

Radial Artery Graft Treatment With Phenoxybenzamine is Clinically Safe and May Reduce Perioperative Myocardial Injury

Alexander Kulik, MD, Fraser D. Rubens, MD, MS, Derek Gunning, MD, Michael E. Bourke, MD, Thierry G. Mesana, MD, PhD, and Marc Ruel, MD, MPH

Divisions of Cardiac Surgery and Cardiac Anesthesia and Department of Epidemiology, University of Ottawa, Ottawa, Ontario, Canada

Background. Phenoxybenzamine effectively reduces radial artery (RA) spasm in vitro, but clinical data supporting its use during coronary revascularization are lacking. Therefore, the purpose of this study was to evaluate the clinical safety and efficacy of RA treatment with phenoxybenzamine.

Methods. Data were collected prospectively on 698 patients who underwent coronary artery bypass grafting with a RA between 1997 and 2005. Of these, 311 patients received RA grafts incubated in 2 mg/mL phenoxybenzamine for 15 minutes, and 387 patients received RA grafts treated with verapamil and nitroglycerin (VG solution). Demographic, operative, and postoperative data were compared retrospectively using multivariate regression techniques.

Results. The incidence of perioperative myocardial events (defined as either low cardiac output syndrome or perioperative myocardial infarction) was significantly reduced in the phenoxybenzamine group (6.8% vs 11.9%, phenoxybenzamine vs VG solution; $p = 0.03$). Perioper-

ative myocardial enzyme release, as measured by postoperative maximum creatine kinase, was also reduced in the phenoxybenzamine group (743.0 ± 677.9 vs 937.2 ± 1236.8 U/L, phenoxybenzamine vs VG solution; $p = 0.014$). After adjusting for patient and procedural factors, the use of phenoxybenzamine was independently associated with reductions in peak creatine kinase (by -343.0 ± 136.7 U/L; $p = 0.012$) and peak troponin T level (by -0.50 ± 0.19 ng/mL; $p = 0.010$). No differences in vasopressor support, length of stay, or other complications were observed.

Conclusions. Treatment of RA grafts with phenoxybenzamine was associated with a reduction in perioperative myocardial injury and adverse cardiac events in this study population. Investigations to further evaluate the potential benefits of phenoxybenzamine in randomized settings are warranted.

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Arteries are increasingly being used as conduits for coronary artery bypass grafting (CABG) because of their clinical and survival benefits. Superior outcomes have been achieved with single [1] and bilateral internal thoracic artery (ITA) grafting [2, 3], and attention has recently focused on the radial artery (RA) as the next conduit of choice for CABG. The RA graft has gained popularity because of its diameter, length, ease of harvest, and its encouraging early and midterm results [4–9]. However, reports of RA vasospasm have limited its universal acceptance [10]. Occurring in up to 10% of cases, early RA vasospasm can lead to graft failure and a state of myocardial hypoperfusion [9, 10].

Vasospasm therefore remains an important drawback of the RA as a conduit for CABG. Compared with other conduits, the RA has a greater reactivity to vasoconstrictors, a thicker and more muscular media, and an increased expression of α -adrenoreceptors [12,

13]. Due to its high propensity for spasm, and the considerable interest in the RA as an alternative conduit for CABG, the prevention of perioperative RA spasm has been a subject of recent investigation. However, the ideal antispasmodic regimen for the RA has not yet been established.

Phenoxybenzamine is an irreversible antagonist to the α 1-adrenoreceptor, the dominant adrenoreceptor in the RA media. In vitro studies have demonstrated the ability of phenoxybenzamine to block completely adrenergic-mediated vasoconstriction [14–19]. Unlike papaverine, phenoxybenzamine does not cause damage to the RA vessel or endothelium [14]. Phenoxybenzamine also appears to have a significantly longer in vivo vasorelaxant effect compared with a combination of verapamil and nitroglycerin (VG solution) [19]. While experimental results have been promising, the safety and efficacy of phenoxybenzamine have yet to be explored in the clinical setting. As an irreversible vasodilator, phenoxybenzamine may reduce myocardial injury through the inhibition of RA spasm, but it also has the potential to cause profound hypotension should systemic distribution oc-

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Address correspondence to Dr Ruel, University of Ottawa Heart Institute, 40 Ruskin Street, Suite 3403, Ottawa, Ontario, Canada, K1Y 4W7; e-mail: mruel@ottawaheart.ca.

cur during or after the operation. Therefore, the purpose of this study was to evaluate the safety and potential benefit of RA treatment with phenoxybenzamine compared with standard VG solution by assessing outcomes after CABG.

