Rat carotid artery dilation by PTCA balloon catheter induces neointima formation in presence of IEL rupture

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The Clowes (4) model of carotid balloon injury has become the standard rat model to study SMC proliferation in vivo in the laboratory (11–14) and that of others (4), and to investigate the factors involved in the restenosis phenomenon and potential treatments (4, 11–14, 16, 17). One of the major criticisms that have been moved to this rat model (and because the injury was performed on a normal nonatheromatous arterial bed), is that in all animals a reproducible neointimal formation is observed after the common carotid artery is injured, whereas in a clinical setting, restenosis occurs in ~50% of treated patients (4, 29). Therefore, the Clowes method could be considered ideal to study the proliferation of nontransformed smooth muscle cells in vivo, but is not a reliable experimental model of human angioplasty. In contrast, the porcine model of arterial injury was introduced to reproduce the mechanisms of human restenosis after angioplasty (3, 18, 24, 25). This is because the porcine balloon angioplasty could be performed on an atherosclerotic-like lesion. The rupture of the internal elastic lamina (IEL) is also considered the conditio sine qua non because the neointima occurs after clinical balloon angioplasty in swine as well as in humans (10, 25). The lack of the IEL rupture induced by the 2-Fr Fogarty-compliant balloon catheter has been hypothesized as one of the major differences between the Clowes angioplasty model and the response of the vessel following angioplasty in humans and their porcine surrogates (25). However, artery dilation using a standard percutaneous transluminal coronary angioplasty (PTCA) balloon catheter was never tested in rats.

Accordingly, the aim of the present study was to assess the effects of rat carotid artery dilation with a standard PTCA balloon catheter on IEL integrity, neointimal formation, and arterial remodeling.
METHODS

Animal preparation. Wistar rats weighing 500–550 g (at 20 wk of age) were included in the present study and received humane care in accordance with the animal use principles of the American Physiological Society. Rats were anesthetized with an intramuscular injection of ketamine (100 mg/kg) and xylazine (5 mg/kg).

Dilation of carotid artery with PTCA balloon catheter. Angioplasty of the carotid artery was performed using a PTCA balloon catheter (ACS RX Comet, Advanced Cardiovascular System; Temecula, CA) 1.5 mm in diameter with a 0.014-in. guide wire (Advanced Cardiovascular System). In brief, the balloon catheter was introduced through the right external carotid artery into the common carotid artery, and then the balloon was inflated at 11 atmospheres with a calibrated inflation device (Everest, Medtronic; Minneapolis, MN) (4, 14). To keep the time of the injury constant (that may influence the SMC proliferation and the arterial remodeling), we decided to maintain the time of inflation constant at 60 s (14).

The effect of the artery dilation was assessed in five groups of animals to study the neointimal formation and the arterial dimension over time. The arteries were removed immediately after the injury (n = 10), 7 days (n = 10), 14 days (n = 10), 21 days (n = 10), and 28 days (n = 10) after the balloon dilation. In all animals, the left common noninjured carotid arteries were also removed to normalize the size of injured arteries.

Morphometric analysis. At the time of the final experiments, the animals were anesthetized and the carotid arteries were carefully fixed in vivo by perfusion at 120 mmHg with 100 ml of phosphate-buffered saline (pH 7.2), followed by 80 ml of prepared phosphate-buffered saline containing 5% paraformaldehyde through a large cannula placed in the left ventricle (14).

The carotid arteries were removed and six cross sections were cut (each 6-μm thick) from the approximate midpoint of the artery, with three of these sections stained with hematoxylin and eosin to demarcate cell types. We have measured the section showing the higher amount of neointimal hyperplasia. The remaining three sections were stained with aldehyde fuchsin and counterstained with van Gieson's solution to demarcate the IEL (14).

