EXPERIMENTAL STUDIES

Vasodilator Drug Effects on Internal Mammary Artery and Saphenous Vein Grafts

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The internal mammary artery has become the preferred conduit for myocardial revascularization because it has excellent long-term patency (1-3) and may result in improved patient survival compared with that obtained with vein grafts (4,5). Vasospasm during isolation of the artery with its pedicle is common (6,7). In addition, postoperative spasm of the mammary artery has been demonstrated (8). Treatment of vasospasm of the internal mammary artery not only may influence the decision regarding use of the artery as a graft, but also may improve the immediate flow in the graft after myocardial revascularization.

The effect of vasodilators on mammary artery spasm has not been previously investigated, and it has not been determined whether vasodilation of the artery will improve blood flow when this artery is used as a bypass graft. This study was designed to 1) determine the effectiveness of nitroprusside and nitroglycerin in inhibiting contraction of human internal mammary arteries studied in vitro, and 2) examine vasodilator drug effects on blood flow in canine internal mammary artery and saphenous vein grafts studied in vivo.

Methods

In Vitro Human Internal Mammary Artery

Tissue preparation and contraction measurement. Segments of 15 different human internal mammary arteries were...
obtained from the Emory University operating room. The extra length of artery not used for coronary artery grafting was used in these studies. The experimental protocol was submitted to the Human Investigations Committee of the Emory University School of Medicine, and permission to use these arterial segments was granted on the basis of their being discarded specimens. The segments of internal mammary arteries were placed directly into lactated Ringer's solution and transported to the laboratory. They were then immediately placed in oxygenated Krebs solution, cleansed of loose connective tissue and cut into 2.5 mm long rings. Two stainless steel wires were placed through the lumen of each ring; the rings were placed in separate muscle baths and one wire was connected to an immovable support whereas the other wire was attached to a Grass FT 0.03 force transducer. The time from collection in the operating room to placement in the muscle bath was <15 min. Attention and care were given to maintaining and not disrupting the integrity of the endothelium of each segment of artery. The presence of intact endothelium with this method of tissue preparation was demonstrated in other studies (9). Isometric contractions were recorded on a Beckman Dynograph (Beckman Instrument Inc.) or a Grass model 5 polygraph (Grass Instrument Co.). The rings were equilibrated in the muscle baths in Krebs solution containing (in millimoles per liter): sodium chloride, 120; potassium chloride, 5.5; calcium chloride, 2.5; sodium bicarbonate, 20; dextrose, 11; and calcium disodium ethylenediaminetetraacetate, 0.029; gassed with 95% oxygen and 5% carbon dioxide and maintained at 37°C. Rings were maintained at 1.5 g resting tension, which was determined to be optimal for maximal tension development in preliminary experiments.

Each ring was equilibrated in Krebs solution for approximately 30 to 40 min with continuous readjustment of resting tension to 1.5 g. Rings were then contracted with either 70 mM potassium Krebs solution or 10 μM norepinephrine. The 70 mM potassium Krebs solution was made by equimolar substitution of potassium chloride for sodium chloride to bring the potassium concentration to 70 μM. Arteries contracted with high potassium were incubated in Krebs solution containing 1 μM phentolamine to block contraction caused by potassium-induced release of norepinephrine. In preliminary experiments, it was determined that 70 mM potassium and 10 μM norepinephrine caused maximal contraction of the human internal mammary artery.

The vasodilators used were sodium nitroprusside and nitroglycerin (American Critical Care). Stock solutions of the drugs (usually 1 mM) were prepared daily in 0.9% saline solution. Stock solutions were diluted by 10- to 1,000-fold with Krebs solution. In separate experiments, we determined that the nitroglycerin vehicle had no effect on potassium or norepinephrine-induced contraction.

Experimental protocol. The experiments were performed by simultaneously studying four to six ring segments from the same or different internal mammary arteries. After the equilibration period, rings were contracted with potassium or norepinephrine, the contractile agent washed out and the tissues equilibrated for an additional 20 to 30 min. This sequence of contractile agent exposure and washout was repeated two to four times until stable and reproducible contractions were obtained. One ring from each segment of artery was not exposed to vasodilator and served as a control, whereas the other rings were incubated with various vasodilators for 20 to 30 min. The rings were then exposed to potassium or norepinephrine plus vasodilator, and peak contraction was measured. The contractile agent was washed out and a higher concentration of vasodilator was added and allowed to equilibrate for 20 to 30 minutes. This sequence of contraction, washout and vasodilator incubation was repeated for each concentration of vasodilator tested.