Patients and Methods

Patient Population

Patients undergoing isolated CABG using an RA graft between 1997 and 2005 at the University of Ottawa Heart Institute were included in the study population. Preoperative, operative, and postoperative clinical data were collected prospectively on 698 consecutive RA patients. Patients received RA grafts incubated in a phenoxybenzamine solution (PB group, $n = 311$), or verapamil-nitroglycerin solution (VG group, $n = 387$). The study was approved by the Human Research Ethics Board of the University of Ottawa Heart Institute. Phenoxybenzamine is considered an experimental pharmaceutical agent in Canada, and was approved for this CABG indication by special release from Health Canada. Patients were warned regarding the potential risks of phenoxybenzamine prior to surgery, and signed consent forms if they agreed to its use. For each patient, the effects of phenoxybenzamine were directly reported to Health Canada after the operation.

Surgical Technique

All operations were performed through a median sternotomy. Grafts were performed with standard cardiopulmonary bypass (CPB) or off-pump CABG (OPCAB) techniques. During standard CABG, bypass flows were maintained at 2.4 to 3.2 L/m²/min and the body temperature was reduced to 32°C to 34°C during the period of cardiac anoxia. Myocardial preservation involved intermittent antegrade cold blood cardioplegia through the aortic root at 20-minute intervals, and topical pericardial saline irrigation. Off-pump coronary artery bypass was performed with the use of the Octopus epicardial stabilizer system (Medtronic, Minneapolis, MN).

Use of the RA as a graft was determined by the operating surgeon. The left ITA was placed as a pedicled graft (nonskeletonized) to the left anterior descending coronary artery. The right ITA was usually chosen as the second conduit (nonskeletonized) and was grafted to the next most important coronary artery. The RA was selected as the third conduit in patients with bilateral ITA grafting, or as the second conduit of choice in patients with relative contraindications to bilateral ITA grafting. The RA was grafted to the circumflex or right coronary system as required, preferably to a target vessel with a stenosis of 90% or more. Sequential grafting with the radial conduit was not performed. The proximal anastomosis of the radial graft was performed directly to the proximal ascending aorta, unless aortic atheromatous disease necessitated a Y-graft arrangement from the left

ITA. The remaining bypass conduits were performed using saphenous vein.

Radial Artery Preparation

The RA was evaluated preoperatively using a modified Allen test in the nondominant hand. During surgery, the RA was dissected together with its satellite veins and connective tissue to minimize arterial wall damage and spasm. Electrocautery, sharp dissection, and hemostatic clips were used for radial harvesting. After resection, the RA was irrigated gently with either phenoxybenzamine or VG solution. For the PB group, each RA was irrigated and incubated in a solution containing 100 mg of phenoxybenzamine in 50 mL of heparinized blood for 15 minutes or greater, as previously reported by Taggart and colleagues [20]. Prior to anastomosis, each phenoxybenzamine-treated artery was internally and externally irrigated with copious amounts of heparinized saline. In the VG group, each RA was incubated in a saline solution containing VG solution (30 μ mol/L verapamil and 30 μ mol/L nitroglycerin). The choice of RA treatment was at the discretion of the operating surgeon. During the study time period, eight surgeons at our institution used exclusively VG solution (270 patients) and two surgeons used exclusively phenoxybenzamine solution (127 patients). One other surgeon altered his practice during the course of the study time period, using the VG solution prior to June 2001 (117 patients), and subsequently the phenoxybenzamine solution (184 patients).