Morphometric measurements of carotid arterial cross sections were evaluated from each balloon region with the use of a computer-assisted image analysis system. The injury index (10) was calculated using the formula (injury index: IELr / IELc × 100), where IELr is the IEL fracture length and IELc is the IEL circumference. The injury index was calculated using only the arteries removed at 14, 21, and 28 days after the arterial injury.

To investigate the effect of balloon dilation on the arterial remodeling, the obtained external elastic lamina circumference measures (IELc) were normalized by the IELc measure of the contralateral noninjured carotid of the same animal; this parameter represented the remodeling normalized ratio (RNR).

Immunocytochemistry. Because the peak time for DNA synthesis in the Clowes model occurs 2 days after injury, we included an additional group of animals (n = 7), in which the balloon angioplasty catheter dilation was performed and the arteries were removed on the second day. On serial arterial sections from all of the arterial groups (0 days, 2 days, 7 days, 14 days, and 28 days), single and double immunocytochemistry experiments were performed to identify proliferating cells. SMCs were identified by use of antibodies to smooth muscle α-actin. The proliferative activity of injured arteries was detected by use of the antibody MIB1, targeting the Ki-67 antigen, as previously described (2, 6, 26). On the MIB1-labeled slides, each field was scored for the extension of IEL fracture, neointimal or media areas, total nuclei number, and for the presence of positive nuclei and of cell type-specific markers. The percentage of MIB1-positive cells in relation to the total cell number was expressed as the proliferative index (PI%) (2).

Endothelial cell integrity. To assess the effects of the balloon angioplasty catheter dilation on endothelial cell integrity, each section of the arteries excised immediately after injury was stained with CD34 antibody (Biogeneces; San Ramon, CA), which is specific for endothelial cell viability (19).

Statistical analysis. All data are shown as means ± SE. Statistical analysis between groups was performed by two-way ANOVA with a SPSS version 10.0 program. When a significant overall effect was detected, Tukey's test was applied to compare single mean values (5). Linear regression analysis was also performed to compare the degree of neointima formation and the amount of IEL rupture. A value of P < 0.05 was considered significant. The coefficient of variation was calculated by dividing the standard deviation of the mean by the mean.

RESULTS

Effect of carotid artery dilation with PTCA balloon catheter on neointima hyperplasia. In sham-operated rats that were not subjected to vascular injury, no neointimal formation was detected. The IEL rupture was detected in 36 of 50 (71%) rat carotid arteries after balloon angioplasty. A significant neointimal formation was detected only in arteries with ruptured IEL (Fig. 1) and a strong positive correlation between the percentage of fracture in the IEL circumference and the magnitude of the resultant neointimal tissue was observed (Fig. 2). Figure 3 shows representative histological cross sections of carotid arteries after dilation with PTCA catheter compared with a normal carotid section from rats not subjected to vascular injury and a histological section of carotid arteries injured with a Fogarty balloon catheter from a previous study from

![Fig. 1. Neointimal hyperplasia in rat carotid arteries 28 days after arterial injury. Bars represent neointimal formation (Neointima Area) in the rat with ruptured internal elastic lamina (IEL) and intact IEL. Significant neointimal formation was observed only when the IEL was ruptured. *P < 0.001 vs. IEL ruptured.](http://ajpheart.physiology.org/)

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our laboratory (14). It is worth noting that although balloon injury using the 2-Fr Fogarty catheter did not result in any fractures in the whole IEL circumference, a concentric neointimal thickening was observed. In contrast, using the PTCA balloon catheter, neointimal formation was negligible when IEL did not present any fractures. In contrast, eccentric neointimal lesions were observed where IEL was ruptured (Fig. 3). In fact, 28 days after balloon angioplasty with a PTCA catheter, in the presence of IEL rupture (n = 8), the neointimal cross-sectional area and the neointima-to-media ratio were 0.066 ± 0.015 and 0.518 ± 0.119 mm², respectively (P < 0.05 vs. IEL preserved) (Table 1). Conversely, where any IEL fractures were not detected, neointimal tissue was actually negligible (neointimal cross-sectional area = 0.001 ± 0.001 mm² and neointima-to-media ratio = 0.011 ± 0.011) (Fig. 1).

