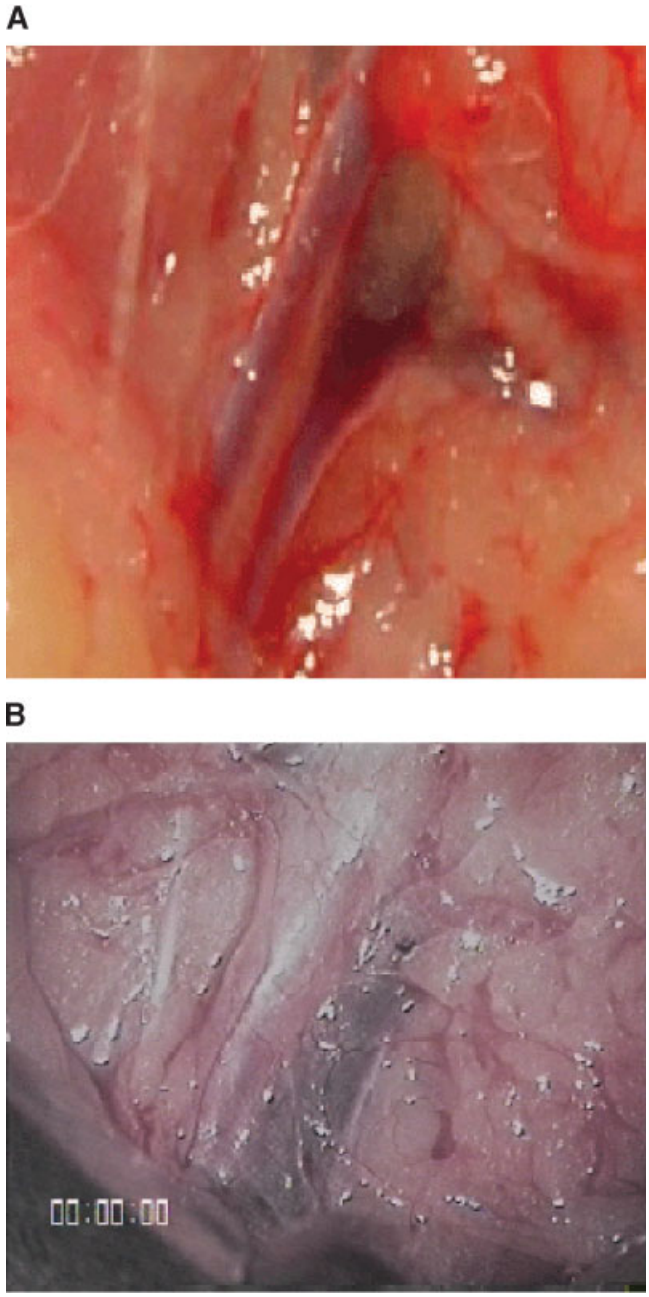

Fig. 2. Photograph **A** shows the fascia covering the iliac artery before the procedure. Photograph **B** shows the increased neovascularization in the fascia covering the treated iliac artery seen after 52 weeks in the treated groups. Here an iliac artery treated at 50 J/cm · dl using a fluence rate of 100 mW/cm · dl.

Histopathology

In the BI group after 2 hours only slight disruption of the internal area of the vessels was seen. In addition, in both