Postoperative Radial Artery Prophylaxis

Postoperative prophylaxis against RA spasm was initiated upon patient arrival in the cardiac surgery recovery room. An intravenous nitroglycerin infusion (0.5 to 2.0 μ g/kg/minute) was administered routinely to all patients after surgery until the morning of postoperative day one. A six-month course of calcium-channel blockers (amlodipine 5 mg, adalat XL 20 mg, or diltiazem CD 120 mg daily) was initiated on postoperative day one. Daily postoperative aspirin (325 mg) was initiated on the same day as surgery. Angiography in the early postoperative period was not routinely performed.

Endpoints

The primary endpoints of this study were perioperative myocardial injury, as measured by the biochemical markers creatine kinase (CK) and troponin T (TnT), and perioperative myocardial events, defined as either low cardiac output syndrome or perioperative myocardial infarction. CK was measured four hours after admission to the cardiac surgery intensive care unit (ICU) and the morning after surgery. Troponin T was measured if the measured CK was greater than 800 U/L (105 patients in PB group, 121 patients in VG group). Secondary endpoints of the study related to safety outcomes. Electrocardiograms (ECG) were performed upon admission to the ICU, and subsequently one and three days after surgery. A perioperative myocardial

infarction was defined as per the Society of Thoracic Surgery criteria, consisting of at least one of the following: (1) ST-segment elevations; (2) development of new Q waves in two or more contiguous ECG leads; (3) new left bundle branch block pattern on ECG; and (4) CK level greater than or equal to three times the upper limit of normal. Inotropic requirements were recorded for all patients after surgery. The presence of low cardiac output syndrome was defined as a low cardiac output (cardiac index less than 1.8 L/minute/m²) for longer than 30 minutes in duration, treated with inotropic support and/or an intraaortic balloon pump. Time to extubation and length of ICU and hospital stay were also recorded. Perioperative mortality was defined as any death occurring prior to hospital discharge or within thirty days of surgery if it occurred after hospital discharge.

Statistical Analyses

Data were analyzed in Intercooled Stata 9.1 (Stata, College Station, TX). Demographic, operative, and postoperative data were compared between the two groups. Continuous variables are presented as mean ± standard deviation and were compared using Student *t* tests. Categorical data were compared using the Fisher exact tests. Predictors of perioperative myocardial damage (peak CK and TnT) were determined with multivariate linear regression methods. Predictors of perioperative myocardial events (low cardiac output syndrome or perioperative myocardial infarction) were determined with multivariable logistic regression methods. Regression models were developed by incorporating variables that had a *p* value of 0.20 or less on univariate testing. In addition, factors known to be predictors of myocardial injury were forced into the model, regardless of their significance level on univariate analysis. These factors included those of potential clinical relevance (age, gender, severity of coronary artery disease, redo-CABG, diabetes mellitus) as well as surgical factors (surgeon, aortic cross-clamp time, use or non-use of cardiopulmonary bypass, urgency status, all arterial conduits) [21-26]. In order to account for confounding, no automated model selection procedure was used and all covariates were used simultaneously. Statistical significance was set at a *p* less than 0.05, and model coefficients or odds ratios (OR) are reported along with their standard error.

Results

Patient Characteristics

The perioperative characteristics of the PB and VG groups are presented in Table 1. Patients in the PB group were significantly older compared with the VG patients (*p* < 0.05). At the time of surgery, patients in the PB group had a significantly higher rate of OPCAB surgery and a significantly greater number of grafts (all *p* < 0.05). Patients in the VG group underwent total arterial revascularization (use of arterial conduits only) more often (*p* < 0.0001). These variables were therefore forced into