Occlusive vessel thrombosis was detected in 5.2% of animals (3 of 50). The coefficient of variation of neointima measurements was 0.007.

Effect of carotid artery dilation with PTCA balloon catheter on arterial remodeling. To standardize the arterial dimensions (that may vary depending on the animal body surface area), the EELₚ measures were normalized by the measure of the EEL of the contralateral noninjured carotid of the same animal and the variation in arterial dimension were expressed as RNR (Fig. 4). A progressive reduction of the RNR was observed after the injury (Fig. 4 and Table 1).

Cell proliferation in injured arteries. Positive staining for at least one Ki-67-positive cell was found in all the analyzed arteries. A strong association between the percentage of IEL circumference fractures and the expression of Ki-67 in the smooth muscle cells of the arterial wall was detected (Fig. 5). Few or no signs of smooth muscle cell proliferation were found in the media of the arteries in which IEL fracture was <5% of the total. In the arteries where IEL fracture was >5%, cell proliferation was more distinct.

The time course of cell proliferation in the intima/media lesions of the arteries, in which IEL fracture was >5%, peaked at 7 days, increased to 14 days, and then progressively decreased to 28 days (Fig. 6 and Table 2).

Endothelial cell integrity. Additional experiments were performed to evaluate the effects of balloon angioplasty catheter dilation on the endothelial surface integrity. The carotid arteries excised immediately after the balloon angioplasty procedure were stained with CD34 antibody (specific marker for endothelial cells) to evaluate the endothelial cell viability. As depicted in the Fig. 7, the balloon dilatation denuded the endothelial surface in correspondence with the IEL rupture whereas absence of denudation was observed in arteries with IEL intact. Therefore, the endothelial denudation is confined to the IEL rupture.

DISCUSSION

There are two major findings of the present study. First, a strong positive correlation between the percentage of ruptured IEL circumference and the magnitude of the resultant neointimal tissue was observed in rats when a standard PTCA balloon catheter was used to perform carotid balloon injury. Second, lumen loss after this new experimental model of balloon angioplasty is related to the arterial negative remodeling and to the neointimal hyperplasia (only in the presence of ruptured IEL).

Small animal models of restenosis, such as the 2-Fr Fogarty catheter-induced rat carotid injury, have been extensively used in our laboratory (11–14, 16, 17) and other laboratories (4), to assess the arterial response to the injury.

However, because of limitations in predicting restenosis in human beings, the effectiveness of agents in minimizing restenosis in these small animal models has not yet well translated to the clinical setting (27, 28). Therefore, other small animal models that may resemble the effects of human vascular injury after interventional procedures could be of great interest for study of the restenosis phenomenon and for assessment of potential therapeutical strategies. In fact, we (15) recently described a new model of arterial stenting in the rat.

Implementation of a secondary large animal model of restenosis (swine) was introduced to improve the predictability of new agents and/or regimens on clinical efficacy (20). Previous studies (3, 10, 18, 24, 25) performed in swine models of restenosis demonstrated that the neointimal lesions after balloon injury in the pig were reparative because they primarily filled the void left in the vessel wall at the point of IEL and medial disruption. Therefore, in the pig, neointimal hyperplasia occurs only when the IEL is ruptured. Similarly, restenotic lesions associated with IEL rupture and underlying medial damage have also been observed in human PTCA patients (7).
A major criticism that has been moved to the rat model using the Fogarty balloon technique is that in all animals a reproducible neointima is observed, whereas in a clinical setting restenosis occurs in ∼50% of patients (29). The presence or the absence of ruptured IEL may explain why restenosis does not develop in all patients undergoing coronary angioplasty. We (14) showed that when the embolectomy catheter is used in the rat, the neointima formation was observed in all animals even if IEL did not present any fractures and the amount of hyperplasia is related only to the degree of balloon inflation pressure.