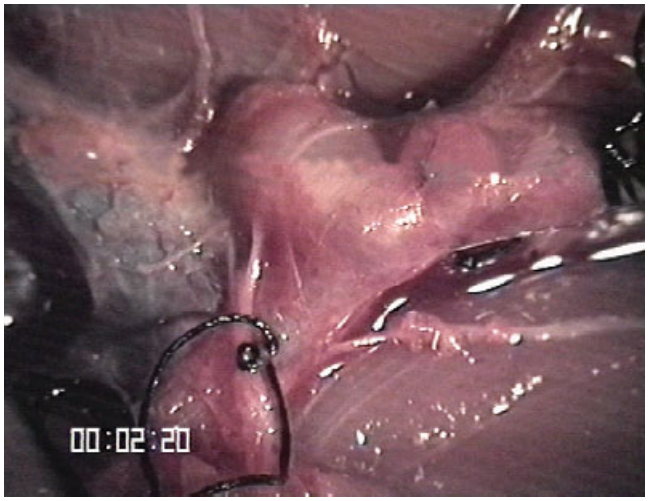

Fig. 3. A photograph showing the developed aneurysm like dilatation after 52 weeks in the proximal segment of the PDT treated iliac artery at 100 J/cm · dl using a fluence rate of 100 mW/cm · dl. Bursting pressure lines are given in the photograph.

the BT + PDT50 and 100 group, the tunica media became partly acellular (Fig. 5A). The most striking difference was seen after 52 weeks. IH was much more prominent in the BI + PDT100 group than in the BI group (Fig. 5B). However, the BI + PDT50 group showed no IH at all. In all groups fragmentation of elastic laminae occurred (Fig. 5C1), but the amount of elastin seemed larger in the PDT groups (Fig. 5C2). Quantitative assessment was not possible with the techniques used. Rupture of the elastic layer with development of aneurysmal dilatation was seen in the PDT100 group (Fig. 5D).

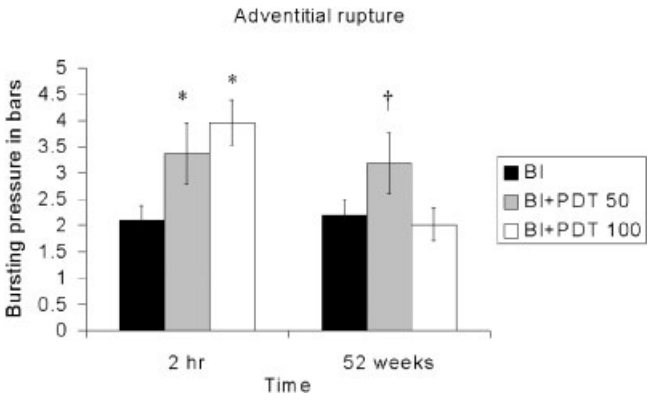

Fig. 4. A bar diagram representing the mean bursting pressure expressed in bar at which the tunic adventitia ruptures. The control group, BI + PDT 50 and BI + PDT 100 group is plotted against the time at 2 hour and 52 weeks (n = 5 per time-point). The error bars are standard errors of the mean (SEM).

TABLE 1. Arterial Diameter

	Arterial Diameter (in mm)	
Groups	2 hours SEM	52 weeks SEM
Control	1.24 ± 0.15	1.42 ± 0.03
BI + PDT 50	1.19 ± 0.11	1.89 ± 0.04
BI + PDT 100	1.07 ± 0.13	2.58 ± 0.14

DISCUSSION

Vascular PDT, intended to inhibit IH, eliminates proliferating smooth muscle cells resulting in a temporary acellular arterial wall [20,26]. A concern of this method is the potential formation of aneurysmal dilatation due to weakening of the arterial wall. This would limit the application of PDT as a measure to inhibit IH.

Grant et al. [26] reported that external PDT with a fluence of 100 J/cm^2 and a fluence rate of 150 mW/cm^2, did not reduce the arterial wall strength in the carotid artery of rabbits at a follow-up of 21 days using a similar method of measuring, despite of an acellular tunica media.

In our study we found that the means of the bursting pressure in all groups were above the normal physiological range (1.0–1.5 bar). The bursting pressure increased significantly at 2 hours after BI + PDT, both at 50 J/cm · diffuser length (dl) and 100 J/cm · dl. After 52 weeks, the bursting pressure was significantly increased in the BI + PDT 50 J/cm · dl group compared to the control and BI + PDT 100 J/cm · dl group. Apparently, a fluence of 50 J/cm · dl increased the arterial wall strength permanently.

