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Chronic Effects of Arterial Balloon Dilatation on Internal Mammary Artery Endothelial Function

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ABSTRACT

Background: Manipulation for harvesting of the internal mammary artery (IMA) for coronary artery bypass grafting has been shown to acutely impair endothelium-dependent, but not endothelium-independent contractions and relaxations. Recently the use of a novel arterial balloon catheter to dilate the IMA has shown an increased IMA flow while preserving endothelial cell integrity and function acutely. This study examines the chronic effects on endothelial function of IMA segments subjected to arterial balloon catheter dilatation in comparison to either no manipulation (control), luminal dilatation with papaverine, or temporary occlusion with soft or hard jaw in a porcine model.

Methods: Porcine IMAs were harvested one month after instrumentation. Ten IMA segments in each group were obtained and placed in organ chambers under isometric tension. Maximal endothelium-dependent contractions with arachidonic acid and relaxations with acetylcholine, and endothelium-independent contractions with norepinephrine and relaxations with sodium nitroprusside were measured.

Results: Endothelium-dependent contractions and relaxations were significantly impaired after hard jaw occlusion one month after IMA manipulation compared to control, long balloon, fibrous jaw, and papaverine groups. Endothelium-independent contractions and relaxations of IMA smooth muscle were unaffected at one month after manipulation.

Conclusion: We conclude that arterial long balloon dilatation is not detrimental to endothelial cell function chronically and is therefore an effective and atraumatic method to relieve IMA spasm before coronary bypass grafting.

INTRODUCTION

The central role of the endothelial cell in the regulation of arterial relaxation and vascular wall homeostasis has been known since 1980 [Furchgott 1980]. Relaxation of arteries such as the internal mammary artery (IMA) occur through both endothelium-dependent and endothelium-independent pathways [Luscher 1988, Ignarro 1989]. Endothelium-dependent relaxation of the IMA requires both the presence and functional integrity of the endothelial cell. Relaxation is mediated by the endothelial cell release of nitric oxide (NO), endothelium-dependent hyperpolarizing factor (EDHF), and prostacyclin [Furchgott 1980, Ignarro 1989]. NO also inhibits smooth muscle cell proliferation, low density lipoprotein oxidation, and platelet aggregation [Furchgott 1980, Ignarro 1989]. This monolayer of endothelial cells is easily damaged by even small amounts of mechanical manipulation. Removal or damage of the endothelial cell has been shown to impair endothelium-dependent arterial relaxation, possibly through a decreased NO production, leading to intimal hyperplasia and favoring the development of atherosclerotic plaques [Shimokawa 1989].

Coronary artery bypass grafting surgery almost universely involves grafting of the left internal mammary artery (LIMA) onto the left anterior descending (LAD) coronary artery. A potential problem with the use of IMAs is the high risk of spasm during dissection which may decrease early graft flow and lead to catastrophic consequences clinically [Sarabu 1987]. Different methods have been described in order to prevent and treat IMA spasm, for example chemical dilatation with papaverine or mechanical dilatation with a metal probe or long balloon [Mills 1989, Cooper 1992]. Intraluminal injection of papaverine increases IMA flow by 87% while preserving endothelium-dependent relaxation [Cooper 1992]. Electron microscopic studies, however, have shown that hydrostatic dilatation may cause damage to the IMA intima and internal elastic lamina [Van Son 1992], thereby predisposing to subsequent intimal proliferation. The use of the long balloon enables an increase in IMA flow without exerting any shear force on the endothelium, thus preserving endothelium-dependent contractions and relaxations as well as minimizing endothelial denudation [Jeanmart, in press].

Temporary occluders are placed on the surface of the IMAs in order to preserve a clear operating field. Temporary clamping of the IMA pedicle is accomplished with either hard (metal), soft (rubber or silicone) or more recently fibrous clamps. Previous studies have demonstrated an initial endothelial injury as well as damage to the underlying vascular smooth muscle when using hard clamps [Fonger 1992]. Use of the fibrous clamp does not have any negative effect on

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endothelium-dependent relaxations when compared to controls but partial denudation of the endothelial layer nevertheless does occur with these clamps [Fonger 1995].

