Morphometric analysis of swine carotid artery angioplasty with or without cobalt-chromium stent implantation

Análise morfométrica da carótida de suínos submetidos a angioplastia com ou sem implante de stent de cromo-cobalto

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Abstract

Background: Intimal hyperplasia is the most common delayed response to angioplasty. The use of cobalt-chromium stents is well studied in the coronary circulation; however, there are few studies on their use in the carotid and peripheral circulation.
Objective: To analyze the intimal reaction in a swine carotid artery undergoing simple angioplasty and angioplasty followed by implantation of cobalt-chromium stent.
Materials and methods: We carried out angioplasty in the right common carotid artery and angioplasty with cobalt-chromium stent in the left common carotid artery in eight swine. Four weeks later, all animals were sacrificed for arterial tissue sampling and preparation of histological slides. Slide images were scanned and analyzed using a digital morphometry program. Statistical analysis was performed by mean values and standard deviations of the areas in each group, using the Student's ***t*** test. A p value of < 0.05 was considered significant.
Results: Angioplasty with cobalt-chromium stent implantation resulted in a higher degree of hyperplasia compared with simple angioplasty. The difference was statistically significant when the lumen area, the internal elastic lamina area, and the external elastic lamina area were compared between the two groups. No statistically significant difference was found when the media layers of both groups were compared.
Conclusion: Cobalt-chromium stent implantation resulted in more intimal hyperplasia than simple angioplasty, however the stent was not enough to reduce the arterial lumen.

Keywords: Angioplasty, stents, swine.

Resumo

Contexto: A hiperplasia intimal é a reação tardia mais comum decorrente da angioplastia. O uso de stents de cromo-cobalto é bem estudado na circulação coronariana, porém não há muitos estudos que abordem o uso desses stents nas circulações carotídea e periférica.
Objetivo: Analisar mediante morfometria a reação intimal presente na artéria carótida de suínos submetidos a angioplastia isoladamente e a angioplastia seguida de implante de stent de cromo-cobalto.
Materiais e métodos: Em oito suínos, foi realizada angioplastia da artéria carótida comum direita e angioplastia seguida de implante de um stent de cromo-cobalto na artéria carótida comum esquerda. Após 4 semanas, os animais foram submetidos a eutanásia para a retirada de amostras de tecido arterial e preparo de lâminas histológicas. As imagens das lâminas foram digitalizadas e analisadas por programa de morfometria digital. A análise estatística foi realizada através da média e desvio padrão das áreas em cada grupo, utilizando-se o Teste *t* de Student. O valor de $p < 0,05$ foi considerado significativo.
Resultados: O implante do stent provocou maior grau de hiperplasia comparado à angioplastia isolada. A diferença em resposta ao implante de stent foi estatisticamente significativa quando as áreas do lúmen, da lâmina elástica interna e da lâmina elástica externa foram comparadas entre os dois grupos. Não se observou diferença significativa quando se realizou a comparação entre as camadas médias dos dois grupos.
Conclusão: O implante de stent de cromo-cobalto gerou um espessamento intimal maior do que o produzido apenas pela angioplastia, porém ele não foi suficiente para reduzir o lúmen arterial.

Palavras-chave: Angioplastia, stents, suínos.

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Introduction

Despite significant advances in percutaneous transluminal angioplasty (PTA) and stenting for focal atherosclerotic lesions, restenosis is still the main long-term limitation of endovascular therapy.[1-3] The choice of stent alloy likely plays a major role in the intimal response to stent placement.[3,4] Although some experimental studies have shown encouraging results with the use of biodegradable alloys, these results have yet to be confirmed in human trials.[5,6] Most commercially available stents are made from metallic alloys that differ not only in mechanical properties (biofunctionality), but also in compatibility with the recipient's body (biocompatibility).[3,7] These two factors are of the utmost importance in analyzing inflammation and cell proliferation in the arterial wall.[3,7-9] At least four mechanisms are involved in long-term post-stenting intimal hyperplasia: vascular injury caused by the procedure itself; continuous presence of an intravascular foreign body; chronic vessel wall strain; and delayed reendothelialization.[10]