Table 1. Preoperative and Intraoperative Patient Characteristics

Patient Characteristic	PB Group (n = 311)	VG Group (n = 387)	<i>p</i> Value
Age at operation (years)	59.2 ± 9.5	56.4 ± 8.9 ^a	<0.0001
Body mass index (kg/m ²)	29.7 ± 5.7	29.2 ± 4.9	0.23
Female gender	49 (15.8%)	73 (18.9%)	0.37
Hypertension	196 (63.0%)	244 (63.0%)	0.88
History of cigarette smoking	222 (71.4%)	283 (73.1%)	0.80
Diabetes mellitus	103 (33.1%)	126 (32.6%)	0.81
Cerebrovascular disease	25 (8.0%)	34 (8.8%)	0.79
Peripheral vascular disease	33 (10.6%)	56 (14.5%)	0.17
LV class 3-4 ^b	22 (7.1%)	37 (9.6%)	0.28
Recent myocardial infarction	66 (21.2%)	71 (18.3%)	0.39
CCS class 4	111 (35.7%)	114 (29.5%)	0.07
Urgent or emergent CABG	104 (33.4%)	145 (37.5%)	0.34
Preoperative intraaortic balloon pump support	1 (0.4%)	1 (0.3%)	1.0
Previous CABG	9 (2.9%)	16 (4.1%)	0.42
Number of grafts	3.2 ± 0.7	3.1 ± 0.7 ^a	0.015
Total arterial revascularization	244 (78.5%)	354 (91.5%) ^a	<0.0001
Cross-clamp time (minutes)	67.9 ± 19.7	54.9 ± 20.6 ^a	<0.0001
CPB time (minutes)	91.1 ± 23.4	90.2 ± 28.5	0.68
Off-pump CABG	41 (13.2%)	7 (1.8%) ^a	<0.0001

^a *p* < 0.05 versus patients in the PB group. ^b LV class 3 = LV ejection fraction of 30-40%; LV class 4 = LV ejection fraction <30%.

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CPB = cardiopulmonary bypass; LV = left ventricle; PB = phenoxybenzamine; VG = verapamil/nitroglycerin.

the multivariate regression models that estimated myocardial injury and perioperative myocardial events.

Perioperative Myocardial Events

Phenoxybenzamine significantly reduced the incidence of perioperative myocardial events, defined as either low cardiac output syndrome or perioperative myocardial infarction (6.8% vs 11.9%, PB group vs VG group, *p* = 0.03). Furthermore, a multivariate logistic regression model was developed by incorporating known factors associated with perioperative myocardial events (anoxia time, urgency, severity of coronary disease) as well as the potential confounders of surgeon identity, patient age, and gender. After adjusting for confounders, RA graft treatment with phenoxybenzamine was independently associated with a lower risk of perioperative myocardial events (OR 0.30 ± 0.11, *p* = 0.001). Table 2 summarizes the results of this logistic regression model for perioperative myocardial events.

Angiography was performed in the early postoperative period in two patients suspected of having myocardial ischemia secondary to graft occlusion. Both of these patients received phenoxybenzamine-treated RA grafts. Neither patient has RA spasm. One patient had a com-

Table 2. Factors Significantly Associated With Perioperative Myocardial Events^a

Factor	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Phenoxybenzamine	0.54 (0.32, 0.93)	0.03	0.30 (0.14, 0.62)	0.001
Age (years)	1.05 (1.03, 1.08)	<0.0001	1.04 (1.01, 1.09)	0.005
Female gender	2.59 (1.49, 4.50)	0.001	1.68 (0.86, 3.27)	0.13
Cross-clamp time (min)	1.01 (1.00, 1.02)	0.06	1.02 (1.00, 1.04)	0.01
Nonelective surgery	1.74 (1.05, 2.89)	0.03	1.59 (0.88, 2.85)	0.12
Total arterial revascularization	1.07 (0.51, 2.24)	0.85	2.10 (0.87, 5.03)	0.10

^a Perioperative myocardial events defined as either low cardiac output syndrome or perioperative myocardial infarction.

Factors not significant in model include surgeon, number of grafts, ejection fraction <40%, redo-coronary artery by pass grafting off-pump surgery, and history of diabetes mellitus.

CI = confidence interval; OR = odds ratio.

pletely patent RA graft, and the other patient had an occluded RA graft to a posterior descending coronary artery. The latter patient was taken back to the operating room for graft revision.

Myocardial Injury

Myocardial injury measured by peak postoperative CK level was significantly reduced in the PB group (743.0 ± 677.9 vs 937.2 ± 1,236.8 U/L, PB group vs VG group, *p* = 0.014). Linear regression models were developed by incorporating patient, surgeon, and procedural characteristics (as described above). After adjusting for confounders, RA graft treatment with phenoxybenzamine was independently associated with a lower peak CK level (by -343.0 ± 136.7 U/L on average; *p* = 0.012) and lower peak TnT level (by -0.50 ± 0.19 ng/mL on average, *p* = 0.010), as illustrated in Figures 1 and 2. Tables 3 and 4 summarize the results of the linear regression models for peak CK and TnT levels.

