Effect of blower-mister devices on vasoreactivity of coronary artery bypass grafts

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Objective: Potential disadvantages, such as lower graft patency rates, that could lead to the need for more subsequent revascularization after off-pump coronary artery bypass grafting are discussed. One mechanism may involve endothelial damage originating from tools to facilitate a bloodless surgical field during anastomosis. We investigated the effect of the use of a blower-mister device on in vitro endothelial and contractile functions of human internal thoracic arteries and greater saphenous veins.

Methods: The distal ends of both bypass graft types were exposed to the air and water stream of the device for 10 minutes, representing the usual time needed for completion of an anastomosis using the off-pump technique. Vessel segments of both groups were cut into 4-mm rings and stored in a modified Krebs–Henseleit solution. Contraction responses to U44619 and relaxation responses to acetylcholine, substance P, papaverine, and nitroprusside were evaluated.

Results: Forty-eight artery ring segments from 8 patients were studied. Absolute maximum contraction to U44619 was significantly less in rings subjected to the blower-mister device than in controls (internal thoracic artery: 17.17 ± 2.57 mN vs 8.67 ± 4.54 mN, $P < .048$; greater saphenous vein: 28.33 ± 9.71 mN vs 11.42 ± 7.97 mN, $P < .026$). Control rings had significantly greater endothelium-dependent relaxation response to acetylcholine (mean difference $29.2\% \pm 3.4\%$, $P < .001$), whereas those subjected to the blower-mister device had reduced responses. Endothelium-independent relaxation to nitroprusside was not significantly different among the groups.

Conclusions: Vessels exposed to the air and water stream of a blower-mister device showed a reduced vasoreactivity. This effect should be studied further, especially if it contributes to lower graft patency rates in off-pump surgery. (J Thorac Cardiovasc Surg 2010;140:923-7)

Although pioneers reported direct myocardial revascularization without cardiopulmonary bypass by anastomosing the internal thoracic arteries (ITAs) to the main coronary arteries as early as in the 1960s,^{1,2} beating heart surgery was largely abandoned in the subsequent years. Coronary artery bypass grafting (CABG) was mainly performed with the use of cardiopulmonary bypass and electromechanical cardiac arrest. These circumstances provide coronary anastomoses in a bloodless and motionless field. Currently, because cardiopulmonary bypass is believed to be a major cause of postoperative morbidity,^{3,4} myocardial revascularization by off-pump CABG to circumvent the harmful effects has become an established and widely used technique.⁵

On the other hand, there have been major concerns about completeness of revascularization during off-pump CABG.⁶ Furthermore, questions regarding reduced quality of anastomoses with subsequent poor graft patency and long-term results have been raised.⁷ These issues may be explained by the reduced view during suture placement as the result of bleeding out of the arteriotomy. Therefore, several tools, such as stabilizers, encircling tourniquets, vascular clamps, intraluminal coronary shunts, and blower-mister devices, to improve the technical ease of beating heart surgery and creation of a bloodless surgical field during coronary revascularization were introduced.⁸⁻¹¹ Blower-mister devices have been shown to safely and effectively clear the operative field by blowing away the blood from the anastomosis site.¹²

Although all of these devices are useful tools to improve the performance of coronary revascularization during off-pump surgery, they may cause alteration of the anastomosis and graft function. The present experiments were designed to elucidate the effects of blower-mister devices on the vasoreactivity and function of coronary artery bypass grafts.

MATERIALS AND METHODS

Harvesting of Vessels

Segments from human ITAs and the greater saphenous veins (GSVs) were obtained from patients undergoing routine CABG in a specialized cardiac surgery unit. ITAs were harvested by the classic pedicled technique.

