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Basic Investigations

Rupture of the Arterial Wall Causes Deflection in Pressure Time Course During Ex Vivo Balloon Angioplasty

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A relation between restenosis and arterial lesions resulting from balloon angioplasty has been suggested in literature. Nevertheless, it is unclear to what extent angioplasty-induced arterial wall lesions contribute to the occurrence of restenosis. One problem is that arterial ruptures cannot be detected during balloon inflation. This study describes a method to detect ruptures in the arterial wall, based on deflections observable in the development of the balloonpressure. We performed ex vivo angioplasty with constant strain rate on 28 human femoral artery segments, showing deflections in 21 cases. In 20 cases wall rupture was confirmed histologically. From seven cases not showing deflections, four showed intact wall at microscopy. These figures result in a selectivity of the proposed method of 87 ± 7% and a predictive value of the positive test of 95 ± 5%. We conclude that this method can enhance detection of arterial rupture during ex vivo angioplasty and may become important clinically. *Cathet. Cardiovasc. Diagn. 42:92–101, 1997.*

Key words: PTCA; dissection; intraballoon pressure measurement; restenosis

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is a fairly safe technique with an immediate success rate of 85% and up [1–5]. Major complications (myocardial infarct, emergency surgery, or death) occur in 3% of patients treated [1], whereas less severe complications occur more frequently [6,7]. The long-term success rate is significantly lower because of restenosis. Between 25% and 50% of all patients with successful first PTCA suffer from restenosis within 6 months [5,8–10].

Many modified procedures to overcome these complications of PTCA have been proposed. So far none of these seem to decrease the restenosis rate significantly [11–14]. Many other procedures for recanalization have been proposed as well—atherectomy [15,16], laser angioplasty [17], stenting [18], and rotablator [19]. From these procedures, only stenting after PTCA showed improved restenosis rates [18,20]. PTCA thus is expected to pertain its important role in the near future.

Results from studies in rabbit and rat models show a proportional relation between the severity of arterial wall injury and the extent of neointimal proliferation [21,22]. From these results a proportional relationship between interventional wall injury and clinical restenosis has been suggested [21]. Results supporting this suggestion have been found after angioplasty [23,24], atherectomy [23], and stent implantation [25].

These results, however, have been contradicted by results showing an inverse proportional [26]. Angiography showed increased restenosis rates after angioplasty with absence of dissection [27]. After successful angioplasty, defined as final gradient <15 mmHg, Leimgruber [28] found significant higher restenosis rates in absence of intimal dissection.

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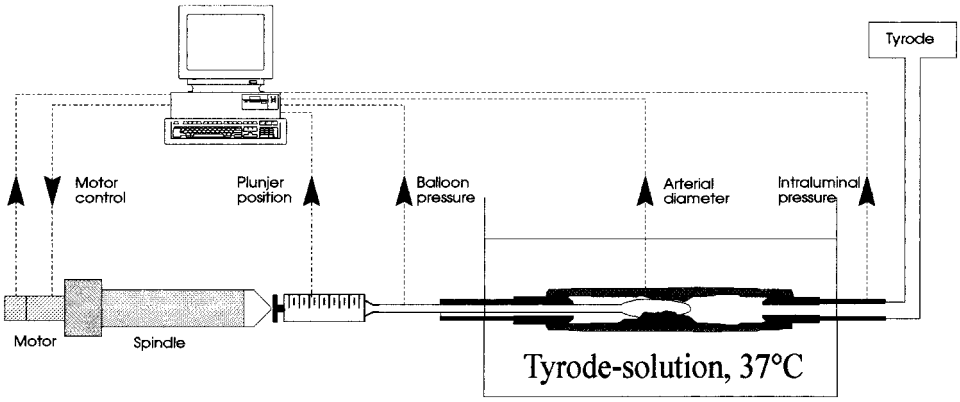

Fig. 1. Experimental setup used for ex vivo angioplasty experiments.

Interventional wall injury and restenosis rates also have been found to be unrelated [29]. Intravascular ultrasound examination after atherectomy intimal dissection or plaque fracture was unable to predict restenosis [30]. Bauters [31] found dissection assessed by angioscopy after angioplasty had no effect on late loss in luminal diameter. From similar results, Van Erven [32] concluded intimal hyperplasia to be an on/off response to injury.

