

Comparative Endothelial Effects of the Arterial Balloon Catheter on Elastic Versus Muscular Arterial Conduits

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ABSTRACT

Background: Harvesting of arterial grafts such as the elastic internal mammary artery (IMA) or the muscular radial artery (RA) for use in myocardial revascularization may result in severe spasm which can impair early graft flow. A new long intravascular balloon (ABC: Arterial Balloon Catheter, Applied Medical, CA, USA) has been developed to relieve arterial spasms without exerting any longitudinal shearing stress that could be damaging to the endothelial layer. The purpose of this study was to determine the effects of ABC balloon dilatation and reperfusion on the endothelial function of muscular and fibroelastic arteries.

Methods: Two groups of swine were studied: group 1 had dilatation of both internal mammary arteries with a 3.5-mm via a medial sternotomy approach and group 2 had dilatation of both femoral arteries with a 3.5-mm ABC balloon. Left femoral and internal mammary arteries were reperfused during 45 minutes before harvesting. Non-instrumented segments of femoral and mammary arteries served as control. Endothelium-dependent relaxations to serotonin (5-HT: an agonist that binds to 5-HT₁ receptors coupled to G_i protein), bradykinin (BK: an agonist that binds to receptors coupled to G_q protein) and the calcium ionophore A23187 (endothelium-dependent receptor independent agonist) were studied in standard organ chambers experiments.

Results: In IMAs, there was a significant decrease in endothelium-dependent relaxations to 5-HT ($p < 0.05$) but not to BK and A23187 after dilatation with the 3.5-mm ABC balloon, with and without reperfusion, compared to controls. Reperfusion did not increase the endothelial dysfunction observed with 5-HT. In femoral arteries, there was a statistically significant decrease of endothelium-dependent relaxations to 5-HT, BK and A23187 after dilatation with the 3.5-mm ABC balloon in comparison with controls ($p < 0.0005$). Reperfusion further decreases endothelium-dependent relaxations to all agonists observed after balloon dilatation ($p < 0.005$).

Conclusions: Arterial balloon catheter dilatation of muscular arteries using the 3.5-mm balloon causes a generalized endothelial dysfunction increased by reperfusion. The 3.5-mm arterial balloon dilatation causes a selective endothelial

dysfunction in the swine internal mammary artery not aggravated by reperfusion. This suggests that the 3.5-mm arterial balloon catheter may be used safely for the fibroelastic IMA but may not be adequate for dilating the muscular RA. Undersizing of the ABC balloon may be crucial for these arteries.

INTRODUCTION

Coronary revascularization is the most frequently procedure and one of the major advance in cardiac surgery [Loop 1981]. Grafting of the internal mammary artery (IMA) to the left anterior descending artery remains the gold standard in surgical myocardial revascularization with a superior long-term patency compared to venous grafts [Grondin 1984, Loop 1986]. The use of the radial artery (RA) for coronary revascularization, after an initial disappointment [Fisk 1976], was reintroduced by Acar and Carpentier with improved early and midterm results [Acar 1998]. However, harvesting of arterial grafts such IMA or RA for use in arterial myocardial revascularization may result in severe spasm which can impair early graft flow and clinical outcome [Sarabu 1987, Jones 1989].

Different techniques have been described to prevent and treat intraoperatively arterial graft spasm such as topical or intraluminal injection of papaverine, and mechanical or hydrostatic dilatation [Mills 1989, van Son 1992, Cable 1998]. Mechanical dilatation with both short balloon catheters and metal dilators can exert an intraluminal shearing force which causes denudation of the endothelium [Johns 1989] which plays a key-role in the regulation of arterial relaxation and vascular wall homeostasis [Vanhoutte 1988]. Endothelium-dependent relaxations require both the presence and the functional integrity of the endothelial cells. This endothelial cell monolayer is easily damaged by mechanical manipulation which can impair endothelium-dependent relaxations [Furchgott 1980] and translate clinically into acute spasms or chronic intimal hyperplasia at the site of denudation, with an increased risk of graft failure.

A new long balloon dilatation catheter: the Arterial Balloon Catheter (ABC balloon, Applied Medical, CA, USA) has been developed to mechanically increase arterial graft diameter and flow without exerting any longitudinal shearing force on the endothelium to ensure preservation of its integrity and function (Figure 1). Prior studies confirmed preservation of endothelium-dependent relaxations and of the endothelial cell coverage after dilatation with the ABC balloon in the porcine IMA in acute [Jeanmart 2001] and chronic models [Dumont 2001], supporting its role as an effective and safe method to relieve perioperative spasm on the IMA after harvesting. However, two types of arterial conduits are frequently used in coronary bypass grafting: the fibroelastic IMA and the muscular RA which is more prone to vasospasm [Chardigny 1993, Kulkarni 1999]. The effect of the ABC balloon on muscular arteries is unknown.

The purpose of this study was to determine the effect on the endothelial function of dilatation and reperfusion of fibroelastic (IMA) versus muscular (femoral artery as a model for the muscular human radial artery) arterial conduits, in a porcine model.