Since the arterial long balloon does not cause any detrimental effects on IMA endothelial function acutely, the aim of this study was to evaluate the chronic effects of this new device on endothelium-dependent and independent contractions and relaxations and to compare it to chemical dilatation with papaverine and mechanical occlusion with hard and fibrous clamps.

MATERIALS AND METHODS

Surgical Protocol

Swines (90 kg) of male and female gender were anesthetized in a supine position and the distal IMA exposed by a left upper quadrant incision and left in continuity (Figure 1, ◎). The fibrous and hard clamps were applied for 30 minutes and then removed. The long arterial balloon catheter is a 15-cm balloon of specially designed latex (Applied Medical, CA) which inflates symmetrically (Figure 2, ◎). The long balloon was introduced into the IMA through a lateral incision and inflated for one minute at 30 g and then deflated. The arteriotomy in the IMA was then closed with Polypropilene 7-0 interrupted sutures, the incision closed, and the animal left to recover for one month, then sacrificed. Sites of device application were identified using suture markers. Control mammary segments were obtained at the time of sacrifice from the right mammary artery.

Vascular Reactivity

After the sacrifice of the animal, the left and right IMAs were dissected and immediately transported to the laboratory in a Krebs bicarbonate solution at room temperature. The periadventitial fat was carefully removed and completely dissected from the IMA before division into vascular rings of 4 mm in length. Sites of clamp application were identified on the vessel. The endothelial function of the different rings was studied in organ chambers filled with 37°C oxygenated Krebs physiological 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 calcium ethylenediaminotetraacetic acid 0.026: control solution). Oxygenation was ensured using a carbogen mixture (95% O_2 and 5% CO_2). The rings were suspended between two metal stirrups, one of which was connected to an isometric force transducer for isometric tension recording.

The rings were stretched progressively in 1 g increments to a final resting tension of 5 g. The rings were allowed to equilibrate for 10 minutes after each 1 g increase. At 5 g, the rings were equilibrated for an additional 45 minutes before testing. The final resting tension of 5 g for similar diameter IMA rings produces a maximal contraction when stimulated with high-dose potassium chloride (KCL 40 mEq/L). The chart recorder scale was zeroed and norepinephrine (an alpha-adrenergic receptor agonist (NE), 10-7 mol/L) was given to obtain a contraction between 50 and 80% of the maximal contraction (with KCl). Once a contraction plateau was reached, testing of IMA ring relaxation was begun.

Endothelium-dependent relaxations were studied using increasing concentrations of acetylcholine (ACh, 10-8 to 10-5 mol/L). Endothelium-independent relaxations were studied using increasing concentrations of sodium nitroprusside (SNP, 10-8 to 10-4 mol/L). After the last dose of vasorelaxing agonist, an organ chamber washout was done and the rings were allowed to equilibrate for 45 minutes before NE 3 x 10-8 mol/L was added to the chambers to obtain a contraction plateau. IMA ring contraction was then begun; endothelium-dependent contractions were studied using increasing concentrations of arachidonic acid (AA, 10-8 to 10-5 mol/L) and endothelium-independent contractions were studied using increasing concentrations of norepinephrine (NE, 10-9 to 10-5 mol/L).

Statistical Analysis

Values from all rings at each concentration and in each group were averaged. The right mammary arteries were used as controls. Contractions and relaxations are expressed as a percentage of maximal contraction for each group. The final percentage relaxation in each group for ACh and SNP, and the maximal percentage contraction after AA and NE were compared by the Kruskal-Wallis nonparametric test followed by the Wilcoxon signed-rank test when differences were identified.

