

# Volumetric assessment of neointimal hyperplasia in iliac arteries after metal stent implantation\*

*Quantificação volumétrica da hiperplasia neointimal em artérias ilíacas após implante de suporte intravascular metálico*

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**Abstract** **OBJECTIVE:** To quantify neointimal hyperplasia in iliac arteries after stent implantation, correlating clinical, arterial factors and stent material. **MATERIALS AND METHODS:** In the period from June/2003 to August/2005, 60 patients were submitted to percutaneous transluminal angioplasty and stenting. Among these patients, 30 were followed-up with intravascular ultrasonography. Data were analyzed in a laboratory of quantitative analysis by means of a specific software. **RESULTS:** Sixteen (53.3%) patients were men, and 14 (46.7%), women, and the mean age was 60.3 years. Arterial hypertension was observed in 22 patients (73.3%), smoking in 18 (62.1%), hyperlipidemia in 20 (66.7%), and diabetes in 9 (30%). A total of 20 nitinol stents (66.7%) and 10 stainless steel stents (33.3%) were implanted. Four patients were classified as TASC A (13.3%), 15 TASC B (50%) and 11 TASC C (36.7%). The neointimal hyperplasia volume ranged from 49.02 mm<sup>3</sup> to 112.87 mm<sup>3</sup> (mean, 80.33 mm<sup>3</sup>). The rate of intrastent obstruction ranged from 18% to 47% (mean, 27.4%). The clinical outcomes achieved with stenting were sustained through the follow-up. **CONCLUSION:** Neointimal hyperplasia is a common finding after percutaneous transluminal angioplasty and stenting, but in the present study the stenosis rate was never higher than 50%. There was no statistically significant difference in intrastent stenosis rates in relation to stents materials, clinical and arterial risk factors. **Keywords:** Stent; Iliac artery; Interventional ultrasonography; Hyperplasia.

**Resumo** **OBJETIVO:** Quantificar a hiperplasia neointimal em artérias ilíacas após *stent*, correlacionando fatores clínicos, arteriais e materiais dos *stents*. **MATERIAIS E MÉTODOS:** De junho de 2003 a agosto de 2005, 60 pacientes realizaram angioplastia transluminal percutânea e *stent*. Desses, 30 foram reestudados com ultrassonografia intravascular. Os dados foram analisados no laboratório de análise quantitativa. **RESULTADOS:** Dezesesseis pacientes eram do sexo masculino (53,3%) e 14 (46,7%), do sexo feminino. A média de idade foi de 60,3 anos. Apresentaram hipertensão arterial 22 pacientes (73,3%), tabagismo, 18 (62,1%), hiperlipidemia, 20 (66,7%), e diabetes, 9 (30%). Foram implantados 20 *stents* de nitinol (66,7%) e 10 de aço inoxidável (33,3%). Quatro pacientes eram TASC A (13,3%), 15 eram TASC B (50%) e 11, TASC C (36,7%). O volume da hiperplasia variou de 49,02 mm<sup>3</sup> a 112,87 mm<sup>3</sup> (média de 80,33 mm<sup>3</sup>). O percentual de obstrução intra-*stent* variou de 18% a 47% (média de 27,4%). Os resultados clínicos obtidos com *stent* se mantiveram até o reestudo. **CONCLUSÃO:** A hiperplasia neointimal sempre ocorre após a angioplastia transluminal percutânea e *stent*, porém os percentuais de obstrução não foram superiores a 50% em nenhum caso. Não houve diferença estatisticamente significativa dos percentuais de obstrução intra-*stent* quanto aos materiais dos *stents*, aos fatores clínicos e aos fatores arteriais.