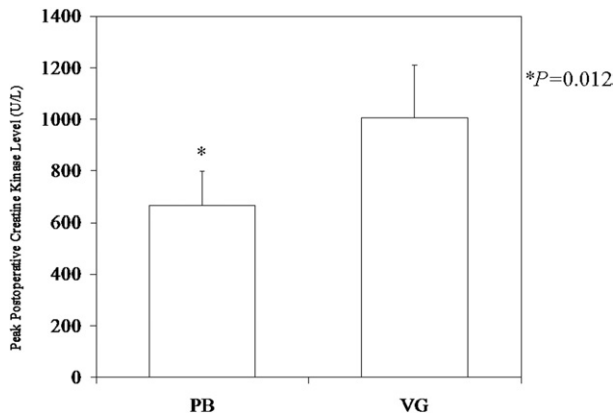


Fig 1. Comparison of peak postoperative creatine kinase levels after radial artery treatment with phenoxybenzamine or standard verapamil-nitroglycerin solution, after adjustment for age, gender, severity of coronary artery disease, redo-coronary artery bypass grafting, diabetes mellitus, left ventricular dysfunction, all arterial conduits, surgeon, aortic cross-clamp time, and urgency status. (PB = phenoxybenzamine; VG = verapamil-nitroglycerin.)

Safety Outcomes

Postoperative patient outcomes are shown in Table 5. Patients who received phenoxybenzamine-treated radial grafts did not have a higher incidence of inotropic or vasopressor support, either at the completion of CPB or upon admission to the ICU (Table 2). The initial 12-hour chest tube drainage and transfusion rates were similar between the groups, and there was no difference in the intubation time, length of stay, or perioperative mortality (Table 5).

Comment

With late patency rates likely superior to saphenous vein [8], and potentially as good as the ITA [4, 5], the RA may have become the next conduit of choice for CABG. However, episodes of vasospasm and graft failure con-

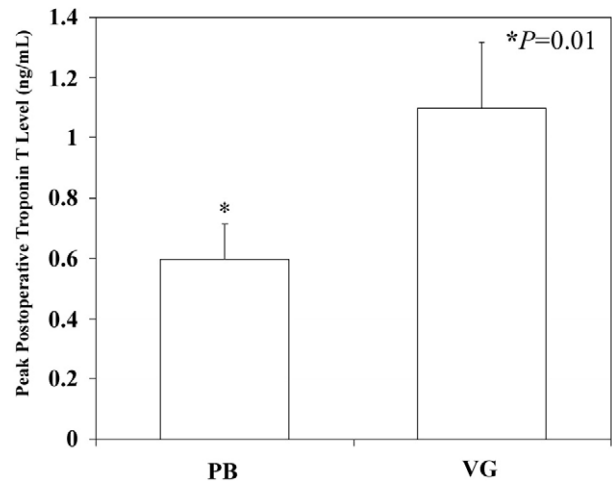


Fig 2. Comparison of peak postoperative troponin T levels after radial artery treatment with phenoxybenzamine or standard verapamil-nitroglycerin solution after adjustment for age, gender, severity of coronary artery disease, redo-coronary artery bypass grafting, diabetes mellitus, left ventricular dysfunction, all arterial conduits, surgeon, aortic cross-clamp time, and urgency status. (PB = phenoxybenzamine; VG = verapamil-nitroglycerin.)

Table 3. Factors Significantly Associated with Peak Postoperative Creatine Kinase Level^a

Factor	Univariate Analysis		Multivariable Analysis	
	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
Phenoxybenzamine	-194.2 (-349.2, -39.1)	0.01	-343.0 (-611.4, -74.6)	0.01
Age (years)	-14.0 (-22.3, -5.7)	0.001	-13.2 (-23.2, -3.2)	0.01
Number of bypass grafts	185.9 (70.2, 301.6)	0.002	142.7 (-24.6, 310.0)	0.09
Cross-clamp time (min)	4.4 (0.5, 8.3)	0.03	4.9 (-1.2, 11.0)	0.11
Total arterial revascularization	-66.3 (-287.0, 154.5)	0.56	213.4 (-75.8, 502.5)	0.15

^a Factors not significant in model include surgeon, female gender, off-pump surgery, ejection fraction <40%, redo coronary artery bypass grafting, urgent or emergent surgery, and history of diabetes mellitus.