Present catheter technology allows performing a carotid angioplasty in rats with a PTCA balloon because

![Fig. 3. Representative histological cross sections. A: common carotid artery from a normal rat (no balloon injury). B: common carotid artery after injury with the 2-Fr Fogarty balloon (4). C: common carotid artery after injury using the angioplasty balloon catheter. D: common carotid artery 28 days after injury using the angioplasty balloon catheter. Balloon injury caused a homogeneous formation of neointima with no IEL rupture when the 2-Fr Fogarty balloon is used (B). In contrast, using the angioplasty balloon catheter, neointimal formation was negligible when IEL was intact (C). Eccentric neointimal lesions were observed where IEL was lacerated (D, arrows). Top, Van Gieson ×100; Bottom, hematoxylin-eosin ×400.](image)

**Table 1. Morphological results of ballooned carotid cross sections from each animal, revealing IEL rupture**

<table>
<thead>
<tr>
<th></th>
<th>0 Days (n = 6)</th>
<th>7 Days (n = 7)</th>
<th>14 Days (n = 8)</th>
<th>21 Days (n = 7)</th>
<th>28 Days (n = 8)</th>
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<tr>
<td>Neointimal CSA, mm²</td>
<td>0</td>
<td>0.04 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>0.05 ± 0.01</td>
<td>0.07 ± 0.01*</td>
</tr>
<tr>
<td>N/M ratio</td>
<td>0</td>
<td>0.31 ± 0.11</td>
<td>0.25 ± 0.08</td>
<td>0.40 ± 0.10</td>
<td>0.52 ± 0.12*</td>
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<tr>
<td>LCN</td>
<td>1.10 ± 0.10</td>
<td>1.05 ± 0.03</td>
<td>0.96 ± 0.03*</td>
<td>1.01 ± 0.02*</td>
<td>1.00 ± 0.02*</td>
</tr>
<tr>
<td>RNR</td>
<td>1.12 ± 0.02</td>
<td>1.05 ± 0.03</td>
<td>1.03 ± 0.02*</td>
<td>1.02 ± 0.02*</td>
<td>1.02 ± 0.01*</td>
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Values are means ± SE; n = no. of animals. IEL, internal elastic membrane; CSA, cross-sectional area; N/M, neointima-to-media ratio; LCN, internal lumen circumference normalized for the noninjured artery; RNR, remodeling normalized ratio equals external elastic lamina circumference normalized for the noninjured artery. *P < 0.05 vs. 0 days.
small angioplasty-noncompliant catheters (1.5 mm) are available. In the present study, we demonstrated that in rats, when a balloon angioplasty with a PTCA catheter is performed (i.e., only the inflation of the angioplasty catheter, without passing the inflated catheter in the vessel lumen for three times as in Clowes model), neointimal tissue is formed only when the rupture of the IEL occurs.

In the carotid arteries, SMC proliferation was tightly correlated with the extent of the injury on the arterial wall. The most preponderant concentration of proliferating cells was observed in the arteries in which the amount of IEL fracture was >5% of the total IEL circumference.