**Unitermos:** *Stent*; Artéria ilíaca; Ultrassonografia de intervenção; Hiperplasia.

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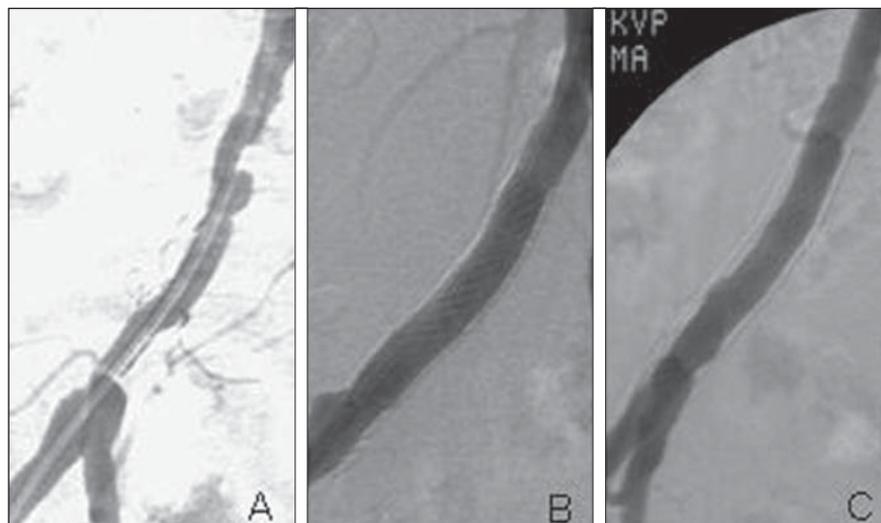
## INTRODUCTION

Percutaneous transluminal angioplasty with metal stents for the treatment of occlusive lesions of iliac arteries is a safe and effective procedure<sup>(1–3)</sup>, generally accepted as the first method of choice for treatment in selected cases<sup>(4–6)</sup>.

Intra-stent restenosis caused by neointimal hyperplasia has its occurrence peak around the sixth postoperative month (Figure 1), and it has been described in other locations such as the coronary arteries<sup>(7–9)</sup> although such occurrence has not been reported with the same frequency as in the case of iliac arteries.

In the present study, intravascular ultrasonography (IVUS) was performed to quantify the volume of neointimal hyper-

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**Figure 1.** A: Pre-stenting iliac artery. B: Thirty days post-stenting. C: Eight months post-stenting.

plasia in iliac arteries treated with percutaneous transluminal angioplasty and stent, correlating with clinical risk factors such as smoking, arterial hypertension, hyperlipidemia and diabetes mellitus as well as stents material and local arterial characteristics such as type of occlusion.

**MATERIALS AND METHODS**

Between July, 2003 and August, 2005, 60 consecutive patients were submitted to percutaneous transluminal angioplasty and stenting for treatment of occlusive lesions in the iliac arteries. Among these patients, 30 were re-studied with IVUS (In-Vision Gold®; Volcano Therapeutics, Rancho Cordova, USA), 16 of them men (53.3%), with ages ranging from 39 to 78 years (mean, 60.3 years).

As regards clinical risk factors, 22 patients had arterial hypertension (73.3%), 18 patients were smokers (62.1%), 20 were hyperlipidemic (66.7%) and nine had diabetes mellitus (30%) (Table 1). According to the Rutherford scale, the patients were classified into categories 2 (moderate claudication), 3 (severe claudication), 4 (ischemic rest pain) and 5 (minor trophic lesion); and regarding arterial involvement by the atheromatous plaque, the TASC I classification was utilized, and the patients were graded as A, B, and C<sup>(4)</sup>.

All patients included in the present study underwent the procedure in a cath lab, with 2% lidocaine hydrochloride local

anesthetic, without vasoconstrictor. The ipsilateral retrograde femoral approach was preferably utilized, followed by the contralateral femoral approach, and the axillary approach as the last option. Among the enrolled patients, 20 received self-expandable nitinol stents and 10 received balloon stainless steel stents based on criteria established in literature<sup>(10)</sup>. In 24 of the arteries, significant stenosis was present (80%) and in six of the arteries, occlusion was present (20%).

Anti-platelet regimen included a loading dose of aspirin (200 mg) at least 2 days prior to the procedure followed by 200 mg/day indefinitely. Additionally, patients were pretreated with ticlopidine (500 mg) or clopidogrel (75 mg) a day, two days before the intervention and maintained for 30 days<sup>(11)</sup>.