CI = confidence interval.

tinue to occur, limiting the universal acceptance of the radial graft [9-11]. Proposed as an ideal agent to prevent RA vasospasm, phenoxybenzamine has an immediate onset and prolonged duration of action against adrenergic-mediated vasoconstriction [14-16]. Despite its apparent in vitro efficacy, no evidence exists verifying either the clinical safety or benefit of phenoxybenzamine use during RA coronary revascularization. In this cohort study comparing RA treatment with phenoxybenzamine with standard VG solution, we observed the following: (1) phenoxybenzamine was associated with a reduction in the incidence of perioperative myocardial events; (2) phenoxybenzamine was independently associated with a reduction in perioperative myocardial injury; and (3) phenoxybenzamine did not contribute to increased vasopressor requirements or perioperative morbidity. Thus, the treatment of RA grafts with phenoxybenzamine appeared to reduce cardiac morbidity without compromising safety.

Since its introduction by Carpentier and colleagues in 1973 [27], the propensity of the radial artery for vasospasm has tempered enthusiasm for its application in CABG. Improved harvesting techniques and perioperative calcium channel blockers recently revitalized interest in the RA [11], but reports of perioperative vasospasm and myocardial hypoperfusion continue to occur [10]. The early hypoperfusion syndrome may develop in up to

10% of cases and could be complicated by a low cardiac output state [11]. Because many cases of spasm may go undetected, the incidence of vasospasm could be even higher [7, 11, 28]. While the exact mechanism of RA vasospasm is not completely understood, it appears to be related to the greater muscularity of the RA media compared with that of other arterial conduits [12, 13]. In vitro studies have shown that RA reactivity to vasoconstrictors is significantly greater than that of the ITA or saphenous vein [12].

Radial artery vasospasm is particularly worrisome in patients that require vasoconstrictor therapy after surgery. Moreover, endogenous catecholamine levels are drastically elevated in the perioperative period [29]. As a result, the prevention of RA spasm and the search for the ideal antispasmodic agent have been the subject of intense research. Although early studies focused on the use of papaverine during RA harvest, organ bath studies by several investigators demonstrated that papaverine prevented RA spasm for only a short period, and yet caused extensive damage to RA endothelium [14, 30]. The combination of verapamil and nitroglycerin (VG solution), on the other hand, has a more rapid onset and longer-lasting vasorelaxant effect compared with papaverine, and it has been shown to have broad efficacy against a wide range of vasoconstrictors, including angiotensin II, vasopressin, and endothelin-1 [17, 18].

Table 4. Factors Significantly Associated With Peak Postoperative Troponin T Level^a

Factor	Univariate Analysis		Multivariable Analysis	
	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
Phenoxybenzamine	0.02 (-0.21, 0.25)	0.84	-0.50 (-0.89, -0.12)	0.01
Age (years)	0.02 (0.01, 0.03)	0.01	0.01 (-0.00, 0.02)	0.13
Female gender	0.19 (-0.14, 0.53)	0.26	0.23 (-0.09, 0.55)	0.16
Number of bypass grafts	0.12 (-0.04, 0.28)	0.13	0.22 (0.03, 0.42)	0.03
Anoxia time (min)	0.01 (0.00, 0.01)	0.02	0.01 (-0.01, 0.01)	0.74
Ejection fraction <40%	0.24 (-0.12, 0.61)	0.20	0.17 (-0.16, 0.51)	0.30
Diabetes mellitus	-0.15 (-0.40, 0.09)	0.22	-0.20 (-0.42, 0.02)	0.08
Nonelective surgery	0.34 (0.10, 0.59)	0.01	0.39 (0.16, 0.62)	0.001
Total arterial revascularization	-0.21 (-0.53, 0.10)	0.85	0.27 (-0.08, 0.62)	0.13

^a Factors not significant in model include surgeon, redo-CABG, and off-pump surgery.