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
 GSV = greater saphenous vein
 ITA = internal thoracic artery

The most distal part of the ITA just before the bifurcation was removed before performing the distal anastomosis and was used for further experimental analyses. GSVs were carefully harvested, and their side branches were clipped by commercially available devices. The distal end was cannulated and heparinized. NaCl 0.9% was injected gently to test for possible leaks. A commercially available blower mister device (Guidant Inc, Natick, Mass), applying air (1 bar) and NaCl 0.9% at a fixed pressure (100 mm Hg), was used to evaluate the effect of constant air and water stream. The distal ends of both bypass graft types were exposed to these conditions for 10 minutes from a distance of 150 mm, representing the average time needed for completion of an anastomosis using the off-pump technique. This method was performed to simulate the effect of the blower-mister device on the vasoreactivity and function of bypass grafts during off-pump coronary artery revascularization. The exposed segments were then cut off and immediately stored. After determining the optimal length and shortening of the grafts, they were anastomosed to the target vessel in a standardized fashion using the blower-mister device. Native, non-exposed segments of the GSV and ITA were also obtained from the same patient and served as respective controls. All off-pump CABG procedures were performed by a single surgeon (B.K.P.).

Preparation of Vessel Segments

Obtained vessel segments were directly transferred to the laboratory using a modified ice-cold oxygenated Krebs–Henseleit buffer (118 mmol/L NaCl, 20 mmol/L NaHCO₃, 4 mmol/L KCl, 1.25 mmol/L CaCl₂, 1.2 mmol/L NaH₂PO₄, 1.2 mmol/L MgSO₄, 4.5 mmol/L glucose, and 10 U/L insulin) as described previously.¹³ The vessel segments were dissected free of surrounding fat and connective tissue and cut into 4-mm rings. They showed no evidence of macroscopic atheromatous plaques. Material from every patient was split and used for its own control to overcome differences in demographics, which are summarized in Table 1. Experimental procedures used in this study conformed to the World Medical Association Declaration of Helsinki. Investigations were designed in accordance with the guidelines of the local ethic committee. All patients gave their written informed consent.

Organ Bath Procedure and Vasomotor Responses

Each vessel segment was mounted in a temperature-controlled 15-mL tissue bath (37 °C) containing a modified Krebs–Henseleit buffer solution. The bath was continuously bubbled with a mixture of 95% O₂ and 5% CO₂, giving a pH of 7.40. Buffer solution was continuously renewed from a reservoir using a peristaltic pump at a steady-state flow of 1.5 mL/min, while excess volume was drained. To measure the isometric circular wall tension of the vessels, each segment was suspended between 2 L-shaped metal pins (0.4 mm in diameter) in a myograph, as initially described by Mulvany and Halpern.¹⁴ To achieve maximal active force development, the vessels were initially stretched to equalize 90% of L_{100} (L_{100} = the distance between the pins if the vessel is exposed to a passive transmural pressure of 13.3 kPa). After approximately 1 hour, the vessels were maximally contracted with the thromboxane A₂ agonist 9, 11-dideoxy-11 α , 9 α -epoxymethano-prostaglandin F₂ α (U46619) at a steady-state concentration of 10 nM. Only vessel segments responding with a reproducible contraction after washout with the normal buffer solution were used for further investigation. This contraction induced by U46619 was set arbitrarily to 100% and used as an internal standard with which the relaxant/constrictant response in the same vessel seg-

TABLE 1. Demographic and clinical patient characteristics

Mean age $\pm$ SD (y)	72.1 $\pm$ 6.5
Caucasian race	8 (100%)
Urgent status	0 (0%)
Previous CABG	0 (0%)
1-vessel disease	2 (25%)
2-vessel disease	4 (50%)
3-vessel disease	2 (25%)
Stroke	0 (0%)
Peripheral arterial occlusive disease	0 (0%)
Diabetes	4 (50%)
Hypertension	6 (75%)
Hypercholesterolemia	6 (75%)
Current smoker	0 (0%)

SD, Standard deviation; CABG, coronary artery bypass grafting.

ment was compared. To prevent tachyphylaxis, only 1 concentration-response experiment was allowed on each artery segment. U46619 was purchased from Alexis Austria (Vienna, Austria). All other chemicals were obtained from Sigma-Aldrich (Vienna, Austria). All peptides were dissolved in ultra-pure water. U46619 was dissolved in dimethylsulfoxide.