Both intimal hyperplasia and increased local thrombogenicity are determined by the characteristics of the metal alloy from which the stent is made and by its surface coating.[4] Among the main alloys used in stent manufacturing (stainless steel, cobalt-chromium, and nitinol), stainless steel is the least resistant to corrosion and should, theoretically, be used only on a temporary basis. Titanium and cobalt-chromium alloys are subject to less corrosion in the body, but release metallic ions that are deposited in the tissues adjacent to the stent. There are no available data on the long-term complications of this metal deposition process.[7]

The present study seeks to conduct a comparative, digital morphology-based analysis of the intimal reaction occurring in the swine carotid artery after simple angioplasty and angioplasty with cobalt-chromium stent placement.

Materials and methods

The study sample comprised eight Large White pigs, from different breeding stock, with a mean age of 8 weeks and a mean weight of 20 kg (range, 18–22 kg). The study itself was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre Graduate Research Group, and followed humane experimentation principles set forth by the Brazilian College of Animal Experimentation (*Colégio Brasileiro de Experimentação Animal*, COBEA).

The balloon-expandable stents used in the study (deployed diameter, 4 mm; length, 16 mm) were kindly provided by Eucateh, with no conflict of interest, as established by Brazilian Federal Concil of Medicine Resolution 1595/2000.

Surgical procedures were performed under intravenous general anesthesia followed by local anesthetic infiltration of the incision site. Preoperative fasting, sedation, IV access, fluid replacement, and postoperative analgesia were provided according to Animal Experimentation Unit protocols.

The criteria for exclusion from the study were thrombosis or rupture of the angioplasty segment, reintervention for bleeding, death of the animal before the established date of tissue collection, and technical issues in tissue preparation or processing.

The procedure began with a left groin cutdown for exposure of the common femoral artery (Figure 1). After direct puncture to the common femoral artery was obtained with an 18G needle, a 0.035-inch hydrophilic guidewire was introduced, and a 6F introducer sheath was placed. Under fluoroscopic guidance, the guidewire was advanced to the aortic arch with a pigtail catheter inserted over it. After aortography and identification of the common carotid arteries, the left common carotid artery was selectively catheterized with a 5F vertebral catheter, and the 0.035-inch guidewire was replaced with a 0.014-inch guidewire. We then performed angioplasty and placed a 4 x 16 mm balloon-expandable stent in the middle segment of the artery, maintaining an expansion pressure of 8 atm for 30 seconds. This was followed by selective catheterization of the right common carotid artery and balloon angioplasty, also with 30 seconds of 8-atm expansion pressure, in the middle third of the artery, with a 4 x 16 mm balloon catheter. A catheter gauge 10–20% wider than the normal diameter of the CCA in 8-week-old swine was chosen to ensure balloon oversizing and subsequent circumferential strain and stretch. After the procedure, control arteriography was performed to confirm artery patency.

Arteriography was performed through a 5F pigtail or vertebral catheter, with manual injection of iothalamate meglumine 1 mL/kg for contrast. Arteriograms were obtained with a portable fluoroscope (SK7-3) and recorded on DVD (Samsung).

Postoperatively, the animals were kept in pens specifically designed for this purpose, under the guidance of a veterinary surgeon. A regular diet was resumed 12 hours after surgery. The animals were provided running water ad libitum and fed as before, with a balanced, age-appropriate diet and no additional lipid supplementation. After 30 days,