CI = confidence interval.

Table 5. Postoperative Patient Outcomes

Patient Outcome	PB Group (n = 311)	VG Group (n = 387)	p Value
Inotropic support to wean from CPB ^a	22 (7.1%)	23 (5.9%)	0.54
Vasopressor support to wean from CPB ^b	20 (6.4%)	27 (7.0%)	0.88
Inotropic ^a or vasopressor ^b support at ICU admission	42 (13.5%)	40 (10.3%)	0.19
Perioperative intra-aortic balloon pump support	1 (0.3%)	5 (1.3%)	0.24
Unadjusted peak postoperative CK level (U/L)	743.0 ± 677.9	937.2 ± 1236.8 ^c	0.014
Unadjusted peak postoperative TnT level (ng/mL)	0.80 ± 0.95	0.78 ± 0.80	0.84
LCOS	18 (5.8%)	35 (9.0%)	0.15
Perioperative MI	6 (1.9%)	15 (3.9%)	0.18
LCOS or perioperative MI	21 (6.8%)	46 (11.9%) ^c	0.03
Atrial fibrillation or atrial flutter	32 (10.3%)	31 (8.0%)	0.29
12-hour chest tube drainage (mL)	734 ± 434	693 ± 392	0.22
Transfusion requirements	104 (33.4%)	118 (30.5%)	0.37
Reopening	20 (6.4%)	16 (4.1%)	0.17
Intubation time (hours)	24.1 ± 77.1	18.3 ± 59.4	0.29
ICU length of stay (days)	2.0 ± 3.9	1.7 ± 2.9	0.22
Hospital length of stay (days)	7.3 ± 5.9	6.6 ± 4.0	0.12
Perioperative mortality	5 (1.6%)	4 (1.0%)	0.52

^a Inotrope support includes milrinone, dobutamine, epinephrine, or intraaortic balloon pump. ^b Vasopressor support includes vasopressin, norepinephrine, or dopamine. ^c $P < 0.05$ versus patients in the PB group.

CK = creatine kinase; CPB = cardiopulmonary bypass; ICU = intensive care unit; LCOS = low cardiac output syndrome; MI = myocardial infarction; PB = phenoxybenzamine; TnT = troponin T; VG = verapamil/nitroglycerin.

The RA treatment with phenoxybenzamine renders grafts insensitive to catecholamines due to the irreversible inhibition of the $\alpha 1$ -adrenoreceptor. Several in vitro studies have demonstrated the ability of phenoxybenzamine to completely and irreversibly block adrenergic-mediated vasoconstriction without producing damage to the vessel or endothelium. This vasorelaxant effect appears to last up to 48 hours with an exposure as short as 20 minutes [14–16]. While VG solution has the advantage of preventing vasoconstriction mediated by additional noncatecholamine factors, phenoxybenzamine has a much longer duration of action, as demonstrated during both in vitro and in vivo experiments [17–19]. Moreover, phenoxybenzamine reduces spasm in native coronary arteries and has been used for the treatment of angina [31].

This report demonstrates the clinical safety of phenoxybenzamine during RA coronary revascularization. Furthermore, our results indicate that RA treatment with phenoxybenzamine may reduce perioperative myocardial injury and the incidence of adverse cardiac events. Myocardial injury, manifested as either transient contractile dysfunction or myocardial infarction, is one of the most frequent complications after cardiac surgery and is an important cause of hospital morbidity and mortality [32]. Enzyme measurement provides a convenient and inexpensive method to screen for perioperative myocardial events, and cardiac enzyme elevations correlate significantly with ECG- and echocardiography-assessed myocardial injury [33]. Several studies have confirmed that perioperative myocardial injury, assessed using peak CK or troponin levels, independently predicted adverse clinical endpoints, such as low cardiac output syndrome and mortality during the initial postoperative period, as

well as long-term nonfatal and fatal cardiac events [22, 34]. Pharmacologic interventions that decrease the incidence of perioperative myocardial ischemia may therefore improve short- and long-term outcomes after CABG.