Contraction

Cumulative contraction curves to U46619 (range: 10^{-10} – 10^{-6} mol/L) were performed to assess receptor-mediated contraction. Median effective concentrations (EC₅₀; concentration at 50% maximum contraction) were calculated.

Relaxation

Vessel segments were precontracted to approximately 50% of their maximum contractile capacity with U46619. Endothelium-independent relaxations were studied by the addition of a bolus of sodium nitroprusside (10^{-5} mol/L), an exogenous nitric oxide donor, and papaverine (10^{-8} mol/L) to assess the maximal dilation. Endothelium-dependent relaxation responses to acetylcholine (10^{-8} – 10^{-4} mol/L) and substance P (10^{-9} mol/L) were measured, and cumulative relaxation curves were constructed for acetylcholine.

Data Analysis and Statistics

Vessel responses are given in millinewtons for contraction experiments and in percentages of the maximal contraction induced by U46619 for relaxation experiments. Logarithmic median effective concentrations (LogEC₅₀) were calculated using the 4-parameter Hill-Slope model (BioDataFit 1.02 HTTP), and results are presented as mean $\pm$ standard error of the mean. Statistical analysis was performed by Levene's test for equality of variances followed by an independent-sample *t* test for equality of means.

RESULTS

Receptor-Mediated Contraction

There was a significant difference in the maximum contraction achieved with U46619 comparing rings of both vessel segments subjected to the blower-mister device with the control group. GSV rings of the control group obtained 28.33 ± 9.71 mN ($n = 6$), whereas segments exposed to the air and water stream of a blower-mister achieved only 11.42 ± 7.97 mN ($n = 9$, mean difference $\pm$ standard error of the mean: 16.92 ± 6.01 mN, $P < .026$). Similarly, unexposed ITA segments showed 17.17 ± 2.57 mN ($n = 6$)

FIGURE 1. ITA contraction by U46619. ITA, Internal thoracic artery.

versus 8.67 ± 4.54 mN ($n = 9$, mean difference $\pm$ standard error of the mean: 8.50 ± 3.00 mN, $P < .048$). GSV rings exposed to the blower-mister device achieved 48% less in magnitude compared with control rings, whereas ITA rings exposed to the blower-mister device showed a 23% reduced magnitude; respective curves are shown in Figures 1 and 2. The LogEC₅₀ values for U46619 for all rings subjected to the blower-mister device were not significantly changed, indicating no reduced sensitivity when compared with control groups (GSV: -8.22 ± 0.09 vs -8.74 ± 0.28 ; ITA: -8.54 ± 0.09 vs -8.84 ± 0.13). R² values were greater than 0.995 for all estimations.

Endothelium-Dependent Relaxation

Endothelium-dependent relaxation of vessels induced by acetylcholine demonstrated a significantly reduced maximal percentage of relaxation at all concentrations of acetylcholine compared with controls (ITA control: 34.5 ± 5.7 mN, $n = 6$ vs segments subjected to the blower-mister device: 5.4 ± 1.7 mN, $n = 3$, mean difference $\pm$ standard error of the mean: 29.2 ± 3.4 mN, $P < .001$) (Figure 3).

Endothelium-Independent Relaxation

The maximum endothelium-independent relaxations of both vessel segments achieved with nitroprusside and

FIGURE 2. GSV contraction by U46619. GSV, Greater saphenous vein.

FIGURE 3. ITA relaxation by acetylcholine (rel. % from precontraction with 10 nM U46619) *ITA*, Internal thoracic artery; *Ach*, acetylcholine.

papaverine were not significantly different between the investigated groups (data not shown). Comparison of EC_{50} values for papaverine and nitroprusside did not reach statistical significance between vessel segments exposed to the blower-mister device versus control.