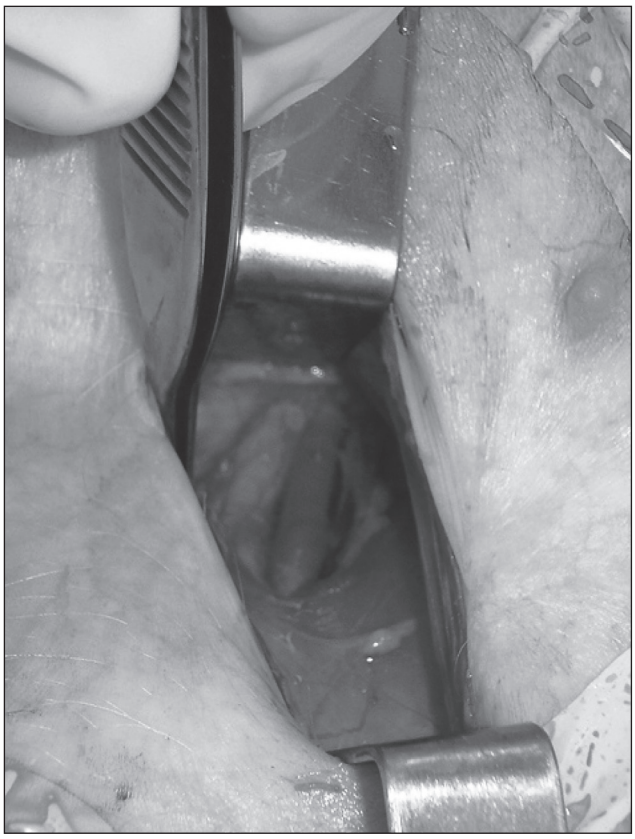

Figure 1 – Approach to the common carotid artery

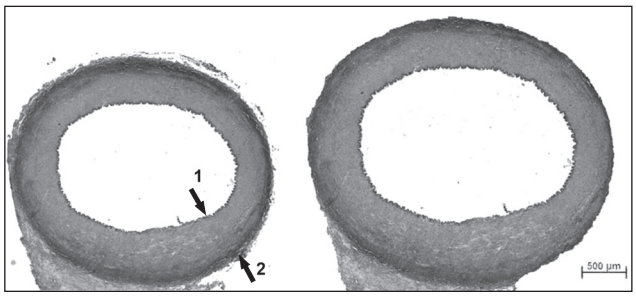

Figure 2 - Histological cross sections of the carotid artery. The elastic fibers that make up the internal and external elastic laminae (blue and red arrows respectively) are shown in black (Verhoeff–Van Gieson stain, 2.5× magnification).

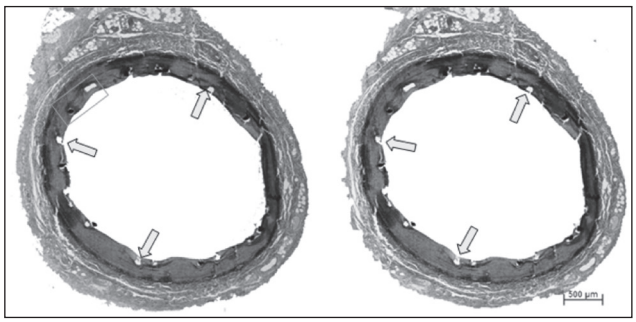

Figure 3 - Histological cross sections of the carotid artery showing stent fragments, some highlighted by green arrows (Verhoeff–Van Gieson stain, 2.5× magnification).

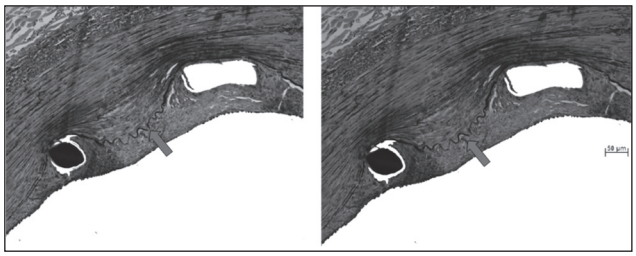

Figure 4 - Histological cross sections of the carotid artery, expanded view of the previous figure. Stent compression of the internal elastic lamina (blue arrow) is visible, as is formation of neointima between the internal lamina and the arterial lumen (Verhoeff–Van Gieson stain, 20× magnification).

animals were returned to the Animal Experimentation Unit for anesthesia and euthanasia according to Unit protocols.

Collected specimens were sent for digital morphometric analysis. Histology sections were obtained with a sliding microtome (Polycut S®, Leica AG, Germany), equipped with a type D, 16 cm-long, 5-micron tungsten carbide knife (Leica AG, Germany), and stained according to the Verhoeff–Van Gieson protocol (Figures 2, 3, and 4).