Myocardial ischemia and infarction are major complications after CABG that may be the result of incomplete surgical revascularization, perioperative anesthetic management, or vasospasm of arterial grafts. While it cannot be proven in the absence of early postoperative angiography, phenoxybenzamine likely reduced myocardial injury in this cohort of CABG patients through the prevention of RA vasospasm. However, it is also possible that phenoxybenzamine caused localized myocardial vasodilatory effects, despite our practice of vigorously irrigating phenoxybenzamine-treated arteries before implantation. Previous myocardial protection research at our center demonstrated that the perioperative infusion of intravenous nifedipine, a potent coronary and arterial graft vasodilator, reduced myocardial injury and the incidence of perioperative myocardial ischemia [35]. Because phenoxybenzamine has been shown to prevent spasm both in native coronary arteries [31] as well as radial grafts, both mechanisms may have contributed to the reduction of myocardial injury in this study.

Potential Limitations

Although phenoxybenzamine appeared to be the more superior RA antispasmodic agent in this cohort, the data presented must be interpreted in the context of the study design. Group differences and known confounders were controlled in this observational study using multivariable analysis. Despite the sample size and statistical adjust-

ments applied, unmeasured and unknown confounders may have influenced the results. Furthermore, myocardial enzyme release was used as a surrogate of RA spasm in this study. Myocardial enzyme release during cardiac surgery may not always reflect perioperative myocardial ischemia or necrosis. While other measures of myocardial ischemia, such as ECG or echocardiography, could have been used, they too have important limitations in the perioperative setting [36]. Reported TnT levels for both groups in this study are probably overestimated because TnT was measured only in patients whose CK levels were greater than 800 U/L (226 patients). Finally, our center does not routinely perform angiography on RA patients. As such, the apparent benefit of phenoxybenzamine over VG solution in reducing radial spasm and myocardial injury should be confirmed in a prospective randomized controlled trial studying early angiographic outcomes.

Conclusion

This study demonstrates the clinical safety of phenoxybenzamine during RA coronary revascularization. Compared with VG solution, phenoxybenzamine was associated with a reduction in myocardial injury and the incidence of perioperative myocardial events. Investigations to evaluate further the potential benefits of phenoxybenzamine in randomized settings are warranted.

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INVITED COMMENTARY

This article by Kulik and colleagues [1] nicely describes a prospective nonrandomized comparison of phenoxybenzamine versus a combination of verapamil with nitroglycerin for the treatment of radial arteries prior to coronary bypass grafting. Postoperative plasma concentrations of creatine kinase and troponin T and the number of adverse myocardial events were significantly less in the phenoxybenzamine patients.

The strengths of the study are its prospective design and its inclusion of multiple variables that describe myocardial infarction. However the details of how to use the radial artery and the method for how to pharmacologically treat it were left to the discretion of the operating surgeon. Thus there is a potential for selection bias in this study. There also may be unaccounted differences between each surgeon's techniques that affected the results. If postoperative angiography or some other method had been used to document radial artery dimension or flow early after surgery, it would have strengthened the argument that phenoxybenzamine is the superior treatment to prevent radial artery spasm and consequent myocardial ischemia. However, such measurements are expensive and can entail substantial risk for a patient within the first 24 to 48 hours after surgery.

The details for optimal use of radial arteries remain controversial. As pieces of the puzzle are assembled, it is important to recognize the strengths as well as the limitations inherent in the experimental design for each study. For instance, there is sufficient information in the present study to justify further use of phenoxybenzamine for pre-implant treatment of radial arteries with appro-

priate oversight and evaluation of results. However, a single nonrandomized study does not definitely describe the best treatment.

This study highlights the need for carefully designed prospective randomized trials that will provide the most complete information possible on the radial artery used as a conduit for coronary grafting. One such multicenter trial based in Canada has been published, and a multicenter trial funded by the Veterans Administration Cooperative Studies Program is well underway. The results of these trials, together with the information from other studies such as this one by Kulik and colleagues [1] will help us continuously improve our results and put the radial artery in well-defined perspective with the internal mammary artery, saphenous vein, and other conduits for coronary bypass grafting.

William L. Holman, MD

*Department of Surgery
University of Alabama at Birmingham
1530 3rd Ave S—ZRB 719
Birmingham, AL 35294-0007
e-mail: wholman@its.uab.edu*

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