MATERIALS AND METHODS

Experimental Surgery

Twelve Landrace swine of either gender, aged 8 ± 1 weeks and weighing 24.3 ± 0.5 kg were included in this study. Animals were maintained and tested in accordance with the recommendations of the Guidelines on the Care and Use of

Laboratory Animals issued by the Canadian Council on Animals and the Guidelines of the Animal Care and were approved by a local ethic committee.

All animals were sedated by an intramuscular injection of 25 mg/kg of ketamine hydrochloride (Ayerst Veterinary Laboratories, Guelph, ON, Canada) associated with 10 mg/kg of xylazine (Boehringer Ingelheim, Burlington, ON, Canada), intubated and mechanically ventilated with an oxygen/air mixture (3:2). Anesthesia was maintained with 1-2.5% halothane inhalation (Halocarbon Laboratories, River Edge, NJ, USA). The electrocardiogram was recorded from three subcutaneous limb electrodes.

After skin preparation, both FAs were dissected over 2 cm via a bilateral groin approach. During dissection, arterial external diameter decreased about 50% (external diameter from 4.0 ± 0.2 mm to less than 2 mm in severe spasm). Both IMAs were exposed by median sternotomy and dissected with fascia and veins.

Two groups of swine were studied: group 1 (n = 5) had dilatation of both IMAs with the 3.5 mm ABC balloon and group 2 (n = 7) had dilatation of both FAs with a 3.5-mm ABC balloon. For each swine in group 1, the 3.5-mm balloon was first inserted into the left IMA via a distal arteriotomy, and inflated for 30 seconds. The circulation was then restored for 45 minutes. For each swine in group 2, the 3.5-mm ABC balloon was first inserted into the left FA via a collateral branch and inflated for 30 seconds (Figure 2). The circulation also was restored for 45 minutes. At the end of the procedure, the right IMAs or FAs were dilated without any reperfusion and both IMAs or both FAs were harvested and placed in a cold (5-10°C) modified Krebs-bicarbonate solution (composition in mmol/l: NaCl 118.3, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.2, glucose 11.1, CaCl₂ 2.5, NaHCO₃ 25, and ethylenediaminetetraacetic acid 0.0026).

Functional Internal Mammary Arteries and Femoral Arteries Testing

Less than 10 minutes after harvesting, IMA and FA were carefully dissected free of the surrounding tissue in a Petri dish filled with oxygenated modified Krebs and divided into 4 mm long rings. Special caution was taken to avoid endothelial injury during this procedure. Non-dilated parts of IMA and FA (downstream to the dilated portion) served as controls. All rings were placed in organ chambers (Emka Technologies Inc, Paris, FRA) filled with 20 ml modified Krebs solution heated at 37°C and oxygenated with a carbogen mixture (95% O₂ and 5% CO₂). The rings were suspended between two metal stirrups with the upper one connected to an isometric force transducer connected to a signal amplifier and then allowed to stabilize for 30 minutes. Data was collected with a biological signal data acquisition software (IOX 1.203, Emka Technologies Inc, Paris, FRA).

Each arterial ring was stretched at the optimal point of its active length-tension curve (approximately 3.5 g), as determined by measuring the contractions to potassium chloride (30 mmol/l) at different levels of stretch. The maximal contraction of rings was then obtained with addition of potassium chloride (KCl 60 mmol/l). Rings were excluded if they failed to contract to KCl. After obtaining a plateau, all baths were washed twice with modified Krebs solution and indomethacin (10^{-5} mol/l to exclude production of endogenous prostanoids), propranolol (10^{-7} mol/l to prevent activation of β -adrenergic receptors) and ketanserin (10^{-6} mol/l to block serotonin 5-HT₂ smooth muscle cells receptors) were added to each bath.

After 45 minutes of stabilization, prostaglandin F_{2 α} (range 2×10^{-6} - 3×10^{-5} mol/l) was added to obtain a contraction averaging 50% of the maximal contraction to KCl. Endothelium-dependent relaxation to serotonin (5-hydroxytryptamine creatine sulfate: 5-HT; an agonist which binds to 5-HT₁ receptors coupled to G_i-proteins) at various concentrations (10^{-10} - 10^{-5} mol/l),

bradykinin (BK; an agonist which binds to BK receptors coupled to G_q-proteins) at various concentrations (10⁻¹² -10⁻⁶ mol/l) and the calcium ionophore A23187 (CI; endothelium-dependent receptor independent) at various concentrations (10⁻⁹ - 10⁻⁶ mol/l) were recorded. Endothelium-independent relaxations were studied with sodium nitroprusside (SNP) at 10⁻⁵ mol/l at the end of all experiments.

All drugs were prepared daily. Serotonin, bradykinin, calcium ionophore, indomethacin, ketanserin and sodium nitroprussiate were obtained from Sigma Chemical Co. (ON, CA). Propranolol was obtained from Biomol Research Laboratories, Inc. (Plymouth Meeting, PA, USA) and prostaglandin F_{2α} was obtained from Cayman Chemical Company (Ann Arbor, MI, USA).

