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Interrupted Coalescent Nitinol Clip versus Continuous Suture Coronary Anastomosis: A Comparative Endothelial Function Study

Dr. Demaria

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ABSTRACT

Background: A new penetrating stapled anastomotic system using nitinol microclips (Coalescent Surgical U-Clip) has been developed to facilitate the construction of compliant interrupted sutures for minimally invasive and robotic surgery as well as for conventional procedures. The purpose of this study was to determine the effect of nitinol U-Clips used for coronary anastomosis in the development of endothelial dysfunction, compared with conventional running sutures.

Methods: In a porcine model, both internal thoracic arteries were harvested, and the heart was removed. In a Krebs solution, 2 anastomoses were realized ex vivo between internal thoracic arteries and the left anterior descending artery. One was carried out with 12 Coalescent microclips, and the other used conventional running 7-0 polypropylene suture material (Prolene). Coronary rings on the anastomotic sites were then placed in organ chambers filled with oxygenated Krebs solution. Vascular reactivity studies were performed in standard organ chamber experiments. After the contraction of the coronary arteries in response to prostaglandin $F_{2\alpha}$, the endothelium-dependent relaxation response to bradykinin was studied. The other coronary arteries served as controls.

Results: There was no statistically significant difference among the groups ($P > .05$) in the amplitude of the contraction response to KCl and prostaglandin $F_{2\alpha}$. There were no statistically significant differences in endothelium-dependent relaxation response to bradykinin between the nitinol microclip group and controls, between the suture group and controls, and between the nitinol microclip and suture groups.

Conclusions: Coalescent nitinol U-Clips used as anastomotic devices do not induce an endothelial dysfunction and allow a compliant anastomosis under satisfactory conditions.

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INTRODUCTION

Minimally invasive coronary artery bypass surgery, including off-pump coronary artery bypass surgery and robotic surgery, has enjoyed a spurt of development in recent years [Pfister 1997]. However, specific technical difficulties are associated with these procedures, including the limited surgical approach, the stabilization of the beating heart, and the completion of knots during anastomosis. Moreover, compliance is a known important factor in arterial physiology, and the compliance mismatch at the anastomotic site is one of the main predictive factors of the development of subintimal hyperplasia [Baird 1976, Stewart 1992, Okuhn 1989], resulting in anastomotic and graft failure [Abbott 1987]. Also, end-to-side anastomosis with interrupted stitches results in a better compliance match than anastomosis performed with running sutures [Tozzi 2001].

A new penetrating stapling anastomosis technique using nitinol U-Clips (Coalescent Surgical, Sunnyvale, CA, USA) has recently been developed to facilitate the construction of anastomoses with interrupted stitches without the need for knot tying. Concomitant with these technical advances in cardiac surgery, improvements in the understanding of the endothelium's regulation of vascular tone and coagulation control have led to the knowledge that the structural and functional integrity of the endothelial layer is essential to optimize the patency of the results of surgical coronary procedures [Vanhoutte 1989]. The purpose of this study was to determine the effect of a stapled interrupted coronary anastomosis device using nitinol U-Clips on coronary artery endothelial function and vascular contraction at the anastomotic site, compared with anastomosis using a conventional 7-0 polypropylene (Prolene; Johnson & Johnson, Somerville, NJ, USA) running suture.

MATERIALS AND METHODS

Experimental Surgery

Six white Landrace swine of either sex, aged 8 ± 1 weeks and weighing 24 ± 4 kg were included in this study. Animals

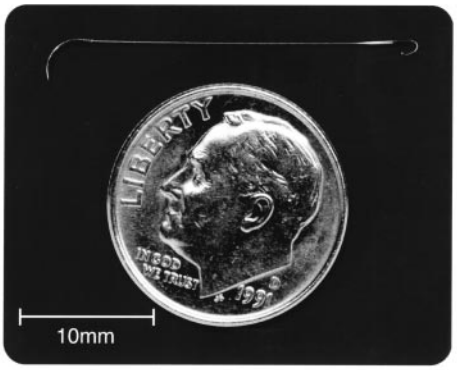

Figure 1. Penetrating stapling nitinol microclips mounted with a thread and needle.

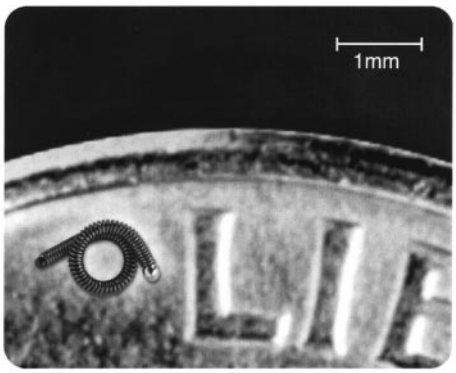

Figure 2. Penetrating stapling nitinol microclips. High magnification view of the microclip in closed position.

were maintained and tested in accordance with the recommendations of the Guide to the Care and Use of Experimental Animals issued by the Canadian Council on Animal Care and the Guidelines of Animal Care, and care protocols were approved by a local ethics committee.