Thus it is not clear whether angioplasty-induced arterial lesions are beneficial for both short- and long-term success. This indecisiveness has not yet been resolved, mainly because angioplasty-induced lesions cannot be detected during balloon angioplasty. The circumstances in which the lesions occur remain unknown. Detection of these lesions directly following angioplasty is not satisfactory. For instance, angiography following angioplasty reveals only the larger lesions [31]. Intravascular ultrasound shows excellent images, but the requirement to insert an additional catheter into the arterial tree is an obstacle for routinely using this technique. We therefore developed a method to detect arterial lesions as soon as they occur during balloon inflation. The method is based on abrupt changes in the development of the pressure inside the angioplasty balloon during PTCA. Such changes have elsewhere been interpreted as ''stress relieving fractures'' during angioplasty of rabbit arteries [33]. However, evidence associating a sudden change in pressure development with angioplasty-induced wall lesion has not been published yet. In this study we present the results of the ex vivo experiments we performed in human femoral artery segments to verify the method under reproducible and controllable conditions.

MATERIALS AND METHODS

Segments of human femoral arteries were obtained during autopsy after informed consent of the relatives. Most of the material was obtained from cardiological clinical patients, who had all died in the hospital. Only segments of femoral arteries of adults were used. No criteria regarding age, gender, race, or cause of death were applied. Both healthy and atherosclerotic artery segments were used. Directly after excision, the segments were stored in Tyrode-solution without glucose at 4°C. Surrounding connective tissue and fatty tissue were dissected before careful ligation of sidebranches. Two femoral artery segments of 20–25 cm were excised at each autopsy, providing four segments for the experiments. The artery segments were connected to two plugs by ligation and coupled to the experimental setup. Mean delay between autopsy and angioplasty was 4 days (range 1–7 days).

Experimental Setup

The experimental setup consisted of a PMMA container (Fig. 1) filled with Tyrode-like solution with the following composition in meq/l: Na^+ 158.7 Ca^{2+} 2.2, K^+ 5.6, Cl^- 143.6, HCO_3^- 21.4, $H_2PO_4^-$ 1.5, and glucose 11.7, in which the artery was extended 20%. This length was considered to be the in vivo length [34–36]. The perfusate was oxygenated by gassing with a mixture of 95% O_2 and 5% CO_2. pH was 7.4 and temperature was kept at 37°C. The pressure inside the artery could be changed by varying the height of a tank also filled with Tyrode solution. Intraluminal pressure was measured with a Spectramed DTXPlus pressure transducer connected to a Philips measuring amplifier. A balloon catheter could be inserted into the artery by pushing it through one of the stainless steel plugs, which connected the artery to the tank. This method was suitable for arteries with a lumen as small as 2 mm. We selected compliant coaxial Olbert angioplasty balloon-catheters of Meadox Surgimed A/S, because of the good reproducibility of the diameter-volume characteristic we found ($\pm$0.07 mm at

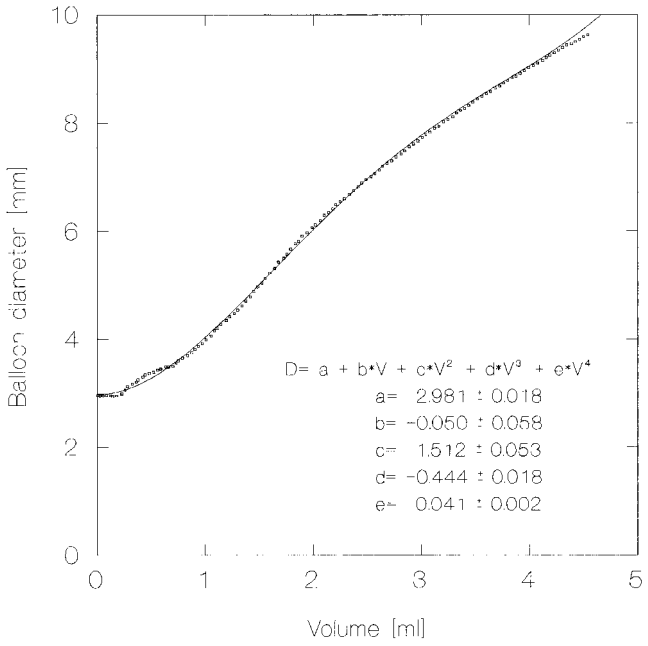

Fig. 2. Relation between volume V injected into the angioplasty balloon and the resulting diameter D. Line is fourth order polynomial regression curve. Reproducibility of the volume-diameter relation was ±0.07 mm at all diameters exceeding the zero pressure diameter with 1 mm.

37°C after a rest of at least 1 hr). These balloons also are used clinically in the femoral arteries. We used angioplasty balloons with maximal external diameters of 12 mm or 14 mm, instead of optimizing balloon-to-artery-ratio, to be able to stretch the arterial wall as far as needed for rupture.