DISCUSSION

Off-pump CABG has become an established method of coronary revascularization without the use of cardiopulmonary bypass. Nevertheless, technical aids to facilitate optimal visualization of the surgical field during the performance of coronary anastomoses are required. Operative manipulations and ischemia-reperfusion can lead to local coronary endothelial dysfunction.¹⁵ Because proper visualization is essential for the quality of the anastomosis, several methods to create a bloodless operative field were developed; however, because of manipulation in the anastomotic site, reports regarding endothelial alterations exist.

Fonger and associates¹⁶ described clamping the coronary arteries with commercially available clamps. Clamping the coronary arteries may injure the vascular endothelium, resulting in a denudation of the endothelial cell coverage and consequently a decrease of endothelium-dependent relaxations. In a previous report, their data suggest that soft jaw clamps significantly reduce the degree of vasoactive dysfunction compared with hard jaw clamps.¹⁷ Hangler and colleagues¹⁸ investigated the coronary arteries of patients undergoing heart transplantation that were locally occluded after starting cardiopulmonary bypass. Immediately after excision of the diseased heart, the vessels were fixed. They presented data on endothelial denudation, microthrombosis, and atherosclerotic plaque rupture after coronary snaring. These coronary endothelial injuries could be ameliorated by using

elastic sutures instead of non-elastic sutures.¹⁹ Intracoronary shunting was introduced to facilitate distal perfusion during coronary anastomosis and shown to prevent regional myocardial dysfunction and hemodynamic deteriorations in off-pump CABG procedures.²⁰ However, intracoronary shunting is not preferred by all surgeons because of technical difficulties during placement and an increased risk of intimal damage. Furthermore, suboptimal fitting of the inserted shunt into the coronary lumen may lead to residual blood flow in the anastomotic region. As an additional method to achieve an improved view during suture placement, blower-mister devices were introduced, but it has been reported that non-humidified gas insufflation deposited blood cells and delaminated endothelial cells with time. With humidified gas insufflation, these adverse effects could be attenuated.¹⁹ Furthermore, Burfeind and colleagues²¹ reported that high-flow gas insufflation denudes the coronary artery of its endothelium. This endothelial loss may promote smooth muscle cell migration and proliferation and sets the stage for early and late graft failure.

The development of modern stabilizers and specific anesthesiologic and surgical management has made off-pump coronary bypass surgery accessible and technically feasible for many surgeons. There is evidence that compared with on-pump coronary bypass surgery, off-pump surgery overall may decrease the incidence of myocardial injury, renal damage, and brain injury.^{22,23} At least for low-risk patients, in prospective randomized trials, no difference in cardiac outcome at 1-year follow-up has been demonstrated.²⁴ Nevertheless, a recently published prospective, controlled, randomized trial to further assess the relative efficacy of on-pump and off-pump CABG concluded that at 1 year of follow-up, patients in the off-pump group had worse

composite outcomes and poorer graft patency than did patients in the on-pump group.²⁵ To perform a technically perfect anastomosis, optimal visualization is required. Therefore, surgeons have to combine different approaches, including shunts, snares, and blowing devices, to achieve this goal. The limitation of the present study is that we used the blower-mister on the graft only and not on the target vessel. This is in contrast with the real clinical situation, where both the graft and the target vessel are exposed to air and water stream. We tried to standardize the exposure as much as possible. Therefore, we fixed the pressure, duration, and distance of exposure to generate reproducible injury with minimal variations. However, because the results of the present study already show detrimental effects on graft relaxation, one can imagine that this is even more pronounced if both vessels are involved. The presented results are a snapshot of the endothelial function, and the impact of these data on the future of the anastomosis is difficult to predict.

CONCLUSIONS

Air and water stream can induce endothelial damage, leading to reduced vascular relaxation and decreased contractile capacity. This trauma on the anastomosis could be one possible explanation for lower graft patency rates in off-pump surgery. Consequently, we encourage every surgeon who performs off-pump surgery to use these devices with caution and the underlying tissue with respect. The optimal device or treatment to achieve a bloodless operative field and minimal trauma still has to be designed.

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