Statistical Analysis

All values of contractions and relaxations are expressed as the mean ± standard error of the mean (SEM). Contractions to prostaglandin F_{2α} are expressed as a percentage of the maximal contraction to KCl (60 mmol/l). Relaxations are expressed as a percentage of the maximal contraction to prostaglandin F_{2α} for each ring; *n* refers to the number of animals studied. Two-way repeated analysis of variance (ANOVA) and t test were performed to compare each point of dose-response curves between control rings and dilated rings. Statistical analysis was performed with the computer software S.A.S System (Instr Inc. Cary, NC, USA). A *p* value less than 0.05 was considered statistically significant.

RESULTS

Experimental Surgery

For the IMAs, the mean diameter was 2.5 mm before dissection. Dissection caused variable but usually minimal spasms which were easily relieved by the 3.5-mm ABC balloon with a satisfactory macroscopic result and flow restoration.

For the FAs, the mean diameter was 3.5 mm before dissection. Dissection caused a more severe and extensive decrease in vessel diameter than in IMAs, which was relieved by the 3.5-mm ABC balloon with a satisfactory macroscopic result and flow restoration.

There was no macroscopic complication during the dilatation procedure such as arterial rupture or dissection in IMAs and FAs.

Contractions of Internal Mammary Arteries and Femoral Arteries

There was a statistically significant difference between contraction to KCl in the IMAs groups versus the FAs groups (*p* < 0.05) with a lower contraction for IMAs groups.

Endothelium-dependent Relaxations in Internal Mammary Arteries

There was a statistically significant decrease in endothelium-dependent relaxation to 5-HT (*p* < 0.05), but not to BK and A23187 with 3.5-mm balloon dilatation without arterial reperfusion, compared with the controls. There was no statistically significant difference in the maximal relaxation to 5-HT after ABC balloon dilatation compared to controls.

There was a statistically significant decrease in endothelium-dependent relaxation to 5-HT (*p* < 0.05), but not to BK and A23187, after 3.5-mm balloon dilatation and arterial reperfusion, compared with the controls. There was no statistically significant difference in the maximal relaxation to 5-HT after ABC balloon dilatation and reperfusion, compared to controls.

There was no statistically significant difference in endothelium-dependent relaxations to 5-HT, BK, and A23187 between rings dilated with the 3.5-mm

balloon dilatation without arterial reperfusion and after arterial reperfusion (Figures 3-5).

In Femoral Arteries

There was a statistically significant decrease in endothelium-dependent relaxations to 5-HT ($p < 0.0005$), BK ($p < 0.0005$), and A23187 ($p < 0.05$) after 3.5-mm balloon dilatation without arterial reperfusion compared with the controls.

There was a statistically significant decrease in endothelium-dependent relaxations to 5-HT ($p < 0.0001$), BK ($p < 0.0001$), and A23187 ($p < 0.02$) after 3.5-mm balloon dilatation and arterial reperfusion compared with the controls.

There was a statistically significant decrease in endothelium-dependent relaxations to 5-HT ($p < 0.005$), BK ($p < 0.005$), but not with A23187 between 3.5-mm balloon dilatation without arterial reperfusion and after arterial reperfusion (Figures 6-8).

Endothelium-independent Relaxations of Internal Mammary Arteries and Femoral Arteries

No statistically significant difference in relaxation to SNP was observed between studied groups (data not shown). A complete relaxation was obtained for each ring after the SNP was added.

DISCUSSION

The major findings of this study are that dilatation of a muscular artery such as the porcine FA with the 3.5-mm ABC balloon induces a severe generalized decrease of endothelium-dependent relaxations for all agonists studied. Reperfusion following the dilatation further increases this endothelial dysfunction. On the contrary, a selective decrease of endothelium-dependent relaxations occurs for only 5-HT after dilatation in the fibroelastic IMA. Reperfusion did not aggravate this endothelial dysfunction.

Endothelial Effects of the Dilatation of IMAs

In order to minimize the risk of spasm or to break it, different medications and techniques have already been developed, such as mechanical dilatation with the use of metal probes or chemically with intraluminal papaverine. Mechanical dilatation with a metallic probe has been tested on canine IMA [Johns 1989]. The increase in IMA flow obtained was associated with a loss of endothelial cells due to the rubbing of the probe. This loss was responsible for impaired relaxation to prostacyclin and to the endothelium-derived relaxing factor (nitric oxide: NO) which predispose to postoperative spasm and early thrombosis of the graft, as well as development of intimal hyperplasia [Saitoh 1998]. Similarly, dynamic dilatation with a Fogarty catheter causes severe alterations of the endothelial layer with platelet attachment. In contrast, hydrostatic dilatation of the IMA with papaverine has the advantage of maintaining the functional integrity of the endothelium [Hillier 1992], although it may damage the intima and internal elastic lamina. The different results obtained with metallic probes or Fogarty catheters versus hydrostatic dilatation is explained by the fact that in the process of exerting a radial dilatation force, metallic probes and Fogarty catheters also exert a longitudinal shear force on the endothelium which is most damaging to the architecture of the endothelial layer.