The volume inside the angioplasty balloon could be changed with a syringe connected to a spindle (Vibo Rolschroef, Hanco, Helmond). The speed and direction of the spindle movement could be continuously controlled by a computer via a DC motor. To measure balloon pressure, a pressure transducer of Baldwin-Lima-Hamilton connected to an HBM amplifier (Hottinger Baldwin Messtechnik, Darmstadt) was used. The volume differences inside the angioplasty balloon were obtained by measuring the changes in the plunger position with a Linear Variable Displacement Transducer (LVDT) with an HBM amplifier. Absolute balloon diameter was measured using two LVDTs (Jensen LDT-5L, reproducibility of mean diameter 0.012 mm). Arterial diameter during dynamic measurements was assessed with four LVDTs in two orthogonal directions to minimise the effects of possible translations of the artery, as well as with B-mode ultrasound (10 MHz linear array scanner, Diasonics Master, resolution 0.15 mm, reproducibility ±0.2 mm) during static measurements as a control.

Relationship Between Balloon Volume and Balloon Diameter

The relation between the volume inside the unopposed balloon and the balloon diameter was measured before each angioplasty. Every time the balloon was inflated, the angioplasty wire was fixed on either side of the balloon to prevent the balloon from shortening and curling inside the artery. For the same reason we also made a small modification to the balloon by fixing the distal end of the catheter. This avoided axial contraction of the balloon and prevented longitudinal stress on the artery during inflation. The temperature during the measurement was kept at 37°C. For interpolation purposes the relation between the volume imposed on the balloon and the resulting diameter was fitted with a fourth order polynomial.

Relationship Between Balloon Volume and Balloon Pressure

The relation between the volume inside the unopposed balloon and the balloon pressure is dependent on the inflation rate. Therefore, reproducibility of this relation was tested by repeating inflations with a known inflation rate. The temperature during the measurement was kept at 37°C.

Measurement of Arterial Dimensions

Before and after balloon inflation mean inner diameter $D_{i,us}$ and mean outer diameter $D_{o,us}$ of the artery segment were obtained with B-mode ultra-sound by measuring the inner and outer diameters of the artery in two perpendicular directions, whereas the artery segment was stretched to its in vivo length [22]. From the means of these measurements the cross-sectional wall area A was calculated, assuming the artery to be circular internally and externally according to:

$$A = \frac{\pi}{4}(D_{o,us}^2 - D_{i,us}^2) \qquad (1).$$

Intraluminal pressure during measurement of the arterial dimensions was maintained with a small container filled with Tyrode solution at 100 cm above the artery. The arterial dimensions as obtained with ultrasound were used to calculate several parameters during the experiments. The inner arterial diameter D_i during balloon inflation was calculated from the outer diameter D_o by assuming that the cross-sectional wall area remained constant throughout the experiment, using

$$D_i(t)^2 = D_o(t)^2 - \frac{4}{\pi}A \qquad (2).$$

Internal circumferential arterial wall strain, (ϵ), segment strain in the following, was defined as the relative

increase of the inner arterial diameter, according to

$$\epsilon(t) = \frac{D_i(t)}{D_i(0)} - 1 \qquad (3),$$

with the arterial wall being unstrained at $t = 0$.

Conditioning of Artery Segment

Each artery segment was conditioned before dilation by changing the intraluminal pressure smoothly and repetitively between 20 and 100 mmHg, until a reproducible relationship between intraluminal pressure and outer diameter was attained. By doing this, we were able to start the dilation of the artery segments from a well-defined arterial condition.

Balloon Dilation of Artery Segment

After conditioning the artery segment, the angioplasty balloon was inserted as described above. To standardise, inflations were performed at constant strain rates of the inner arterial wall. This means that a nonconstant flowrate had to be applied. Actual applied flow to the balloon was thus dependent on the relation between balloon volume and balloon diameter as described before. Inflation was stopped when one of two stopping conditions was met: (1) observation of a deflection (detected by visual inspection) in the development of the balloon pressure, or (2) a balloon pressure of 10 bar.

The balloon was then emptied, which had to be done quickly but not abruptly to prevent the balloon from rupturing. Both the angioplasty wire and the angioplasty balloon were withdrawn from the artery segment. A deflection in the development of balloon pressure was defined as a discontinuity in the slope of the pressure-time relation. We found this moment to be distinct and well observable. Several experiments were performed in pairs as follows: one segment of the artery was inflated until a sudden change in balloon pressure was observed. The strain of the segment at this moment was calculated. The other segment of the same artery was inflated until the strain was 5% smaller than the maximal strain in the first segment. The inflation was then stopped to provide arteries that did not show sudden changes in balloon pressure, but were inflated sufficiently to be compared with the arteries that did show changes in balloon pressure. If either of the two stopping conditions was met before the desired strain was reached, the inflation was stopped.