RESULTS

Relaxation Studies

There was a statistically significant decrease in the endothelium-dependent relaxation to acetylcholine in the hard jaw group (39.6%) compared with controls ($p < 0.0001$). There was no statistically significant difference in relaxations between the control and long balloon (71.7%), papaverine (100.1%) and soft jaw (64.9%) groups at one month after application of the devices (Figure 3, ◎).

Endothelium-independent relaxations of IMA to SNP were unaffected by any of the four manipulations at one month (Figure 4, ◎).

Contraction Studies

There was no statistically significant difference in the maximal contraction to AA (endothelium-dependent) between the long balloon (87.2%), papaverine (96.9%) and soft jaw groups (80.3%) at one month after application compared to controls. There was a significant decrease in contraction in the hard jaw group (59.3%) compared with all three other groups ($p < 0.005$) (Figure 5, ◎).

There was no statistically significant difference in the maximal contraction to NE between groups (Figure 6, ◎).

DISCUSSION

The central role of the endothelial cell in modulating vascular tone under changing physiological conditions is well established [Vanhoutte 1988]. The endothelium releases vasoacting substances in response to circulating hormones, locally released agents by platelets, and shear stress [Furchgott 1989, Vanhoutte 1988]. These substances mediate either relaxation or contraction of the vessel and are in tight balance

in order to assure adequate flow to the different organ systems. The presence and functional integrity of the endothelium is pivotal in this process.

Grafting of the IMA to the LAD is the gold standard in surgical myocardial revascularization with proven superior long-term patency rates compared to venous grafts [Grondin 1984, Loop 1986]. Before it is grafted on the diseased vessel, the IMA must be harvested from its bed with the inherent risk of trauma and vasospasm, resulting in a decreased arterial flow and possibly thrombosis [Jones 1989]. All mammary arteries show some degree of spasm immediately after harvest and flow in the IMA is suboptimal until pharmacologic or mechanical intervention [Mills 1989]. In order to minimize the risk of graft hypoperfusion from spasm, many different techniques have been developed. Hydrostatic dilation of the IMA with papaverine has the advantage of maintaining the functional integrity of the endothelium [Mills 1989, Hillier 1992], although it may damage the intima and internal elastic lamina as assessed by electron microscopy. The use of the arterial balloon catheter has been shown in a previous study to maintain the functional and structural integrity of the endothelium in acute studies performed on IMA segments that were instrumented and immediately transferred to organ chambers [Jeanmart, in press]. The long-term effects of the application of this device on the IMA have not been investigated. In this study, IMA endothelial function evaluated by endothelium-dependent relaxations and contractions was unaltered one month after intraluminal injection of papaverine or long balloon dilatation. These results demonstrate that not only are these methods efficacious in augmenting flow through the IMA by minimizing spasm, as previously reported [Cooper 1992, Jeanmart, in press], but do so by maintaining functional integrity of the endothelium. Thus these techniques have no detrimental long-term effect on the IMA thereby minimizing the risk of graft thrombosis in the early postoperative period or intimal hyperplasia later on.

The effect of external occlusive pressure on the IMA pedicle by temporary clamping in order to preserve a clear operating field has been previously investigated [Fonger 1992, Fonger 1995]. Hard clamps cause immediate impairment of both endothelium-dependent relaxation and endothelium-independent relaxation of the IMA [Jeanmart, in press]. This suggests that trauma from the hard clamp damages the underlying vascular smooth muscle. On the other hand fibrous clamps, which conform to the convexity of the IMA pedicle while minimizing external pressure, preserve endothelium-dependent relaxation as well as islands of intact endothelial cells between areas compressed by the nylon fibrils [Fonger 1995]. These studies have focused on the immediate effect of occlusion techniques. The present study shows that endothelial function and integrity are preserved one month after application of the fibrous clamp on the IMA for 30 minutes. These findings suggest that the IMA remains capable of releasing mediators that are important modulators of endothelial vasomotor tone and inhibitors of platelet aggregation when a fibrous clamp is used to occlude the IMA. On the contrary, hard clamps cause alterations of endothelium-dependent relaxations which persist one month after manipulation, a time frame at which regeneration of endothelial cells would be expected [Shimokawa 1989]. Contrary to the acute studies previously published [Fonger 1992, Fonger 1995], experiments performed one month after application of hard clamps show a recovery of the endothelium-independent relaxation to sodium nitroprusside, thereby demonstrating the integrity of the vascular smooth muscle.