The ABC balloon method of mechanically dilating the artery without exerting any longitudinal shear stress on the endothelium could be the optimal way of relieving spasm, augmenting flow and preserving the endothelium [Jeanmart 2001].

In this previous acute study, there was no dysfunction after dilatation of IMAs with acetylcholine, an other agonist which binds receptors coupled to G_i -proteins, in larger swine (90 kg) and with different sizes of balloon. In our experiment, a slight decrease of endothelium-dependent relaxation was only observed for two doses of 5-HT and finally all rings achieve a complete relaxation. The selective dysfunction found in this study is not contradictory and can be explained by the necessary insertion and removal of the deflated 3.5 mm ABC balloon [Furchgott 1993, Verrier 1997], which remain a drawback of the method compared to topical application of vasoactive drugs. Also, the large diameter of the balloon studied, relative to the IMA, could create some mechanical stress on the endothelium. However, the muscular layer of the IMA is not damaged despite the 3.5-mm diameter dilatation, as attested by complete relaxation to SNP.

Endothelial Effects of the Dilatation of FAs

The use of the ABC balloon is an alternative to treat perioperative arterial graft spasm and has been shown to maintain the functional and structural integrity of the endothelium in acute studies performed on porcine IMA [Jeanmart 2001]. However, further studies to test the reproducibility of these results on other type of arterial conduits such as muscular conduits, notably the radial and right gastroepiploic arteries are also warranted. The swine FA model was chosen because this artery is of the muscular type like the RA. The use of the 3.5-mm diameter ABC balloon implies inflation of the catheter without shearing, as in the IMA studies. However, like in the IMA experiments, insertion and removal of the device probably produces rubbing which causes endothelial damage but the dysfunction is greater and generalized to all agonists studied, and is not as safe in muscular arteries, increasing the risk of spasm and intimal hyperplasia development.

This more spastic muscular artery has a greater susceptibility to endothelial injury than its fibroelastic counterpart when dilated with the ABC balloon catheter. This difference could be explained by the histological [van Son 1990] and functional [Chardigny 1993] differences between the two types of arterial conduits. Indeed, the diameter of these arteries was not the same at the beginning of the surgery (about 3.5 mm for FA and 2.5 mm for IMA), but the FA was more spastic with a 50% decrease of the initial diameter after dissection. Secondly, the two arteries react differently to KCl, probably due to their different histology and pharmacology.

In the case of a moderate dilatation of FAs by the 1.5-mm ABC balloon, which was tested separately, endothelial dysfunction still occurred for both 5-HT and BK, but was not aggravated by reperfusion (data not shown). This suggest that balloon size is a predominant factor in the origin of the endothelial dysfunction observed. Reperfusion increases the damage secondary to mechanical overdilatation of FAs. Proper sizing is mandatory for optimal preservation of endothelium-dependent relaxation on these arteries.

Mechanisms of Endothelial Injury

There are two main mechanisms of endothelial injury during dilatation with ABC balloon. The first is a mechanical injury, due to the transmural pressure against the arterial wall by the inflated balloon, and the second probably an ischemic injury, objectived by the increase of dysfunction after the reperfusion phenomenon.

Ip et al. classified vascular injury into three types. Type I: functional alteration of endothelial cells without significant morphologic changes; Type II: endothelial denudation and intimal damage with intact internal elastic lamina and media; Type III: endothelial denudation with damage of both intima and media [Ip 1990].

Dilatation with the 3.5-mm balloon creates a type I or II injury. The muscular layer is not involved by the trauma because complete relaxation to SNP was obtained for each ring at the end of the experiment. Preservation of the integrity of the endothelium is associated with lesser platelet adhesion and aggregation, due to the preservation of the protective effects of endothelium-derived relaxing factors produced by the vessel wall, which could be potentially followed by a better long-term graft patency. The 3.5-mm arterial balloon catheter causes a generalized endothelial dysfunction in the muscular FA, severely increased by the reperfusion process. This suggests that the 3.5-mm arterial balloon catheter may not be adequate for dilating this muscular artery.

It was also demonstrated that the compliance of iliac arteries after overdilatation was lower compared to the compliance of coronary arteries of same diameter [Ward 2000]. Furthermore, in this study, there was less damage of the internal elastic lamina on iliac arteries than on coronary arteries. Femoral arteries, like iliac arteries, appears more resistant and spastic than other arteries and the transmural pressure applied on the endothelium layer during the dilatation should be in consequence more important, explaining the difference of vasorelaxation results. Due to the difference of the muscular part of the vessel, the transmural pressure applied to the vessel wall when the ABC balloon inflated was probably different for the IMA and the FA. So the effects of the transmural pressure on the endothelium appears more important in the FA, explaining the different results on the endothelial reactivity studies.