Histological Fixation for Further Examination

For further histological examination, the place of maximum inflation was marked on the artery with Indian ink. The place of maximum inflation was defined as the place corresponding with the place of maximal balloon diameter. The proximal end of the segment was also marked. The artery was ligated at both sides, filled under pressure with gelatine by introducing a needle through a ligature, and fixed in 4% neutral-buffered formaldehyde. Gelatin was introduced in order to distinguish between lesions caused during balloon angioplasty and lesions caused afterwards (e.g., during fixation or cutting of the artery).

Reference Measurements

The pressure applied during balloon angioplasty consisted of two components: the pressure needed to inflate the balloon and the pressure exerted on the inner arterial wall related to wall stress. Both terms are dependent of both the inflation rate and time. To calculate the pressure actually applied on the arterial wall, a reference measurement (unopposed inflation) was carried out. The angioplasty balloon was inflated with the same strain rate and starting volume as during inflation of the artery. The difference between the pressure P during angioplasty of the artery and the pressure P_{ref} during unopposed inflation of the balloon with the same strain rate is denoted the dilation-pressure P_{dil}, according to

$$P_{dil}(t) = P(t) - P_{ref}(t) \qquad (4).$$

The strain in the balloon during angioplasty and during unopposed inflation must be equal at all moments to calculate dilation pressure. The dilation-pressure can be interpreted as the pressure inside an angioplasty balloon with infinite compliance.

Histological Analyses

To determine the relative angular position of the slides, the artery segments were carved longitudinally. The segments were cut transversely at the plane of maximum inflation and at 10 mm and 20 mm at both sides of this plane. Paraffin sections were stained with haemotoxilin-eosin (H&E) and van Gieson's elastin stain for histological examination. Of each obduction, a small control segment that had not been dilated was also examined. Histological analyses was performed independently by two pathologists unaware of possible pressure deflections during inflations. During examination, percentage of stenosis and place and severity of lesions were assessed. Percentage of stenosis was defined as the area of the neointima and plaque relative to the area inside the internal elastic lamina. Severity of lesion had to be assessed in four stages, corresponding with rupture of the various layers of the arterial wall: (1) no rupture, intact arterial wall and plaque; (2) intimal rupture (including rupture of plaque); (3) medial rupture; (4) rupture of the adventitia (including rupture throughout the artery).

RESULTS

The balloon volume-diameter relation was measured before every experiment. Minimal (''slack'') diameter of the balloons changed after multiple inflations. The shape of the balloon at zero pressure then became less smooth and less circular. However, at larger volumes the shape of the balloon stayed circular, even after multiple inflations. A new balloon was inflated five times before it was incorporated in the experiments. Figure 2 shows a typical relationship between the volume and diameter of an angioplasty balloon. Reproducibility of the volume-diameter relation of the balloons was examined by repeating the inflation after 1 hr of rest. It decreased at lower diameters because of irregularities in the shape of the balloon. Reproducibility at small diameters decreased with increasing number of inflations. Most of the long-term, nonreversible changes took place during the first few inflations. Reproducibility was ± 0.07 mm at all diameters exceeding the zero pressure diameter with 1 mm.

Pressure-volume relations of the balloon were affected by the elasticity and the viscosity of the balloon material and thus by temperature, as well as by velocity of inflation and number and extent of previous inflations. Pressure-volume relations were also found to reproduce at 37°C after 1 hr of rest, when the same inflation rate was used and the balloon had been inflated five times previously. Dependence of the pressure-volume relation on the strain rate showed to be nonlinear.

The artery segments were conditioned before the experiments. Figure 3 shows five cycles of pressure-diameter changes during conditioning of an artery; reproducibility of the external arterial diameter is clear after only 1 cycle of pressure changes. The hysteresis loops show the viscous behaviour of the arterial wall.

Twenty-eight arteries were dilated successfully. Four more experiments were started, but were not completed because of leaking balloons. Leakage of the balloons was caused by multiple insertion and removal through the stainless steel plugs connecting the artery segment to the experimental setup. Two segments were used to test whether handling of the segments or introduction of the balloon itself were responsible for arterial lesions. With these segments, the whole experimental protocol was carried out, except for the balloon inflation. Microscopy showed an intact arterial wall in both cases. Internal diameters of the segments before dilation, as obtained by external ultrasound (Fig. 4), varied between 2 mm and 7 mm. Strain rates of the internal arterial diameter during inflations were constant, varying between 0.1%/s and 2%/s between inflations. Out of the 28 experiments, 21 showed a distinct deflection in balloon pressure on a certain point of the pressure time curve; seven did not