The late clinical consequences of a damaged ring of endothelium are difficult to assess [He 1988]. The 10-year IMA graft patency rate approaches 95% [Grondin 1984] with presumably a regenerated and abnormally functioning ring of endothelium within their pedicle from intraoperative manipulation. There exists however the potential for this site to develop intimal hyperplasia and eventually an atherosclerotic plaque due to diminished local production of endothelium-dependent relaxing factor (NO) [Fonger 1992], proven to inhibit smooth muscle proliferation, platelet aggregation, and LDL oxidation [He 1988]. However, evidence of focal plaques developing over time at the clamp site in the midportion of IMA pedicles has not been demonstrated.

The use of the radial artery for coronary revascularization has been recently rejuvenated with improved early and midterm results [Brodman 1996, Manasse 1996]. The risk for vasospasm however remains worrisome with this conduit [Shapira 1997]. Most authors emphasize the necessity for pharmacological intervention to prevent vasospasm but the drug of choice is still a matter of controversy [Brodman 1996, Manasse 1996]. The calcium channel blocker diltiazem is used by many surgeons but this treatment remains empirical [Brodman 1996, Manasse 1996]. Diltiazem must be given in the perioperative period and continued for 6-12 months after the operation, a costly treatment which may additionally be associated with symptomatic negative chronotropic and inotropic effects in 30-40% of patients [Brodman 1996, Shapira 1997]. Moreover, organic nitrates may be superior to diltiazem and verapamil in preventing radial artery spasm in the perioperative period [Cable 1998]. Milrinone is also a potent vasodilator for the radial artery and has added positive inotropic effects [He 2000]. The use of the novel arterial balloon catheter in order to prevent long-term vasospasm in the radial artery and forego the necessity of immediate and long-term pharmacological treatment would be an interesting alternative that remains to be investigated.

This study shows the effects of long balloon dilatation on IMA endothelial function at one month. Use of a novel arterial balloon catheter in order to dilate the IMA is not injurious to the endothelium at one month in a porcine model. The current understanding of endothelial function and the clinical consequences of its loss warrant the use of manipulation techniques that do not injure endothelial cells chronically. We demonstrate that functional integrity is maintained at one month after long balloon dilatation, intraluminal injection of papaverine, and fibrous jaw clamps. The use of hard clamps however causes a persistent alteration of endothelial function at one month. Further studies to test the reproductivity of these results on other arterial conduits, notably the radial and right gastroepiploic arteries are warranted.

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REVIEW AND COMMENTARY

1. Editorial Board Member JZ39 writes:

This is a compelling idea and probably very useful, if it indeed made the artery bigger over time. What was its mean diameter at start and finish and did it stay big after dilation a month later? It is not helpful to me without that data. Statistically, it had no differences, but they seem to have a lot of variation in reactivity of the vessels that were not significant in this group size. What would it take to do a statistically valid study?

Authors' Response by Eric Dumont, MD:

The mean diameter of the internal mammary artery was not measured before and after the long balloon dilatation. The balloon visually stretched the IMA as it was inflated but no measures were taken. Therefore the size of the artery one month later, although a very interesting measure, would probably not be bigger than the native one. Also, the purpose of our study was to show that the arterial balloon catheter did not cause structural nor functional damage to the endothelial layer chronically at one month and not that it increased IMA graft flow.

2. Editorial Board Member GX21 writes:

This is a well-written paper, which examines the effects of arterial balloon dilatation on internal mammary artery endothelial function.