Reperfusion worsen ischemic lesions and is due to oxygen derived free radicals, which cause morphological and functional damage on cells [Kontos 2001]. Endothelial cells are oxygenated by the lumen of the vessel and during the dilatation there was no circulation at all into the vessel. When rendered hypoxic and then reoxygenated, endothelial cells become activated to express proinflammatory properties that include the induction of leukocyte-adhesion molecules and vasoconstrictive agents that increase vasomotor tone [Boyle 1996]. However, the duration of ischemia was very short in this experiment (30 seconds). In longer period of ischemia (30 minutes) obtained by snares, followed by 30 minutes reperfusion, there was no decrease of endothelium-dependent compared with the control arteries [Perrault 1997]. Longer periods of ischemia (60 minutes) followed by reperfusion may lead to acute endothelial dysfunction [Pearson 1990]. This means that ischemia is not the principal causal factor of endothelial dysfunction, but mechanical trauma.

Limitations of the Study

Our study is a functional comparative evaluation of effects of the same diameter balloon on two different types of artery before and after reperfusion. The main limitation of the study is the lack of morphological assessment of effect of ABC balloon dilatation on IMA and FA, which could explain a part of the differences among the functional results such endothelial denudation or lesions of the internal elastic lamina. The second limitation is that this study is only an acute study and the time-course of the endothelial dysfunction was not studied. However, Dumont et al. showed on a porcine model that the ABC balloon dilatation of IMA is not detrimental to endothelium chronically [Dumont 2001], as confirmed by the slight and selective dysfunction found in our experiment. A chronic study on FA could be of relevant.

CONCLUSION

The ABC balloon dilatation technique is a satisfactory method dilatation of the fibroelastic IMA because of the slight endothelium dysfunction observed, which should translate into satisfactory clinical results. On the opposite, this method creates severe endothelial dysfunction in muscular arteries worsened by reperfusion.

ABC dilatation may not be an innocuous technique to treat perioperative spasms in muscular arteries such FA in a porcine model. Dilatation with a 3.5-mm ABC catheter may not be optimal for dilating the muscular RA in the clinical setting, but is safe to dilate the IMA. However, further experimental studies with different diameter of ABC balloon, and on human arteries, are mandatory to confirm this hypothesis.

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Table 1. Amplitude of contraction to potassium chloride (KCl 60 mmol/l) and prostaglandin F_{2α} (PG F_{2α}) with the concentrations used for all groups studied

	IMA	FA	P
KCl 60 mmol/l contraction (g)	3.01 ± 0.65	12.15 ± 1.80	<0.05
	2.99 ± 0.9	13.35 ± 2.3	<0.05
	1.34 ± 0.33	8.23 ± 1.69	<0.05
PG F _{2α} contraction (g)	2.738 ± 0.44	10.58 ± 1.78	<0.05
	2.67 ± 0.46	10.11 ± 2.07	<0.05
	1.78 ± 0.26	6.07 ± 0.88	<0.05
PG F _{2α} contraction (% of KCl contraction)	90.7 ± 13.7	87.08 ± 12.48	NS
	89.3 ± 12	75.73 ± 6.7	NS
	132.8 ± 13	73.75 ± 11.34	<0.05
Concentration of PG F _{2α} used (10 ⁻⁶ mol/l)	2.33 ± 0.21	3.91 ± 1.22	NS
	3.5 ± 0.85	6.00 ± 1.98	NS
	3.0 ± 0.27	2.50 ± 0.15	NS

Values are expressed as the mean ± standard error of the mean. From the top to the bottom: control, dilatation without reperfusion, dilatation and reperfusion.
IMA = Internal Mammary Artery, FA =

FIGURE LEGENDS

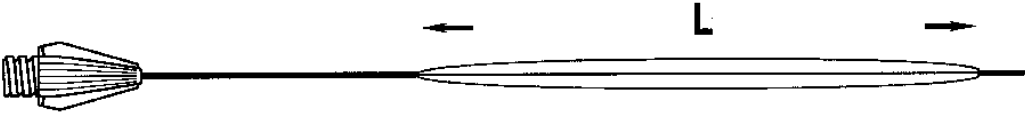


Figure 1 3.5 mm ABC balloon (ABC: Arterial Balloon Catheter, Applied Medical, CA, USA) used in these experiments (L: length, L = 12.6 cm).

Figure 2 Schematic depicting the experimental setup on swine internal mammary (group 1) and femoral arteries (group 2). RIMA = right internal mammary artery, LIMA = left internal mammary artery, RFA = right femoral artery, LFA = left femoral artery.