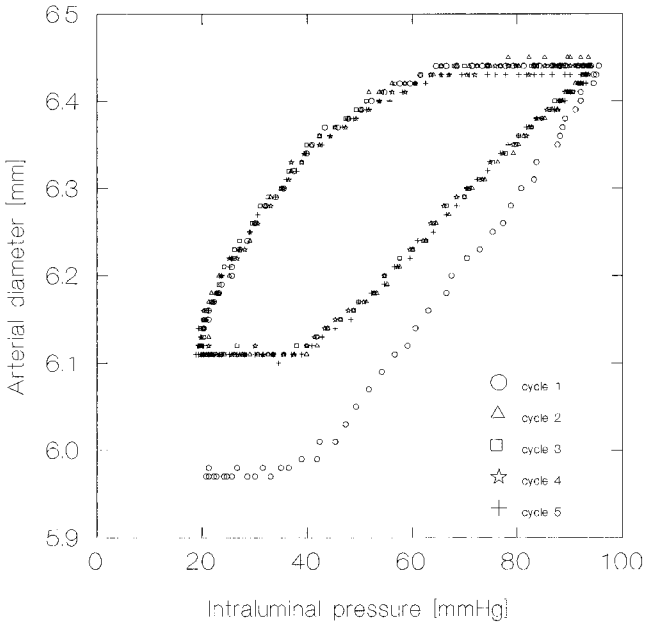

Fig. 3. External diameter of an artery before angioplasty. After one cycle arterial diameter-pressure relation becomes reproducible.

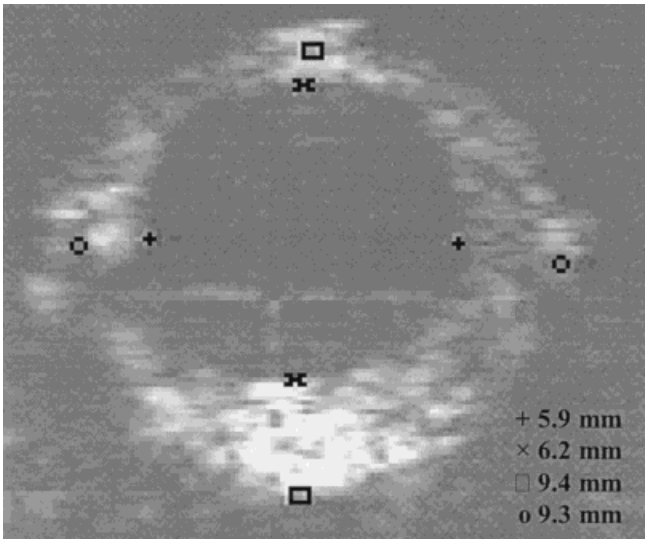

Fig. 4. Transversal ultrasound measurement of arterial dimensions.

(Table I). Inflation of the balloon inside the artery was stopped as soon as this deflection in pressure was noticed. Maximal balloon pressure during inflation (i.e., the pressure at the moment of deflection) varied significantly between the experiments (3–9 atm). Dilation pressure also varied between experiments but did not exceed 4 atm. These variations are caused by differences in the strain rates and consistencies of the artery segments.

TABLE I. Occurrences of Deflections in Pressure-Time Course and Arterial Ruptures in 28 Angioplasty Experiments

		Pressure-deflection		
		Yes	No	Total
Arterial rupture	Yes	20	3	23
	No	1	4	5
	Total	21	7	28

Figure 5 shows the pressure time courses in six experiments. Figure 6 shows dilation pressure in one of the experiments of Figure 5. It clearly shows the pressure inside the balloon during angioplasty to be equal to the pressure during unopposed inflation, demonstrating both reproducibility of the pressure-volume relation of the balloon and the concept of dilation pressure.

Figure 7 shows photomicrographs of lesions in four artery segments. Table II shows the number of times each type of lesion occurred.

Microscopy of the 21 segments that had showed a deflection during angioplasty revealed rupture of the arterial wall in 20 cases ($P < 0.001$). From the seven experiments that did not show such a pressure deflection, four had intact arterial wall at microscopy. The other three did show rupture of the arterial wall; two up to the medial layers, one with damaged elastica externa. Thus, 24 segments showed results supporting the proposed method: 20 experiments showing pressure deflection and wall rupture and four experiments showing intact wall and no pressure deflection. The other four experiments showed contradicting results: three segments with wall rupture without pressure deflection, one segment with pressure deflection and intact wall. The plaques of the 20 segments showing pressure deflections and wall rupture varied from 0–60% area stenosis (mean: 31%, standard deviation: 16%). We found no relation between the undetected wall ruptures and rupture severity, thus concluding the proposed method is sensitive for all types of ruptures. We neither found any relation with age, plaque severity, normal versus atherosclerotic arteries or gender.