Some suggestions for clarification and improvement are as follows:

- In the Results section, it is unclear what the numbers in parentheses relate to and they do not appear to match the results in the figures. The authors should explain the results in the text.
- In Figure 4, there appears to be a marked difference between the response in group A compared to the other groups. From this data, the authors have concluded that endothelium-independent relaxations of IMA to SNP were unaffected by any of the four manipulations. However, the sample size is too small to detect the differences that can be seen between the groups. The authors should

explain what the clinically important differences are and the power they have to detect them, and then amend their conclusions accordingly.
- To facilitate comparison, the graphs should be plotted with the same scale on the vertical axis.

Authors' Response by Eric Dumont, MD:

The numbers in parentheses relate to the percentage relaxation to acetylcholine of the pre-contracted rings to norepinephrine in each test groups compared to controls (ratio). Therefore the greater the relaxation, the greater the functional integrity of the endothelium. Although Figure 4 seems to show a significant decrease in endothelium-independent relaxations when IMAs are dilated by papaverine infusion, no significant difference was evident after statistical analysis. A greater sample size would probably corroborate these findings.

3. Editorial Board Member LO23 writes:

This study compares the effect (after one month) of a one minute balloon inflation with a 30 minute hard clamp application to the "non-dissected in situ" internal mammary artery. The relevance of this comparison must be questioned, as the use/objective of these two interventions are differant; the balloon to "dilate a "spastic artery" - in this experiment the IMA was not dissected and presumably not subjected to spasticity prior to the intervention, and the clamp to prevent flow through the IMA after harvesting.

The relevance of intraluminal papavarive (no methodology provided for this intervention) in a non-dissected IMA again must be questioned. Moreover, it has also been shown that external applied papavarine is equivalent in the dissected vessel.

The authors further state that there are no short term effects of the use of this device — unpublished data.

Authors' Response by Eric Dumont, MD:

The comparison of a one-minute balloon inflation with a 30 minute hard clamp application is possible because these are approximate times which would be realistic for the use of these two devices clinically. The goal of this study was to evaluate the chronic effect of different manipulations on the IMA endothelium and moreover to prove that the arterial catheter was not harmful to the endothelium at one month.

We tested intraluminal papaverine dilatation instead of externally applying it because this intervention is still used in many cardiac surgery centers today and is more likely to cause endothelial dysfunction by hydrostatic dilatation effects and direct toxic effects than is external application.

4. Editorial Board Member NH413 writes:

This is a well designed experimental study which may have important clinical relevance in the future once it undergoes clinical trials. However, there are a few points which need to be elaborated.

The authors have not mentioned whether there is a learning curve in the use of the ballon catheter and in clinical situations damage to the IMA is possible.

They have suggested in the discussion that a single dilatation of the radial artery would prevent long term vasospasm. I wonder how this is possible.

Authors' Response by Eric Dumont, MD:

Yes, there is a learning curve in the use of the balloon catheter. Uniform inflation of the balloon must be done in order to assure proper function and to prevent injury to the IMA. Also, proper catheter size is essential to avoid overdilatation and damage to the endothelium.

A single dilatation of the radial artery would not prevent long term vasospasm. Rather the arterial balloon catheter could be used in the radial artery if vasospasm is present after dissection in order to break the vasospasm and prevent graft hypoperfusion. The use of the ABC in the radial artery remains theoretical and must be tested in the laboratory.

5. Editorial Board Member YT31 writes:

This is a good review and documentation of some of the related and relevant articles.

There could be more done to verify intact endothelial function. There can be some relaxation of vessel segments using acetylcholine in a porcine model even with damaged endothelium. Substance P or scanning EM would have been corroborative evidence.

Authors' Response by Eric Dumont, MD:

We agree that silver nitrate staining or scanning electron microscopy could have been used for corroborative evidence of endothelial dysfunction but we feel confortable with the conclusions that be drawn from endothelium-dependent relaxation to acetylcholine and contraction to arachidonic acid.