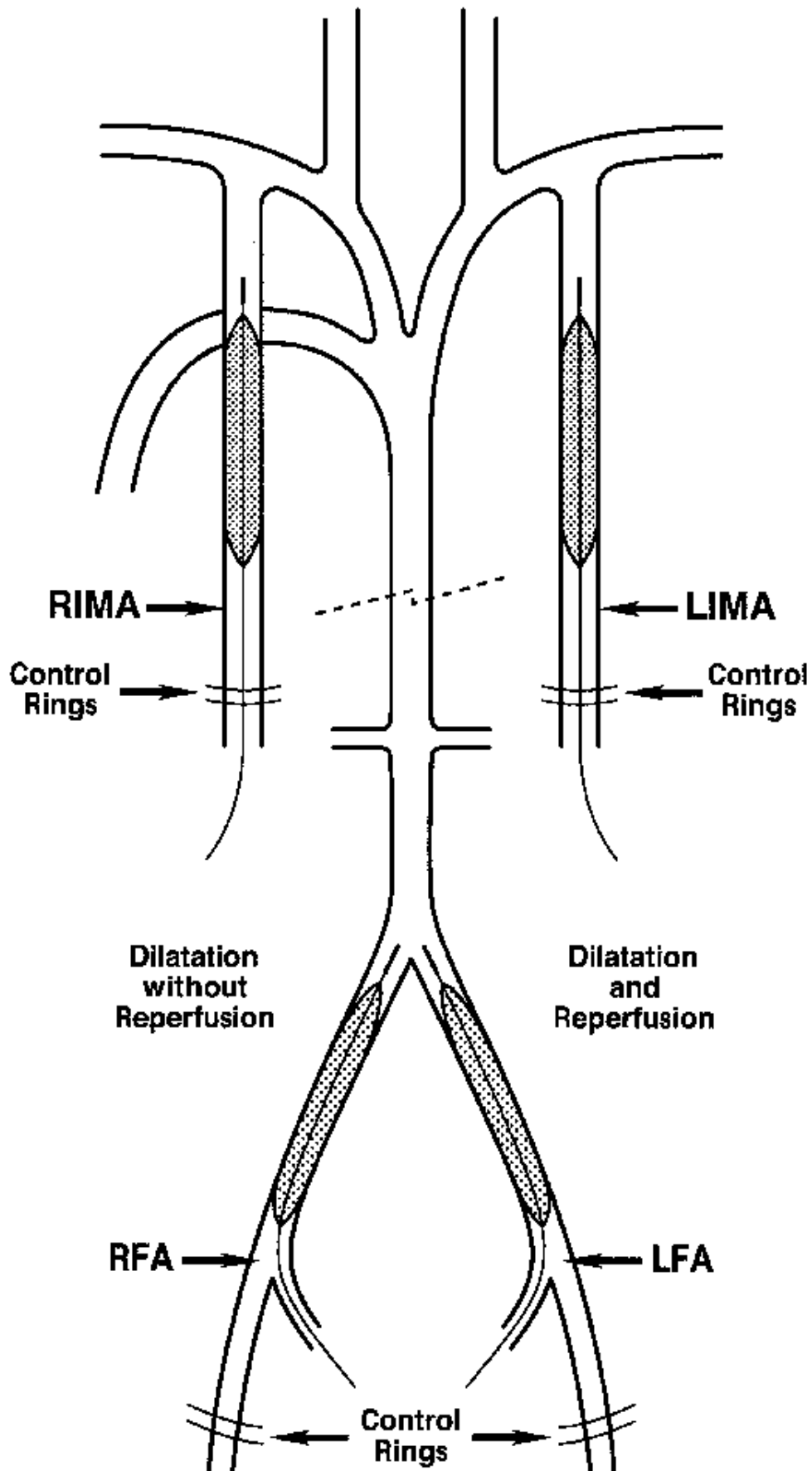


Figure 3 Cumulative concentration-relaxation response curves to serotonin (5-HT) in porcine mammary arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

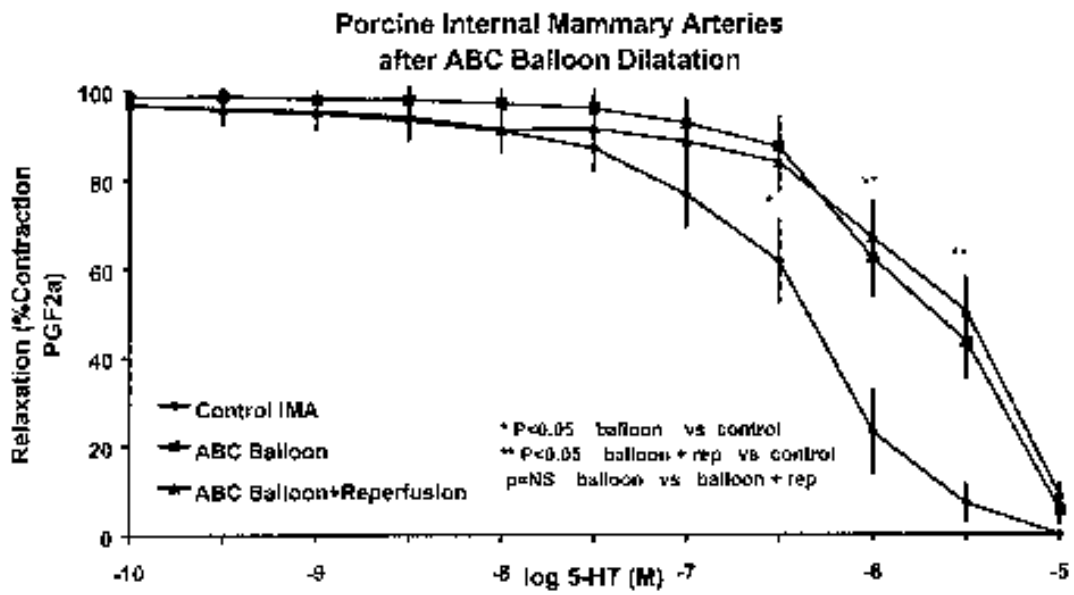


Figure 4 Cumulative concentration-relaxation response curves to bradykinin (BK) in porcine mammary arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