The increase in arterial wall strength shortly after 100 J/cm · dl was transient and after one year aneurysmal dilatation developed in this treatment group. This indicates that the light dose for endovascular PDT is limited to a value between 50–100 J/cm · dl.

But how can the increase in bursting pressure of the arterial wall be explained after endovascular PDT? Statius van Eps et al. [20] suggested that PDT induces clustering or cross-linking of various protein components in the extracellular matrix, which seals the damaged vascular wall. In a chicken microvascular in vivo model it was also found that ALA based PDT led to an increased deposition of collagens in the arterial wall [27,28]. Furthermore, experiments in rats with methylene blue based PDT showed post treatment a significant increase of the amount of procollagen type I in the vascular wall, which may strengthen the blood vessel wall [29].

An important enzyme of the normal arterial healing response is lysyl oxidase that cross-links (tropo)collagens, fibrils and elastin, and is located in cellular lysosomes and in the extracellular matrix [30–33]. An earlier report described that high laser light output inhibited this particular enzyme in arteries [34]. However, relatively low energy PDT may activate this particular enzyme to induce an increased cross-linking of matrix proteins. In this manner, the vascular PDT-modified healing may form a

barrier for smooth muscle cell migration preventing the development of IH [35].

While that latter phenomenon could be beneficial, a possible disadvantage of the vascular PDT-modified healing is that the arterial contractility might be lost. However, the low fluence used in the present study enabled the repopulation of SMCs in the tunica media and tunica adventitia as reported in our earlier study [20]. Furthermore, we found that at long-term follow-up endovascular PDT at 50 J/cm · dl resulted in arterial dilatation and at 100 J/cm · dl even to an increase in the mean arterial diameter with a factor 2, leading to aneurysmal proportions.

Histopathologically, it seems that the amount of IH development is inversely related to bursting pressure after 52 weeks, with prominent IH in the BI + PDT 100 group and no IH in the BI + PDT 50 group. This could be due to unequivocal distribution of pressure forces at the arterial wall. In vivo, this is probably also reflected by the occurrence of aneurysmal dilatation in the BI + PDT 100 group. Histopathologically it is not clear how the differences in bursting pressure after 2 hours can be explained. The only histological difference after 2 hours was the partial acellularity in the vascular wall of the PDT groups.