Morphometry was performed with the aid of a Quantimet 500 computerized image analysis system, under a Leica® microscope, at a magnification of ×2.5. The slides were examined in a blinded fashion, with no observer interference. In each section, the area of the arterial lumen, the area within the internal elastic lamina (corresponding to the arterial lumen if no intimal proliferation were present) and external elastic lamina (external diameter of the vessel), and the approximate area bounded by the innermost points of any stent struts present in the section (that is, the approximate area bounded by the stent if no intimal proliferation were present) were measured. Based on these results, we calculated the area of the neointima and of the tunica media. The total area occupied by any stent fragments present in the section was also measured, as was the extent of neointimal obstruction. Mean overall wall thickness, thickness of the intima, and thickness of the media—at stent-containing points and the points between these—were calculated from the measurements of all stent segments present in each section. Mean minimum distance between the stent and the arterial lumen

and the stent and the external elastic lamina were calculated in a similar fashion.

Data analysis was performed with the SPSS for Windows software package, with descriptive statistics (mean and standard deviation) for all parametric variables. Student's t-test was used for comparison between groups. The significance level (α) was set at 5%.

Results

All eight animals completed the study. Stent patency and patency of the angioplasty segment were assessed directly during specimen collection. Gross (macroscopic) examination revealed a perivascular inflammatory reaction adjacent to the angioplasty segment and stented area; stents appeared to be well adhered to the vessel wall.

Digital morphometry and statistical analysis were conducted on the means and standard deviations of luminal, intimal, and tunica media area in the analyzed specimens. Sections were obtained from the middle segment of the carotid artery and the middle of the stent, sliced with a tungsten carbide knife, for intrastent assessment of the intimal hyperplasia process. Animals were divided into two groups, group 1 (angioplasty + stent) and group 2 (angioplasty only), as shown in Table 1.

Intimal thickening (Figure 5) occurred to a greater extent in the stent placement group (group 1) than in the angioplasty-only group (group 2), but there was no difference in tissue reaction in the tunica media.

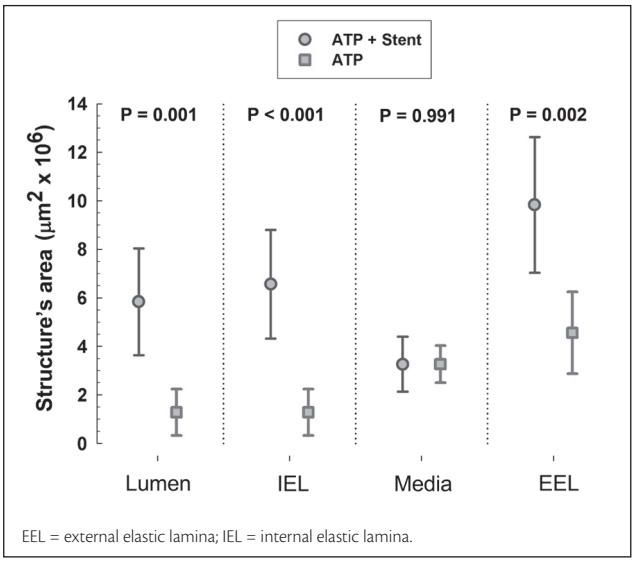

Figure 5 – Comparison of lumen, IEL, media, and EEL measurements between the angioplasty only and angioplasty + stenting group. There is a significant difference in luminal area, IEL, and EEL measurements between the two groups. There is no statistically significant difference in tunica media measurement between the two groups.