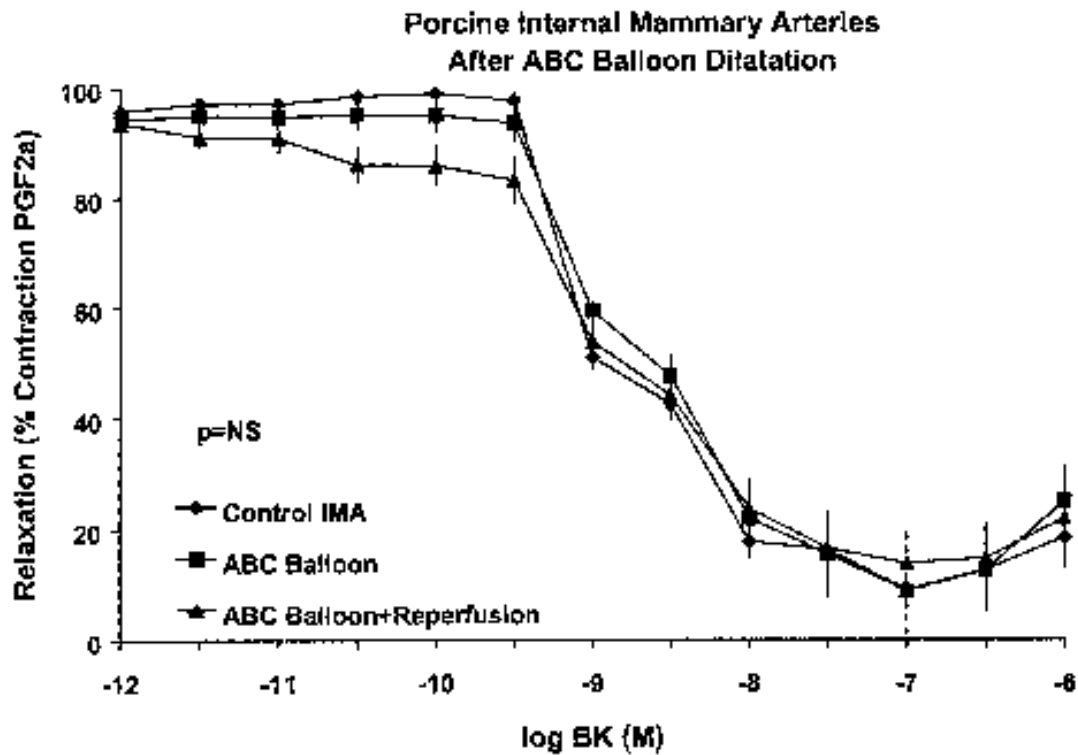


Figure 5 Cumulative concentration-relaxation response curves to the calcium ionophore (A23187) in porcine mammary arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

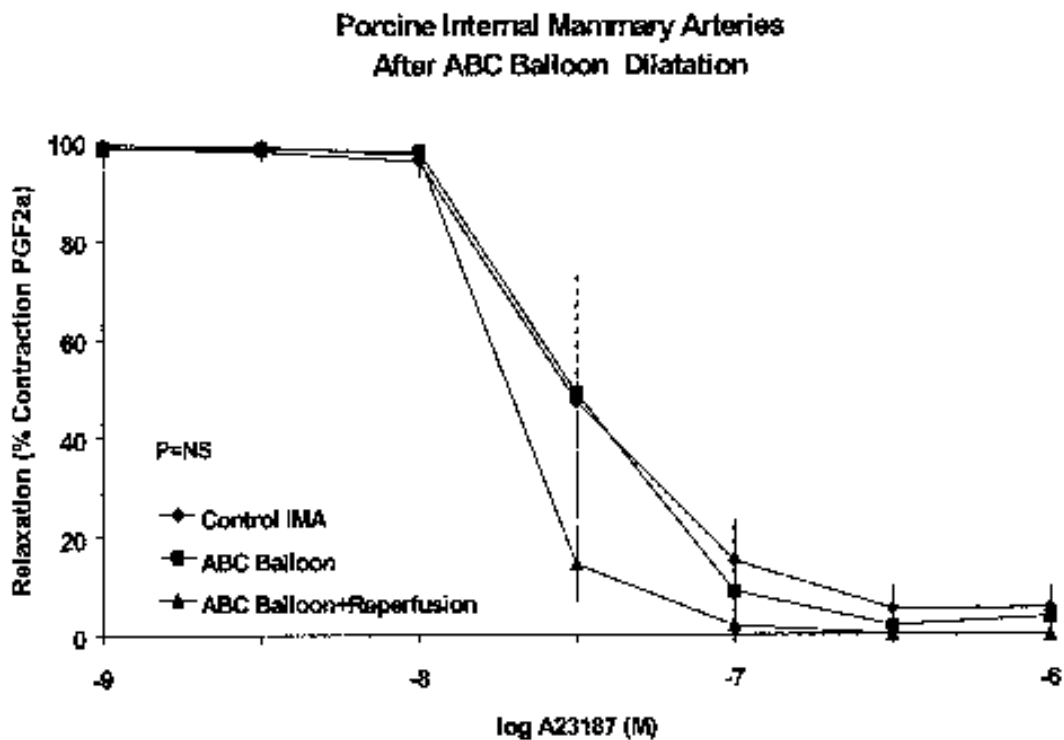


Figure 6 Cumulative concentration-relaxation response curves to serotonin (5-HT) in porcine femoral arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