The animals were anesthetized by an intramuscular injection of 20 mg/kg ketamine hydrochloride (Ayerst Veterinary Laboratories, Guelph, Ontario, Canada) with 2 mg/kg of xylazine (Boehringer Ingelheim, Burlington, Ontario, Canada), intubated, and mechanically ventilated with an oxygen-air mixture (3:2). Anesthesia was maintained with 2% halothane inhalation (Halocarbon Laboratories, River Edge, NJ, USA). The electrocardiogram was recorded from 3 subcutaneous limb electrodes. The hearts were exposed via a median sternotomy approach, and after dissection of both internal thoracic arteries (ITAs), 300 U/kg heparin (Leo Pharma, Ajax, On., Canada) was given intravenously. An intraluminal injection of papaverine was not used to avoid endothelial damage. The heart and ITAs were then rapidly excised and placed in a cold (4°C) modified Krebs-bicarbonate solution (118.3 mmol/L NaCl, 4.7 mmol/L KCl, 1.2 mmol/L $MgSO_4$, 1.2 mmol/L KH_2PO_4, 11.1 mmol/L glucose, 2.5 mmol/L $CaCl_2$, 25 mmol/L $NaHCO_3$, and 0.026 mmol/L ethylenediaminetetraacetic acid).

The coronary arteries and the ITAs were dissected free of the surrounding tissues in a silicone dish irrigated with the cold modified Krebs-bicarbonate solution. An end-to-side anastomosis of an ITA to the left anterior descending artery (LAD) was performed in the silicone dish with the nitinol U-Clips (Figures 1 and 2). Twelve to 14 microclips were used to complete the anastomosis (Figure 3). Each microclip was connected to a thread and passed through the ITA and LAD walls. The thread then was cut off with the needle holder, leaving the microclip closed. An end-to-side anastomosis of the ITA to the LAD of approximately 2 cm and randomly upstream or downstream from the previous anastomosis site was performed in a conventional fashion with a 7-0 polypropylene running suture. The coronary rings bearing the anastomosis were then excised for organ chamber experiments. Proximal segments of the LAD, circumflex, and right coronary arteries were used randomly as control rings.

Functional Coronary Ring Testing

All rings were placed in organ chambers (Emka Technologies, Paris, France) filled with 20 mL modified Krebs-bicarbonate solution heated at 37°C and oxygenated with carbogen (95% oxygen and 5% carbon dioxide). The rings

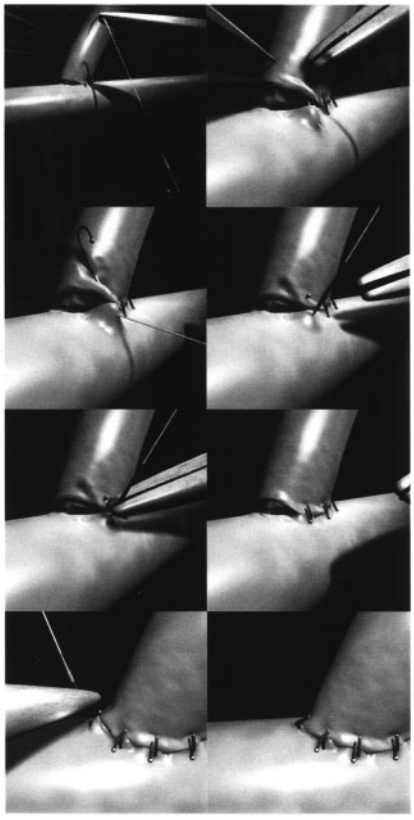

Figure 3. Coalescent microclip anastomosis between the internal thoracic artery (ITA) and the left anterior descending artery (LAD). Twelve to 14 microclips were used to complete the Coalescent anastomosis. Each microclip was passed through the ITA and LAD walls following the needle-mounted thread, and the thread then was cut off with the needle holder, leaving the microclip closed (computer-assisted representation).

Amplitude of Contraction Response to 60 mmol/L KCl and Prostaglandin $F_{2\alpha}$*

	Coalescent	Polypropylene	Controls	*P*
KCl (60 mmol/L contraction), g	7.1 ± 2.4	9.8 ± 1.0	8.7 ± 1.6	NS
$PGF_{2\alpha}$ contraction, g	3.4 ± 1.1	4.4 ± 1.5	6.3 ± 1.24	NS
$PGF_{2\alpha}$ concentration used, (10^{-6} mol/L)	15.3 ± 6.4	20.0 ± 10	13.5 ± 3.53	NS

*The prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) concentration range was 2 ± 10^{-6} to 3 ± 10^{-5} mol/L. Values are expressed as the mean ± SEM; a *P* value <.05 was considered statistically significant. NS indicates nonsignificant.

were suspended between 2 metal stirrups with the upper one connected to an isometric force transducer connected to a signal amplifier and allowed to stabilize for 30 minutes. Data were collected with biological signal data acquisition software (IOX 1.203; Emka Technologies).