These figures result in a selectivity of the proposed method of 0.87 ± 0.07. Specificity is 0.80 ± 0.18. The predictive value of the positive and negative test are 0.95 ± 0.05 and 0.57 ± 0.19, respectively. This means that the creation of a lesion during angioplasty is expected to be detected in 87% of all cases. If a deflection occurs in the pressure time course, the chance of having a lesion at that moment is 95%.

DISCUSSION

This study provides a method to detect arterial wall dissections during balloon angioplasty by observing the balloon pressure. Dissections varying from plaque rupture to rupture of the adventitia have been detected, both in normal and atherosclerotic arteries. This method has advantages over the methods commonly used, namely, angiography and intravascular ultrasound. By monitoring the balloon pressure, the origination of dissections can be detected real-time during angioplasty instead of afterward. Also, the dissections can be detected while the balloon is in situ. Angiography requires the addition of contrast medium, whereas intravascular ultrasound requires insertion of an extra catheter into the arterial tree. Together with the increased procedure-time, this will augment the risk of complications. The method we propose here can thus be used more easily and without increasing procedure risk. Contrary to angiography, small dissections also can be detected with this method. Furthermore, knowledge of the exact moment of the origination of the dissection makes it possible to obtain procedure-related parameters such as balloon-pressure, dilation pressure, arterial wall stress, and lumen diameter at that precise moment. This can increase the insight into the mechanisms behind angioplasty and restenosis and may lead to improved angioplasty procedures.

Detection of angioplasty induced arterial wall dissection is important because the relationship between these dissections and clinical restenosis is still unresolved. Recent studies show that migration of adventitial fibroblasts through medial dissections plays a more important role in arterial remodelling than was recognised earlier [37,38]. This indicates that further research on the relation between angioplasty-induced dissections and restenosis is necessary. We hypothesise that the detection of the first sign of arterial wall dissection can be used to restrict the dissection to the intimal or medial layer. The external elastic lamina will stay intact in this way and remain an important barrier against migration of adventitial fibroblasts.

Our method shows good results, but seems to overlook some ruptures. We cannot explain why the three cases did not show a pressure deflection, nor could it be explained by a common factor in their pathology. At the moment of rupture a pressure deflection could possibly be introduced, but was masked by noise in the pressure signal.

During in vivo angioplasty pressure variations originating from the cardiac pulse wave will be added to the balloon pressure measurement. The pressure changes associated with arterial dissection that we measured during the experiments varied between 5 kPa (38 mmHg) and 38 kPa (289 mmHg). The pressure variations induced on the angioplasty balloon by the pulse wave are estimated at maximum 5 kPa (40 mmHg) if they are passed through undiminished. Furthermore, the pressure changes caused by arterial wall dissection occur at once, whereas the pulse wave induced pressure variations will be

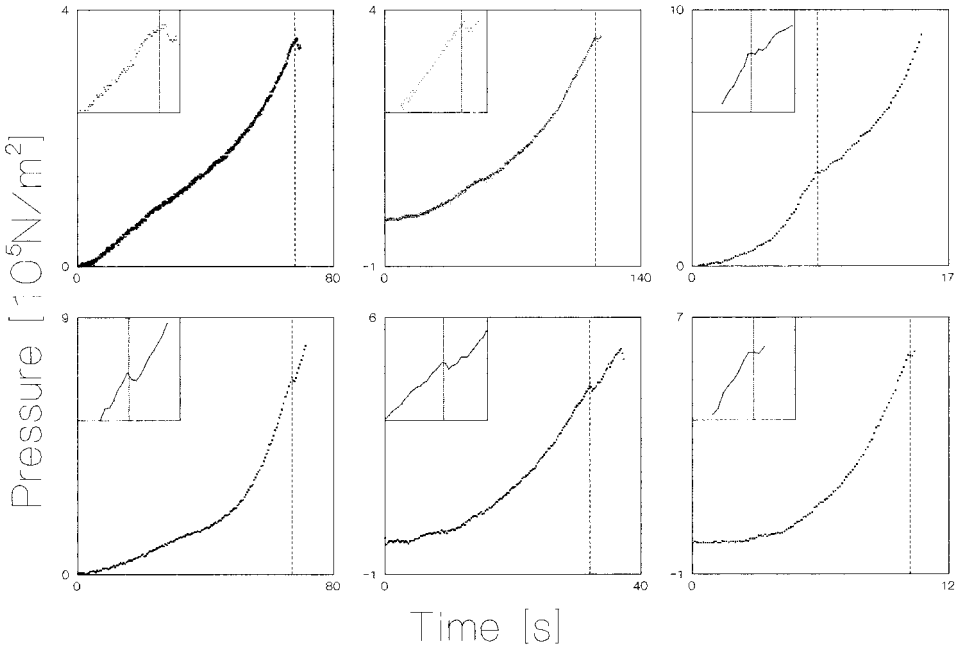

Fig. 5. Balloon pressure during 6 balloon angioplasty procedures. Deflection in the pressure time course are observable at 68, 115, 8.3, 67, 32, 10.2 (from left to right, upper row first). Inserts show moment of deflection more clearly.