The patients were followed up on an outpatient basis at one week, one month, three months, six months and eight months postoperatively, when the IVUS re-studies were then performed.

The patients who agreed in participating in the present research, signed a term of free and informed consent and were submitted to the re-study. In a cath lab, with the

patient under local anesthesia, a 6F valved introducer was inserted by ipsilateral retrograde femoral approach, and 5000 UI intra-arterial heparin was injected. Next, a 0.014" guidewire was inserted and positioned in the thoracic aorta distally to the stent. Over the guidewire, a catheter with a 20 MHz transducer on its tip, connected to a IVUS module table, reading module of the IVUS, was advanced and positioned distally to the stent location. Then, the catheter was connected to a pullback device (Trak Back II®; Volcano Therapeutics, Rancho Cordova, USA) with a constant 1 mm/s pullback rate.

The acquired images were digitized and recorded on a compact disc (CD) and later analyzed in a quantitative analysis laboratory with (the aid of the) a dedicated software (Echoplaque®; Indec Systems, Mountain View, USA).

By using the IVUS, it was possible to identify and delimitate the external elastic layer, the stent and the lumen (Figure 2). With these measurements, the vessel, the stent, and lumen areas could be calculated at each millimeter within the stent; subsequently, the volumes calculations were performed with the aid of the software. By subtracting the luminal volume the stent volume, the neointimal hyperplasia volume was determined.

A linear regression model was adjusted to evaluate the correlation between the intrastent occlusion rate, arterial hypertension, smoking, hyperlipidemia, diabetes mellitus, stainless steel, stenosis and occlusion<sup>(12,13)</sup>.

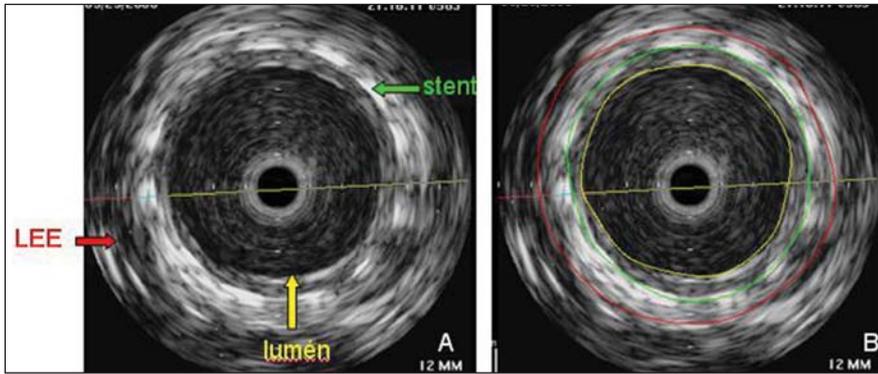
**RESULTS**

All patients underwent follow-up IVUS, and no complication was observed in these patients.

Eight stents were implanted in the right common iliac artery, 14 in the left common iliac artery, 5 in the right external iliac artery and 3 in the left external iliac artery.

**Table 1** Distribution of clinical factors in the sample.

	Systemic arterial hypertension	Diabetes mellitus	Smoking	Hyperlipidemia
Yes	22 (73.3%)	9 (30%)	18 (62.1%)	20 (66.7%)
No	8 (26.7%)	21 (70%)	12 (37.9%)	10 (33.3%)
Total	30 (100%)	30 (100%)	30 (100%)	30 (100%)



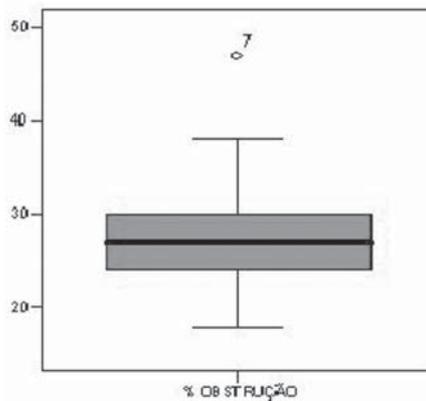
**Figure 2.** Cross section of the vessel and of the stent. **A:** Structures identification: LEE (external elastic layer), stent, lumen. **B:** Construction of transverse areas.