Each arterial ring was stretched to the optimal point of its active length-tension curve (approximately 3.5 g), which had been determined in previous experiments by measuring the contraction response to 30 mmol/L KCl at different levels of stretch. The maximal contraction of the rings was then obtained with the addition of 60 mmol/L KCl. After a plateau was obtained, all baths were washed twice with a modified Krebs-bicarbonate solution and 1 ± 10^{-5} mol/L indomethacin (to exclude the production of endogenous prostanoids) with 1 ± 10^{-7} mol/L propranolol added to prevent the activation of β-adrenergic receptors.

After 45 minutes of stabilization, 2 × 10^{-6} to 3 × 10^{-5} mol/L prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was added to obtain a contraction averaging 50% of the maximal contraction response to KCl. The endothelium-dependent relaxation to various concentrations (10^{-12} to 10^{-6} mol/L) of bradykinin, an agonist that binds to a receptor coupled to G_q proteins, was recorded. At the end of the experiment, the endothelium-independent relaxations were studied with a bolus of 1 ± 10^{-5} mol/L sodium nitroprusside, a nitric oxide donor.

All drugs were prepared daily. Bradykinin, indomethacin, and sodium nitroprusside were purchased from Sigma Chemical Company (On., Canada). Propranolol was obtained from Biomol Research Laboratories (Plymouth Meeting, PA, USA), and $PGF_{2\alpha}$ was obtained from Cayman Chemical Company (Ann Arbor, MI, USA).

Statistical Analysis

Relaxations are expressed as a percentage of the maximal contraction response to $PGF_{2\alpha}$ for each group and expressed as the mean ± SEM. Two-way repeated analysis of variance was performed to compare each point of the concentration-response curves for the control rings and the anastomosis rings. Statistical analysis was realized with SAS Institute computer software (Cary, NC, USA). A *P* value <.05 was considered statistically significant.

RESULTS

Experimental Surgery

Satisfactory completion of the anastomosis was obtained in all cases. There were no nitinol microclip–related technical problems, and the times required to perform a stapling anastomosis decreased regularly with practice.

Coronary Reactivity Study

Contractions. There was no statistically significant difference in the amplitudes of contractions in response to 60 mmol/L KCl and to 2 ± 10^{-6} to 3 ± 10^{-5} mol/L $PGF_{2\alpha}$ between the 2 experimental anastomosis groups and the control group. There was no statistically significant difference in the concentrations of $PGF_{2\alpha}$ needed to achieve the target level of contraction among the 2 anastomosis groups and the controls (Table).

Endothelium-Dependent Relaxations. There was no statistically significant difference in the endothelium-dependent relaxation response to bradykinin between the nitinol microclip group and the controls, between the suture group and the controls, and between the nitinol microclip and the suture groups (Figure 4).

COMMENT

In comparisons with a conventionally fashioned anastomosis with running polypropylene suture and with controls, the major finding of this study is that the use of the penetrating Coalescent nitinol microclips for ITA-to-LAD anastomosis does not cause endothelial dysfunction. In addition, the contractile capacity of the ring bearing the anastomosis is preserved, reflecting the preservation of the arterial wall physiology. Coalescent nitinol microclips facilitate the performance of interrupted suture ITA–coronary artery anastomosis.

The development of minimally invasive coronary artery bypass grafting surgery via limited approach, off-pump coronary artery bypass, and robotic coronary artery bypass grafting may benefit from new nonsuture-based anastomotic techniques that do not require knot tying and that enable the completion of the anastomosis with more ease. Recently, some studies have shown the feasibility of performing a microvascular, stapled anastomosis with nonpenetrating stapling [Cook 2001, Baguneid 2001, Komori 2001], and one [Lisi 1998] has evaluated the effect of these devices on endothelial reactivity after completion of the anastomosis. Moreover, an improved knowledge of endothelial physiology has shown that the maintenance of a functional endothelial layer is important for technical success, because endothelial dysfunction is associated with spasm, increased thrombogenicity, and, potentially, a regenerated endothelium that is at high risk of developing intimal hyperplasia [Vanhoutte 1989].