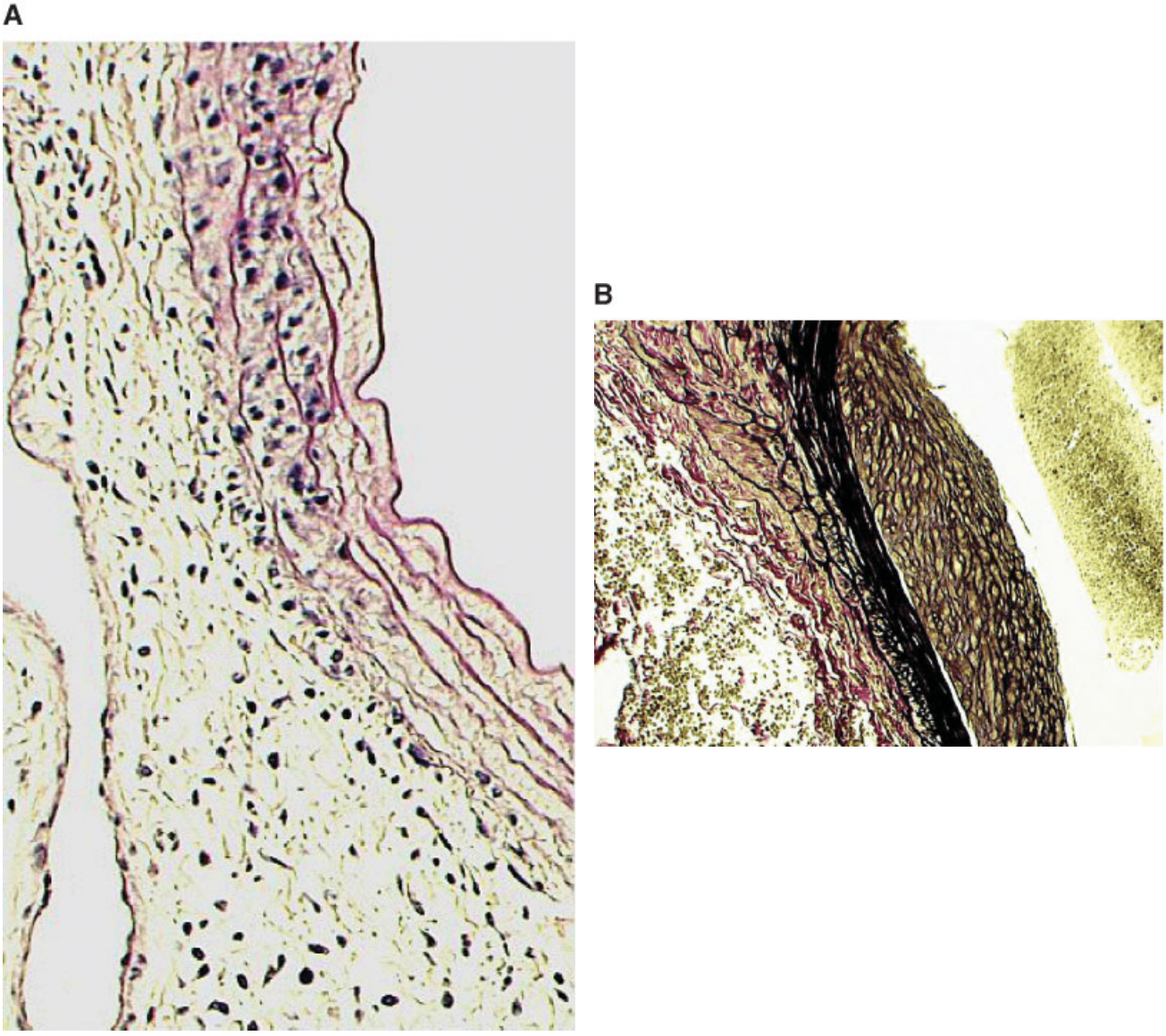

Fig. 5. Photograph **A** shows the partial acellularity in the tunica media at 50 J/cm · dl after 2 hours at a magnification of 200. Photograph **B** shows focal intimal hyperplasia (IH) at 100 J/cm · dl at a magnification of 200 after one year. Photograph **C1** shows a fragmentation of elastin in the tunica media at 50 J/cm · dl after 2 hours at a magnification of 400. An increased density of elastin is shown in photograph **C2** at a magnification of 400 in the same group. Photograph **D** shows an aneurysmal dilatation in the PDT group at 100 J/cm · dl after 1 year at a magnification of 100.