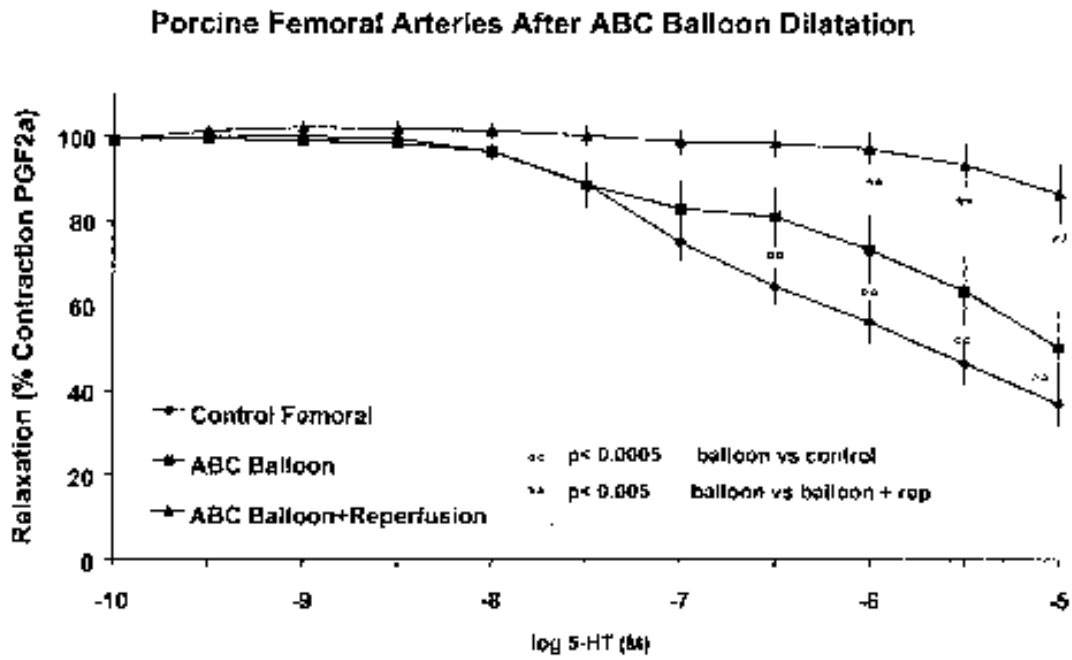


Figure 7 Cumulative concentration-relaxation response curves to bradykinin (BK) in porcine femoral arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

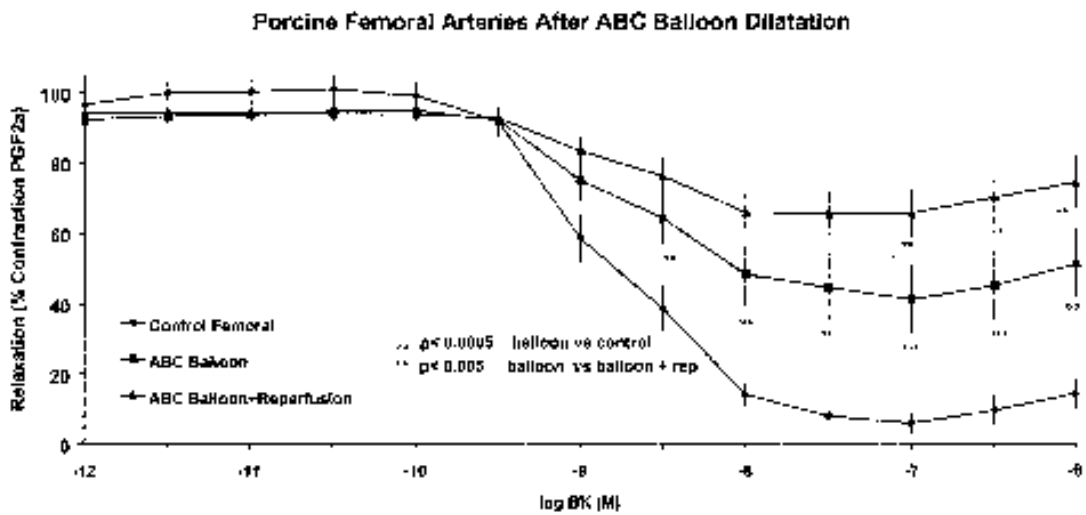


Figure 8 Cumulative concentration-relaxation response curves to the calcium ionophore (A23187) in porcine femoral arteries rings submitted to the 3.5-mm balloon catheter dilatation with and without reperfusion, and in control rings.