Smooth muscle cell turnover in the media and intima of the arterial wall after vascular injury has been measured experimentally (as in other cell types) on the basis of incorporation of nucleotides, such as [3H]thymidine and bromodeoxyuridine or labeling by proliferating-cell nuclear antigen, which is implicated in the transition from G1 to S phase (1, 21). However, these findings have been questioned as indicators of cell proliferation (1, 21). The detection of SMC nuclei that are positive for thymidine and bromodeoxyuridine does not indicate whether DNA synthesis is coupled with nuclear hyperplasia, ploidy formation, or DNA repair. Limitations apply to staining of proliferating-cell nuclear antigen in cell nuclei. Proliferating cell nuclear antigen is a cofactor of DNA polymerase, which is implicated in DNA synthesis, cell cycle progression, and DNA repair (1, 21). We overcame these difficulties by using Ki-67 as a marker of cell proliferation. There is not a single example of a Ki-67-positive cell that cannot divide (1, 21). Biochemically, Ki-67 is an essential element of the outer dense fibrillar compartment of the nucleolus, where it acts as an efficiency factor in the rapid production of ribosomes for the increased metabolic requirements of dividing cells. Structurally, Ki-67 is a molecule of 395 kDa that contains a motif typical of several transcription factors. Ki-67 has a
preference for binding to adenine- and thymidine-rich sequences similar to the consensus site of p53. This competition emphasizes the role of Ki-67 in cell replication. It may be recognized by the monoclonal antibody MIB1 that recently has been introduced in routine surgical pathology as a reliable proliferation marker and prognostic indicator for several malignant tumors (9, 26) and for carotid endoatherectomy (2). With this technique it is possible to investigate the time course of cell proliferation in the tunica media after the arterial injury. It was evident that the proliferative response in the proposed new balloon angioplasty model peaked at 7 days and was prolonged up to the second week after the injury, in contrast to what happen with the Fogarty-induced injury where the peak of proliferation in the tunica media is at 2 days and was prolonged to the first week.

There are several possible explanations for the association between the proliferating activity and the arterial damage. First, it might be argued that proliferating cells represent a mechanism of repair of the void left in the arterial wall after the damage induced by the balloon dilation. In this condition, the more is the damage the more is the proliferative response. Second, the focal accumulation of Ki-67-positive cells in the proximity of an IEL fracture suggests that the cells in that area are replicating under the effect of several factors generated in that specific site after the exposure of the connective tissue of the arterial wall to the circulating blood. The quiescent SMCs are recruited in the cell cycle to promptly replace the cells migrating toward the IEL fracture and localize beneath the endothelium to form the neointima. In summary, the tight correlation of Ki-67 reactivity with arterial damage documents that proliferation contributes to the repair of the arterial wall consequent to balloon dilation.

The results of the present study demonstrated that in rats, the structural integrity of the IEL appears essential to minimize neointimal proliferation when an angioplasty catheter is used. This finding was originally described in swine (18) but was never shown in rats. The differences between the types of injury induced by the Fogarty catheter and by the PTCA balloon catheter might partially explain why many pharmacological studies were successful in rats and negative in swine and in humans (27, 28).

Further studies will be needed to investigate whether or not the response to therapeutical approaches using the new method suggested in this study will be confirmed in standard swine models of restenosis, which are more expensive and available only in few laboratories. It should be pointed out that the new transgenic technologies encourage the use of small animals as well.

### Table 2. Time course of the proliferation index in carotid arteries after PTCA catheter-induced injury

<table>
<thead>
<tr>
<th>Inj ind &lt; 5%</th>
<th>0 Day</th>
<th>2 Days</th>
<th>7 Days</th>
<th>14 Days</th>
<th>21 Days</th>
<th>28 Days</th>
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<tr>
<td></td>
<td>2.6 ± 0.8</td>
<td>3.5 ± 0.7</td>
<td>7.6 ± 2.0</td>
<td>3.6 ± 0.7</td>
<td>8.8 ± 1.0</td>
<td>8.4 ± 2.4</td>
</tr>
<tr>
<td>Inj ind &gt; 5%</td>
<td>2.6 ± 0.8</td>
<td>7.6 ± 3.20†</td>
<td>16.3 ± 4.5*</td>
<td>15.6 ± 2.0*</td>
<td>9.2 ± 1.3†</td>
<td>4.2 ± 0.5</td>
</tr>
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</table>

Values are means ± SE. PTCA, percutaneous transluminal coronary angioplasty; Inj ind < 5%, injury index in the arteries that presented <5% of IEL fracture; Inj ind > 5%, injury index in the arteries that presented >5% of IEL fracture. *P < 0.01 vs. 0 days, 2 days, 21 days, and 28 days; †P < 0.01 vs. 0 days, 7 days, 14 days, and 28 days.