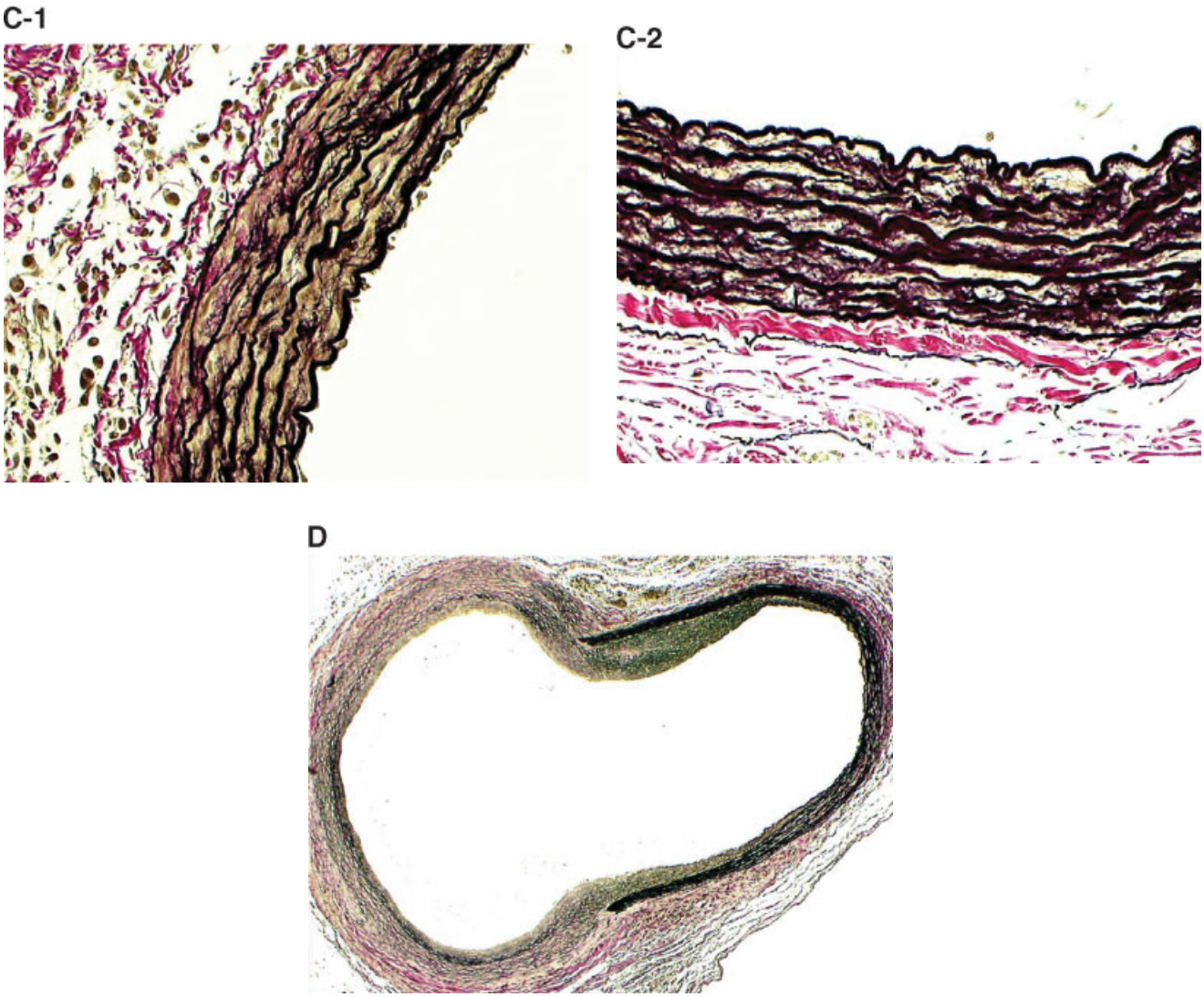

Fig. 5. (*Continued*)

A relative limitation of the open liquid-based bursting pressure set up used in this study, is the difficulty of fixing the cannula waterproof. However, the location of ruptures at the origins of vasa vasorum in the tunica adventitia in the treated artery could accurately be detected, which can easily be overlooked in models, using a balloon catheter for detection of bursts in the tunica adventitia.

In our model, a transient ischemic period was obtained during PDT as similar to the clinical practice of balloon angioplasty and endarterectomy. A relative bloodless environment is necessary to avoid excessive absorption of the laser light by hemoglobine that would prevent light penetration into the vascular wall. This would result in an unpredictable photodynamic effect.

We conclude that PDT at 50 J/cm · dl increases the arterial wall strength, maximal wall diameter and lumen diameter permanently in a rat IH model. However, high fluences (100 J/cm · dl) promote the development of aneurysmal dilatation. Therefore, the therapeutic window of high energy endovascular PDT is limited.

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