Discussion

Post-angioplasty restenosis is a multifactorial process that depends on two basic mechanisms: intimal hyperplasia and arterial remodeling.[11,12] Experimental studies have shown that the response to vascular injury, regardless of mechanism, involves migration and proliferation of smooth muscle cells to and in the intima, with synthesis and deposition of extracellular matrix. These events play a critical role in the pathophysiology of intimal hyperplasia, which leads to restenosis.[13]

Balloon angioplasty is currently accepted not only as a method for treatment of arterial occlusive disease, but also as a model for vascular injury.[14,15] Angioplasty-induced circumferential strain on the vessel wall leads to tearing of the internal elastic lamina and stretching of collagen and elastin fibers in the tunicae media and adventitia. Endothelial injury is followed by endothelial dysfunction, with subsequent platelet aggregation on the surface of the disrupted area and an inflammatory reaction that may extend to all layers of the vessel wall. Furthermore, hemodynamic

Table 1 – Morphometric data (N = 8)

Variable	Group	Mean (x 10^6 μm²)	SD (x 10^6 μm²)	SE (x 10^6 μm²)	p
Lúmen	1	5.841	2.200	0.777	p = 0.001
	2	1.287	0.956	0.338	
LEI	1	6.566	2.240	0.792	p < 0.001
	2	1.287	0.956	0.338	
LEE	1	9.832	2.787	0.985	p = 0.991
	2	4.559	1.685	0.595	
Média	1	3.266	1.134	0.401	p = 0.002
	2	3.271	0.763	0.269	

EEL = external elastic lamina; IEL = internal elastic lamina.

changes secondary to vascular trauma may trigger cellular responses leading to arterial contraction, thus contributing to fibrocellular hyperplasia of the intima. Smooth muscle cells take on a "synthetic/proliferative" phenotype and migrate to the intima, becoming the dominant cell type in intimal hyperplasia.[12-15]

Stents were developed with the purpose of mechanically supporting the arterial wall. As compared with balloon angioplasty, stent placement improves short- and midterm outcomes by reducing negative remodeling. The metallic alloys from which stents are manufactured seek a compromise between biofunctionality and biocompatibility; however, the choice of material must focus primarily on biocompatibility. The main aspects to be taken into account in this respect are susceptibility of the alloy to corrosion and the effects of this corrosion on the recipient's body.[3,7]

Experimental human models have firmly established that the extent of injury caused by angioplasty and stent placement is directly associated with intimal hyperplasia.[12,13,15] Large-animal models (mostly porcine) appear to reflect the pathogenesis of restenosis better than small-animal models (mouse and rabbit) do, particularly with respect to preoperative care and artery handling.[16] Mouse studies suggest that bone marrow progenitor cells may also play a role in the restenosis process.[17] The key limiting factor of animal models is the lack of preexisting atherosclerosis, which is present in humans. Dietary lipid supplementation of laboratory animals induces the formation of vulnerable atherosclerotic plaques,[18] but subsequent intimal hyperplasia and restenosis are similar to those occurring in animals fed a normal diet.[19] The use of an atherogenic diet thus appears to provide no advantage in porcine animal models of restenosis.

A four-week interval between intervention and tissue sampling is enough in experimental studies of post-angioplasty intimal hyperplasia. Past studies have reported development of full-blown intimal hyperplasia, similar to that found in humans, within 28 days.[12-14,20]

In prior studies, Pasa et al.[21] conducted morphometric analysis of intimal thickening in the swine carotid artery after placement of 316L-grade stainless steel stents, without angioplasty, and concluded that intimal thickening induced by the stent is greater than that produced by injury of the contralateral artery by the introducer sheath. The mere presence of a stent, even in the absence of rupture of the internal elastic lamina, is therefore enough to produce intimal hyperplasia. Grudtner et al.[22] and Dutra & Pereira[23] investigated the process of neointimal formation in the swine aorta after angioplasty and placement of e-PTFE and Dacron-coated 316L-grade stainless steel as compared with results obtained after placement of uncoated stents. The authors found no difference between the study groups, but confirmed that all stents, coated or otherwise, are associated with significant formation of neointima. Castro et al.[24] assessed the neointimal response to angioplasty with 316L stainless steel stenting in the swine iliac artery as compared with simple balloon angioplasty of the contralateral iliac artery. In their study, stenting was associated with increased intimal hyperplasia, but no reduction of the arterial lumen, due to positive remodeling of the elastic lamina.