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**Fig. 7. Endothelial cell denudation.** A: in absence of IEL fracture after balloon angioplasty catheter dilation, no loss in the circumferential endothelial layer was observed. Bottom, example (indicated by arrows) at higher magnification. B: balloon dilation denuded the endothelial surface in correspondence with the IEL rupture (indicated by arrow above), where it is evident the endothelial loss demonstrated by the absence of positive CD34 cells (bottom).
Recent studies (22, 23) have indicated that clinical restenosis after balloon angioplasty is the sum of geometric remodeling and neointimal formation. Specifically, human studies (22, 23) have shown that arterial circumference can change in response to arterial intervention (called “geometric,” “negative,” or “inward” remodeling) and explain up to 70% of late lumen loss after balloon angioplasty. In the present study, we have described for the first time, the phenomenon of negative remodeling in rat arteries after balloon dilation with a PTCA catheter. However, although the arterial geometric remodeling contributes to reduce lumen narrowing, the mechanisms responsible for this phenomenon are still unknown. Therefore, this animal model might be of major relevance to evaluate the potential mechanisms responsible for arterial remodeling as well as the possible therapeutic strategies.

It has been demonstrated that the use of swine may have certain advantages in the study of restenosis (3, 10, 18, 24, 25). However, a good model of restenosis requires animals that are inexpensive, readily available, easy to use, and that develop lesions over a fairly short period of time. Thus although a hierarchical strategy should be always used to test new therapeutic approaches (first by screening small animals, and when a promising agent is identified, preclinical studies could be eventually tested in swine models), the animal model described in the present study could be used to investigate the mechanisms of restenosis after angioplasty and to assess potential therapeutic approaches.

Limitations. As mentioned earlier, the lack of the IEL rupture induced by the 2-Fr Fogarty-compliant balloon has been hypothesized as one of the major differences between the rat Clowes model and the response of the vessel after angioplasty in humans (25). In the present study, we described a new balloon angioplasty model in rats that is similar to the one used in humans regarding the finding of IEL rupture. However, it should be pointed out that the neointima in humans is part of generalized atheroma formation, which includes fibrous, fatty, and smooth muscle cells. These components can be found in some porcine models of atherosclerosis but there is no evidence that the rat can actually have these components within their atheroma. Although our method demonstrated the importance of IEL rupture, the data should be interpreted with extreme caution.

The carotid is not similar to other arterial beds with respect to its reaction to stimuli. Coronary arteries and peripheral arteries, such as the iliacs and femorals, may have different media, lumen diameter, and physiological characteristics and also different elastic lamina than the carotid. Because it is not possible that angioplasty could be performed on the coronary beds in rats, we tried to assess the effects of balloon angioplasty catheter dilatation in the ileo-femoral trunk in a separate set of experiments not included in the present study. To this aim, it should be pointed out that it is not possible to reproduce in rats the porcine/rabbit model of ileo/femoral arterial injury model that uses a femoral approach and then to maintain the flow in femoral artery, we approached this artery via an arteriotomy of the common carotid artery. After an excision in the common carotid artery was performed, we introduced a metallic guidewire into the femoral artery and the balloon catheter over the wire was positioned and dilated in the common right femoral artery (we surgically exposed the two femoral arteries before introducing the guidewire and the balloon). In our hands, these experiments were reproduced poorly and were not standardizable. Therefore, we think that the carotid artery, even with the above mentioned limits compared with coronary and peripheral arteries, is the best arterial bed to perform the experimental balloon angioplasty model in the rats.

In conclusion, our animal method could be useful to study the pathophysiology of balloon-induced arterial injury. In fact, the Clowes-Fogarty method induces the formation of neointima with the IEL intact, which is quite different from the injury induced by an angioplasty balloon in humans. The method proposed in the present study, in which the neointimal formation occurs only when IEL is ruptured, resemble the consequences of vascular injury induced by a reliable balloon angioplasty and might be of importance to assess potential therapeutic strategies.

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