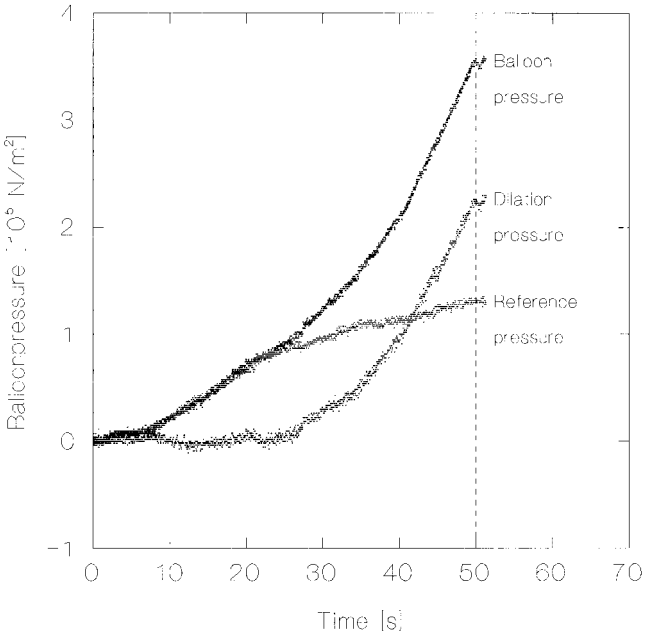

Fig. 6. Balloon pressure, reference pressure and dilation pressure during balloon angioplasty. Deflection in pressure development, associated with arterial rupture, is visible at 50 seconds.

periodical. We therefore expect that the pressure variations induced by arterial dissection can be distinguished from noise during in vivo angioplasty. Pressure measurement during in vivo angioplasty will, however, be seriously hampered by the use of contrast medium. Contrast fluids have viscous properties, thus damping pressure variations.

In vivo application of this technique will be possible with standard balloons and devices, with the exception of three modifications. First, the balloon has to be inflated smoothly, without inducing large pressure fluctuations. This can be achieved with the computer-controlled motor we described, or, e.g., by using a modified perfusion-pump. Second, a nonviscous fluid has to be used for inflation of the balloons. To maintain angiographic contrast, low concentration KI-solution can be used. Finally, to obtain pressure recordings, a pressure transducer has to be connected to the angioplasty balloon. These modifications will not affect inflation time or procedure time. With these modifications we expect pressure deflections to be visible during in vivo angioplasty. For in vivo validation of the method, angiography or intravascular ultrasound is necessary to determine wall rupture. The consistency of the excised arteries changes with increasing time. Histological studies with femoral arteries of rabbits showed that after 1 wk of storage in cold saline solution, endothelial cells in addition to most smooth muscle cells were necrotic [39], thus prohibiting active response to changed circumstances. In vitro arteries may react differently to angioplasty than in vivo arteries. However, the passive mechanical properties of the arterial wall will depend mostly on the extracellular framework in media and adventitia. This framework remained intact even after