The aforementioned studies, all conducted in Brazil, only assessed intimal hyperplasia in the stent margins, as no cross-sections were obtained from the stented segments (Figures 2, 3, and 4). In the present study, microtome cross-sections of the middle segment of the stent were obtained with the aid of a tungsten carbide knife, which allowed assessment of the extent of intrastent injury. No study conducted thus far had gone beyond assessing alloy behavior in the coronary circulation, where device placement was associated with less intimal hyperplasia than other metallic alloys.[25,26]

In the early days of histology, fine sections meant for microscopic examinations were obtained manually with the aid of razors and knives. In the late 19th century, Chevalier and Purkinje separately developed the first mechanical microtomes.[27] In the present study, we used a tungsten carbide knife-equipped microtome due to the resistance of the stent mesh and the need for precise sections. Unlike diamond blades, tungsten knives keep stent struts intact on cross-sectioning, minimizing the potential for stent removal artifacts.

Histological sections were obtained to assess intimal hyperplasia and luminal area preserved after intervention. Luminal area was calculated by direct measurement of the area bounded by endothelium or by the stent itself. Intimal area was calculated by subtracting the luminal area from the area bounded by the internal elastic lamina, while the area of the tunica media was calculated by adding the values obtained from luminal and intimal measurement and subtracting them from the value measured for the external elastic lamina. Intima and media measurements were expressed as absolute figures, in square micrometers, by averaging the values of eight circumferential measurements.

We found a significant difference between groups 1 (angioplasty plus stenting) and 2 (angioplasty only) on comparison of changes in the arterial lumen (5.841 vs. 10^6 μm^2 vs. 1.287 x 10^6 μm^2), the internal elastic lamina (6.566 vs. 10^6 μm^2 x 1.287 vs. 10^6 μm^2), and the external elastic

lamina (9.832 vs. 10^6 μm² vs. 4.559 x 10^6 μm²). There was no statistically significant difference in tunica media measurements between the two groups (3.266 x 10^6 μm² vs. 3.271 x 10^6 μm²).

Our luminal area findings highlight the importance of negative arterial remodeling after simple angioplasty. Conversely, as it widens the arterial lumen (positive remodeling), stent placement prevents intimal hyperplasia from significantly reducing luminal area. Stenting thus prevents negative arterial remodeling and supports the arterial wall.

Cobalt-chromium stents were developed for use in smaller and sinuous arteries, as cobalt-chromium alloys produce a more resistant and flexible mesh than stainless steel. Their struts are also thinner and provide greater radial strength, allowing treatment of tortuous and calcified atherosclerotic lesions, particularly in the coronary circulation.[26] Theoretically, these stents' thinner struts—which, of course, mean a lower amount of metal is present – could be associated with improved biotolerance. Another very useful feature of this alloy is that recipients of cobalt-chromium stents may undergo magnetic resonance imaging. Experimental studies in the swine coronary artery have shown that polyphosphazene-coated cobalt-chromium stents may induce less neointimal formation than stainless steel stents coated with the same polymer.[25] However, our review of the literature did not yield any experimental studies in the peripheral circulation to corroborate these findings.

The cobalt-chromium stents used in the present study did not appear to be associated with a reduction in intimal hyperplasia. The hyperplasia secondary to angioplasty and cobalt-chromium stent placement does not appear to differ from that found after placement of devices made from 316L-grade stainless steel or nitinol in previous studies conducted in our experimental unit. Various studies conducted by Pasa et al., Grudtner et al., Dutra et al. e Castro et al.[21-24] have shown the role of angioplasty- and stent-induced vascular injury, regardless of alloy and coating, in the intimal hyperplasia process.

Long-term maintenance of arterial lumen patency is the ultimate purpose of stenting. Several studies have addressed the possibility of pharmacotherapy to suppress the intrastent restenosis process. The search for drugs that suppress myointimal proliferation and devices that induce a lesser degree of parietal reaction remains a challenge.

Conclusion

We conclude that, in swine, angioplasty of the common carotid artery with cobalt-chromium stent implantation produces an arterial wall reaction characterized by a greater extent of intimal thickening than that induced by simple angioplasty of the contralateral artery. However, this intimal thickening was not sufficient to effect a reduction in arterial lumen size due to positive remodeling.

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