PHENOXYBENZAMINE PREVENTS SPASM IN RADIAL ARTERY CONDUITS FOR CORONARY ARTERY BYPASS GRAFTING

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Received for publication Dec 14, 1999; accepted for publication April 20, 2000.

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J Thorac Cardiovasc Surg 2000;120:815-7

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0022-5223/2000 \$12.00 + 0 12/54/108167

doi:10.1067/mtc.2000.108167

Over the past decade, there has been a marked increase in the use of arterial conduits to perform coronary artery bypass grafting (CABG).¹ The clinical and survival benefits of bilateral internal thoracic artery grafts have established them as conduits of first choice for CABG,² whereas the radial artery has rapidly become the third most commonly used arterial conduit.³

The radial artery is a versatile conduit, which can be harvested easily and safely, has handling characteristics superior to those of other arterial grafts, and comfortably reaches any coronary target. Several studies³ have reported superior patency of radial artery grafts compared with vein grafts at up to 5 years after CABG. Enthusiasm for widespread use of the radi-

Fig 1. The effects of phenoxylbenzamine on 10 radial arteries. Response of radial artery to KCl and epinephrine (Adrenaline) before and after phenoxylbenzamine administration. ACh, Acetylcholine.

al artery as a conduit for CABG has, however, been tempered by its greater proclivity to spasm in the perioperative period. This can result in severe postoperative myocardial hypoperfusion, as well as adversely affecting the grafts long-term patency.³ The capacity of the radial artery for vasospasm is several-fold greater than that of the internal thoracic artery⁴ because of its more muscular media, and this risk is further increased in patients who require inotropic or vasoconstrictor therapy.

Various pharmacologic maneuvers⁵⁻⁸ have been recommended to reduce the risk of radial artery vasospasm in the perioperative period, but all have significant limitations. Intravenous infusions of calcium channel blockers⁵ cause hypotension, bradycardia, and significant rhythm disturbances, whereas the topically applied agents, such as papaverine⁶ and nitroglycerin,⁷ have relatively short half-lives. The elegant technique of adenoviral transfer of endothelial nitric oxide synthetase to prevent radial artery spasm⁸ is not yet ready for clinical application.

To minimize the perioperative risk of radial artery spasm, we irrigate the harvested artery internally and externally with a solution of 100 mg of phenoxylbenzamine in 50 mL of warm heparinized blood before anastomosis. Phenoxylbenzamine is a nonselective α -adrenoceptor antagonist with a half-life of approximately 24 hours, which covalently and irreversibly binds to its target receptor.⁹ There is, however, no report of its use or efficacy as a topical vasodilatory agent in the preparation of arterial conduits for CABG.

Patients. Left radial arteries were harvested (standard techniques) from 10 patients undergoing CABG by using only Hartmann solution.

Methods. One inch of the distal (wrist) radial artery was excised and placed into chilled (4°C, pH 7.4) *N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid (HEPES)-buffered physiologic saline solution (PSS) and transported, in a 20-minute bicycle ride, from the John Radcliffe Hospital to the University Laboratory of Physiology. Specimens were then

immediately transferred to warmed (37°C) PSS (recipe as above but with 24 mmol/L NaHCO₃ and no HEPES) and bubbled with 95% oxygen and 5% carbon dioxide to maintain a pH of 7.4. These conditions were maintained throughout all subsequent stages of the experiment, except for the brief periods required for transferring the vessels or changing solutions.

Vessel mounting and normalization. Arteries were placed in organ baths and mounted onto hooks with transducers attached to an automated myograph (AM10; Cambustion Biological, Cambridge, United Kingdom). The theory and protocol have been described by Mulvany and Halpern.¹⁰ Initial tension was set to be equivalent to 100 mm Hg, according to the Laplace relation.

Experimental protocol. To determine their viability, we first constricted vessels with PSS containing 75 mmol/L KCl and then with a 5-minute exposure to 1 mmol/L epinephrine. The vessels were then incubated for 1 hour in the presence of the irreversible α -adrenergic blocker phenoxylbenzamine (1 mg/mL) and subsequently tested for constriction with a 10-minute exposure to epinephrine. After the effectiveness of phenoxylbenzamine was determined, the viability of the vessel and that of its endothelium were tested with 75 mmol/L KCl followed by acetylcholine or its synthetic analog carbachol. If the constriction of a vessel by this second KCl challenge was greater than 80% of the first response, and if acetylcholine or carbachol relaxed the vessel, it was considered to be in good condition. The protocol is illustrated in Fig 1.

Analysis. A Dell (386) microcomputer was used with Cambustion software (1991) to digitize tension at 1 Hz. Data were plotted by using a custom-written Turbo Pascal microcomputer program and Microsoft Excel software. The latter was used to normalize each trace to the baseline and peak tensions obtained in response to the first addition of KCl.

Results. Results for the 10 individual radial artery segments are presented in Fig 1. All arterial segments demonstrated marked constriction to KCl, which resolved when the

KCl was removed with PSS. Exposure of the arterial segments to epinephrine produced marked constriction, which was abolished by the addition of phenoxybenzamine. After exposure to phenoxybenzamine, the segments did not constrict when re-exposed to epinephrine. However, subsequent exposure of the segments to KCl produced further constriction, which was reversed by the addition of acetylcholine or carbachol, confirming the viability of the vessel and its endothelium.

Discussion. Our observations demonstrate that phenoxybenzamine abolishes adrenergic-mediated vasoconstriction of the radial artery without producing irreversible damage to the vessel or its endothelium.

Although our study is based on samples of radial arteries from only 10 patients, the results are remarkably consistent. The empiric use of 100 mg of phenoxybenzamine in 50 mL of heparinized blood is consistent with the *in vitro* dose-response curve, showing a maximal radial artery vasodilatory response with 1 mg/mL phenoxybenzamine.

Advantages of topical phenoxybenzamine in clinical practice are its relatively long half-life (24 hours) in comparison with other vasodilators,⁵⁻⁸ whereas its topical application eliminates adverse systemic effects. Similarly, avoidance of intravenous calcium antagonists obviates the significant hemodynamic problems they can cause in patients undergoing CABG. Although our study does not answer how long the effect of phenoxybenzamine persists, this is likely to be several days because the drug binds irreversibly to α -receptors, necessitating the growth of new receptors before the vessel regains its responsiveness to adrenergic agonists.

Equally important, our study suggests that phenoxybenzamine does not significantly damage the radial artery because it retains its responsiveness to both KCl and acetylcholine.

Our findings may have significant implications for increasing the safety and scope of radial artery use in clinical practice. By preventing radial artery vasospasm, phenoxybenzamine abolishes, or at least significantly reduces the risk of, perioperative myocardial hypoperfusion. It has allowed us to expand the use of the radial artery to those patients who are

likely to require modest inotropic support in the perioperative period and in particular to patients receiving angiotensin-converting enzyme inhibitor medication who frequently require vasoconstrictors to maintain systemic blood pressure.¹¹

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