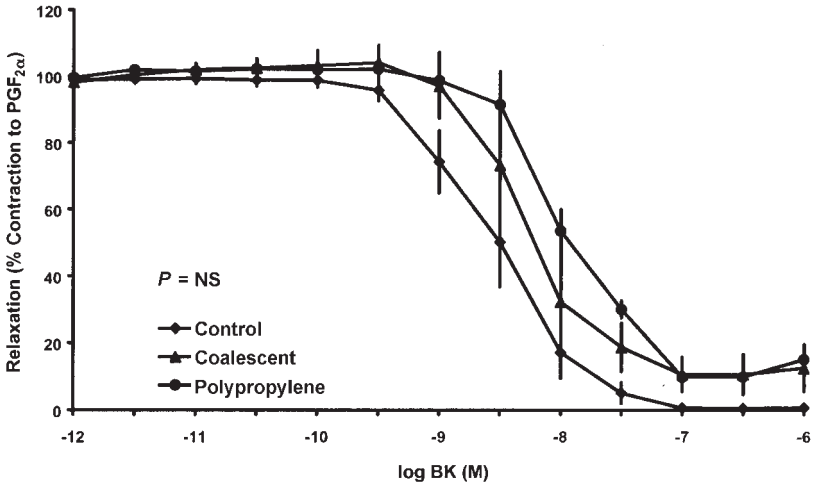

Figure 4. Cumulative concentration-relaxation response curves to bradykinin (BK) in porcine coronary artery rings submitted to a Coalescent microclip anastomosis or to a 7-0 polypropylene running suture anastomosis. Proximal segments of the left anterior descending, circumflex, and right coronary arteries were used randomly as control rings. A *P* value <.05 was considered statistically significant. NS indicates nonsignificant.

A previous study using nonpenetrating staples (Auto Suture VCS clipping device; United States Surgical, Norwalk, CT, USA) demonstrated a satisfactory functional result in a swine model and no significant difference between stapling and conventional running polypropylene suture in the maximal relaxation response to bradykinin [Lisi 1998]. After this study, devices for performing a totally 1-shot anastomosis began to be developed. A stapler prototype for short-occlusive, sutureless end-to-side grafting on the beating porcine heart was developed but caused early endothelial and medial damage that could decrease the late patency rates [Heijmen 1999].

Severe surgically induced endothelial lesions and dysfunction [Chavanon 1999] are usually secondary to forceful contact with the endothelial layer. This mechanism of injury of rubbing of the inner surface of isolated blood vessels is well known and is used in pharmacology experiments to remove the endothelial layer [Vanhoutte 1989]. However, the individual punctures secondary to breaching by needles with the 2 compared techniques (interrupted microclips and running sutures) are not sufficient to create significant endothelial dysfunction, as was demonstrated in our experiments, even if some degree of endothelial damage remains inevitable at the site of penetration. Indeed, compared with nitinol microclip anastomosis and the controls, the running suture did show a trend of endothelial dysfunction, but this trend did not reach statistical significance.

The main limitation of this acute study is the use of an ex vivo swine model. This in vitro method of acute testing does not allow the development of the expected long-term cellular and humoral alteration associated with the in vivo perfusion of the anastomotic site. However, it is a comparative endothelial function study of 2 different end-to-side anastomotic devices used on the same arteries submitted to the same conditions on each animal. However, the satisfactory endothelium-dependent relaxation responses obtained for all rings prove that the integrity of the endothelial layer was preserved. The second limitation is the use of healthy coronary arteries. Experiments performed on atherosclerotic arteries would reproduce more closely the clinical reality. However, because the endothelium of atherosclerotic arteries is already dysfunctional [Shimokawa 1987], the endothelial trauma induced by anastomosis in these arteries may not have any additional functional drawbacks, but this supposition remains to be proven by further experimental studies specifically focused on the vascular reactivity of atheromatous vessels.

In conclusion, the nitinol microclip interrupted anastomotic technique has the same effect on the endothelial function as conventional running suture with thread. However, the main interest of this new anastomotic technique is that it easily allows a faster completion of separated stitches than with conventional threads without the necessity to tie knots. A comparative study of the compliance of the anastomosis should be done with conventional stitches to identify another potential clinical interest of this new technique, as it has already been realized for other types of new anastomosis procedures [Demaria 2000, Perrault 2002].

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REVIEW AND COMMENTARY

1. Editorial Board Member SG14 writes:

The present article sets a clear question and answers also pretty clearly. The results gained can even initiate further studies to understand and maybe correct technical anastomotic problems.

The authors found a difference in endothelial dysfunction in the continuous suture group, however this difference did not reach statistical significance. My question is if that was so due to the limited number of probants? Please seek statistical advice. Only 6 seems very few.

Authors' Response by Dr. Roland G. Demaria:

In the setting of paired experiments from controlled studies with a sensitive marker of endothelial function such as organ chamber experiments, 6 reproducible experiments (n = 6 animals) are sufficient to achieve statistical validity. In the setting of the evaluation of vascular reactivity of coronary anastomosis, this protocol has been previously published by our group [Lisi 1998].