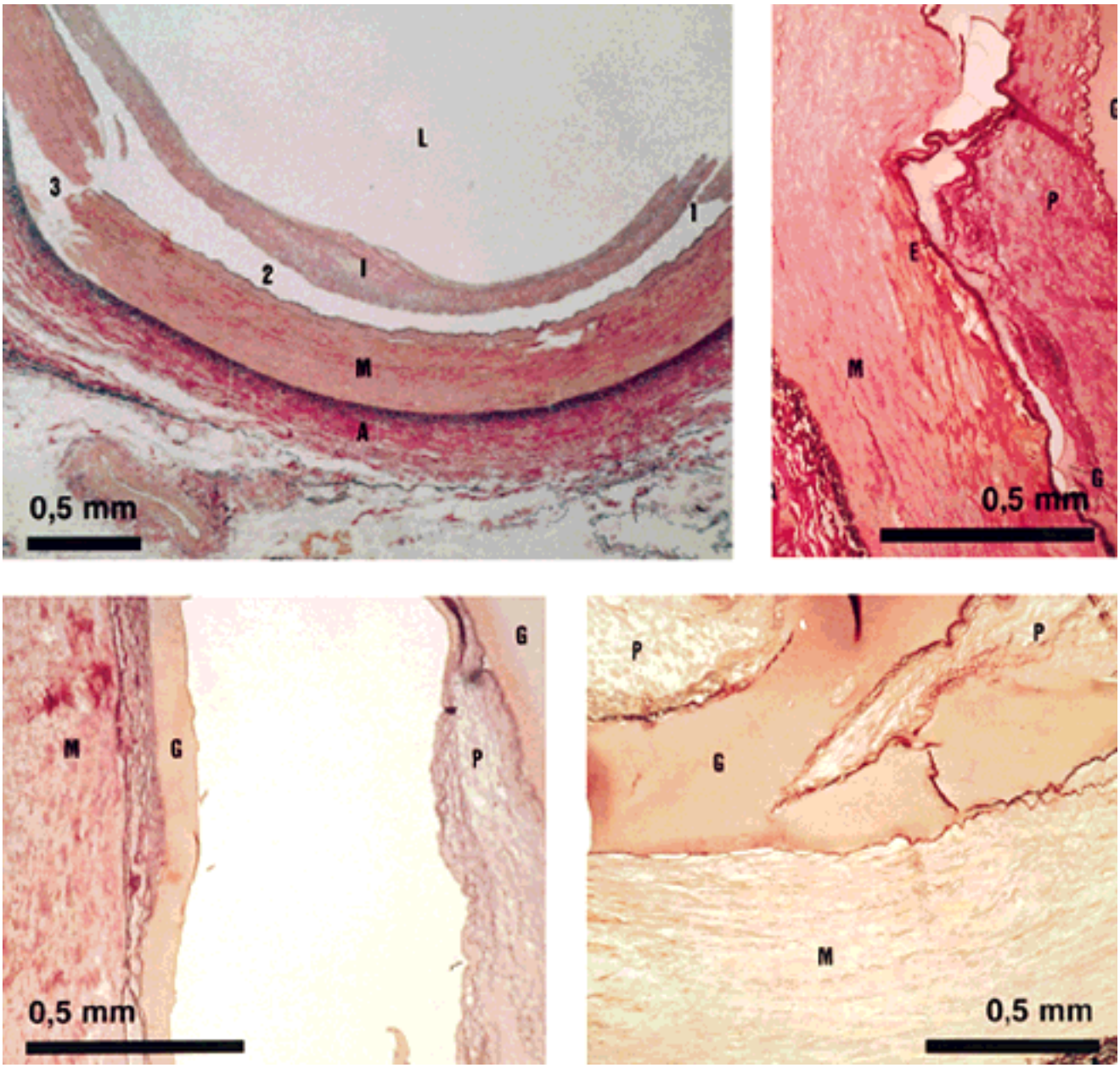

Fig. 7. Photomicrographs of sections of femoral artery segments showing lesions of various parts of the arterial wall. EvG. A (top left): Intima rupture (1) and dissection (2) as well as rupture of internal elastic lamina and media (3). External elastic lamina is intact. B (bottom left): Gross dissection of plaque and media. Note gelatin at luminal side and at rupture margins. C (top right): Rupture of intimal plaque at the side of the shoulder. Note gelatin in between plaque and media. D (bottom right): Dissection of excentric plaque at the side where two shoulders almost touch. Gelatin is visible in between plaque and media. A = adventitia, E = internal elastic lamina, G = gelatin, L = lumen, M = media, P = plaque. Magnification: A: 36; B, C: 69; D: 55.

TABLE II. Occurences of Various Degrees of Arterial Lesions Observed at Microscopy

Intact wall	Intimal rupture	Medial rupture	Rupture of adventitia
5	4	12	7

several weeks of storage [39]. On histology we did not find any lysis on any arterial segment. We thus conclude that excised arterial segments can be used to obtain data on the passive mechanical behaviour of arteries.

Microscopy of the two arteries used in the experiments that were performed without balloon inflation showed an intact arterial wall in both cases. We conclude that

dissection of the arterial wall in our experiments is not caused by handling of the artery before and after dilation, or by introduction of the catheter, but by the balloon inflation itself. This conclusion was supported by the observation that the dissections after in vitro angioplasty were located at the ''shoulders'' of the plaque. Arterial wall lesions were observed there after in vivo angioplasty and after spontaneous dissection of in vivo coronary obstructions too [40].

Our results show that a sudden decrease in balloon dilation pressure can be used effectively to indicate dissection of the arterial wall during PTCA.

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