The first report of the TransAtlantic Inter-Society Consensus (TASC I) was utilized to classify the anatomic arterial involvement by the atheromatous plaque, as follows: four were TASC A (13.3%), 15 were TASC B (50%) and 11, TASC C (36.7%).

With regard to the clinical status of the patients at the time of the percutaneous transluminal angioplasty and stenting, and also with follow-up purposes, the Rutherford scale was utilized. Thus, nine patients (30%) were in category 5 (minor trophic lesion), nine (30%) were in category 4 (rest pain), nine were in category 3 (severe limiting claudication) and three (10%) were in category 2 (moderate claudication) at the time of the percutaneous transluminal angioplasty and stenting. At follow-up, 15 patients (50%) were asymptomatic, 13 presented long distance claudication (Rutherford category 1) and two presented moderate distance claudication. The mean neointimal hyperplasia volume was 766.26 mm<sup>3</sup> (minimum of 204 mm<sup>3</sup> and maximum of 1774 mm<sup>3</sup>). The intrastent occlusion rate caused by neointimal hyperplasia ranged from 18% to 47% (mean, 27.4%) (Figure 3).

**DISCUSSION**

Follow-up with IVUS demonstrated that after percutaneous transluminal angioplasty and stenting all patients developed neointimal hyperplasia and that this is a common result from the intravascular treatment. However, neointimal hyperplasia was self-limited and did not cause significant restenosis among the 30 patients participating in the present study, suggesting that in vessels of larger caliber, like iliac



**Figure 3.** Intrastent occlusion rate. Sample distribution.

artery, only a larger volume hyperplasia could cause restenosis. However, even in cases of significant restenosis, a new catheter balloon or cutting balloon angioplasty can be performed, without the use of a new stent<sup>(14)</sup>.

The use of IVUS in the evaluation of intrastent restenosis has shown to be superior to catheter angiography and transcutaneous Doppler ultrasonography with high-frequency transducers, for being able to better identify the structures and also for not underestimating the lumen diameter<sup>(15)</sup>.

Neointimal hyperplasia remains as the main cause of failure of endovascular treatment with metallic stents, and much has been done to diminish this response, as follows: the use of heparin stents; the use of anti-ICAM-1 monoclonal antibodies<sup>(16)</sup>, that inhibit the ICAM-1 molecular adhesion, hence neointimal hyperplasia; the use of probucol<sup>(17)</sup>, which accelerates stents endothelialization and reduces the formation of hyperplasia; hyperplasia inhibiting

drug-eluting stents<sup>(18)</sup>; and even the oral use of neointimal hyperplasia inhibiting drugs<sup>(19)</sup>. So far, the coating with polytetrafluorethylene (Teflon) has not been able to reduce hyperplasia response<sup>(20)</sup>.

Comparative studies between the primary use of stents and utilization of stents in selected cases where catheter balloon angioplasty failed to show good outcomes<sup>(21)</sup> suggest that stenting should only be used in the iliac arteries, in case of failure of percutaneous transluminal angioplasty with catheter balloon. On the other hand, the type of material utilized in the composition of the stents utilized in the present study – stainless steel and nitinol – did not present differences as far as neointimal hyperplasia is concerned. Causal factors, such as arterial hypertension, diabetes mellitus, smoking and hyperlipidemia were not determinant of statistically significant differences in neointimal hyperplasia and intrastent occlusion, and also no difference was observed in cases of arterial occlusion or stenosis. Thus, the high research costs and the final price of stents are not justifiable for treatment of large caliber arteries such as the iliac ones, even in cases where the patients present a history of diabetes mellitus, arterial hypertension, smoking, hyperlipidemia or complete vessels occlusion.

**CONCLUSION**

The results of the linear regression analysis did not demonstrate statistically significant differences for arterial hypertension, smoking, hyperlipidemia, diabetes mellitus, nitinol, stainless steel, stenosis and occlusion, when correlated with the intrastent occlusion rate in the treatment of atherosclerotic lesions of iliac arteries.

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