Data analysis. The contractile force of arterial rings not exposed to vasodilator was used as the control (100%) response. The contraction after exposure to vasodilator was compared with the parallel control contraction to calculate the response as a percent of control. Dose-response curves were generated by plotting the percent of control contraction versus the log of concentration of vasodilator. The mean EC_{50} (effective concentration of vasodilator required for 50% maximal inhibition of contraction) was calculated for nitroprusside but not for nitroglycerin because a large amount of nitroglycerin was needed to produce an effect.

The data collected comprised five to six ring segments for each intervention.

In Vivo Canine Internal Mammary Artery and Saphenous Vein Grafts

Preparation. Eight heartworm-free mongrel dogs were used. All animals received humane care in compliance with the Principles of Laboratory Animal Care set forth by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication #80-23, revised 1978). The dogs were sedated and anesthetized with alphachloralose (0.2 mg/kg) and urethane (2 g/kg). Auffed endotracheal tube was inserted and ventilation was provided with a volume respirator. A canine right heart bypass preparation was established by way of a median sternotomy with cannulation of the right atrial appendage and right iliac vein for venous return. Arterial flow was provided through the pulmonary artery for right heart bypass and the left subclavian and left femoral arteries for total heart bypass.

A saphenous vein dissected from the hind limb was anastomosed to the proximal ascending sorta with a continuous monofilament suture. The right internal mammary artery was dissected from the chest wall as a pedicle and its side branches clamped with metal clips. The animal was
placed on total cardiopulmonary bypass but was kept normothermic. The heart was then arrested with 10 ml/kg body weight of cold potassium cardioplegic solution (25 mEq KCl/filliter, pH 7.8) after the application of an aortic cross clamp. An end to side anastomosis was constructed from the vein graft to the proximal left anterior descending coronary artery with a continuous monofilament suture. The aortic cross clamp was released and a recovery period allowed while the right internal mammary artery was anastomosed to the distal portion of the vein graft in an end to side fashion with a continuous monofilament suture. The left anterior descending coronary artery was then ligated after the first diagonal branch proximal to the coronary anastomosis and right heart bypass resumed.

Measurements. Graft flow was measured with an electromagnetic flow probe (Carolina Medical Electronics) placed around the proximal aspect of each graft. Flow was measured through each graft while the other was clamped. In this manner, both grafts perfused the same coronary vascular bed. Care was taken not to clamp both grafts simultaneously to avoid reactive hyperemia. Aortic and left atrial pressures were measured through fluid-filled catheters inserted through a common carotid artery and a pulmonary vein, respectively, and monitored with Hewlett-Packard quartz pressure transducers. Left ventricular pressure and its first derivative were monitored with a Mikael Instruments inserted through the left ventricular apex and secured with a pledgeted suture. All pressure and blood flow recordings were made on a Hewlett-Packard 7758B multichannel recorder (Hewlett-Packard Medical Electronics).

Cardiac output was kept constant at 100 ml/kg per min by right heart bypass with infusion of blood into the pulmonary artery. Blood pressure was kept constant by systemic arterial blood infusion or withdrawal. Heart rate was also maintained constant by atrial pacing when needed. PaO₂, PaCO₂, and pH were maintained within normal limits throughout the experimental procedure. Hematocrit was maintained at 25%.

Experimental protocol. The drugs were given in random order by continuous infusion through the left atrium. The vasodilator drugs selected were those that are commonly used after cardiac operations, namely, nitroglycerin (1 μg/kg per min) and nitroprusside (1 μg/kg per min). Control measurements of blood flow and hemodynamic variables were repeated before each drug administration. Each pharmacologic intervention was effected ±15 min before measurement. In addition, a rest interval of 10 min was allowed between each intervention. All hemodynamic variables were held constant to isolate the effect of vasodilator drugs on graft flow.

Statistical analysis. The effect of each drug on graft flow and hemodynamics was compared with control measurements in each graft and the responses of the internal mammary artery and saphenous vein grafts were compared. In addition, the percent change from control in graft flow and hemodynamics was calculated and compared for each drug. All comparisons were made using the Student's t test for paired differences and considered statistically significant when p < 0.05.

Results

In Vitro Human Internal Mammary Artery

Contractile response to potassium and norepinephrine. Control segments of internal mammary artery not exposed to vasodilator drugs maintained relatively consistent maximal contractions with repeated potassium stimulation (Fig. 1). The maximal contractile response elicited by 70 mM of potassium chloride produced a mean peak contraction of 2.585 ± 300 mg (based on measurements in at least five segments). Higher potassium concentrations did not increase the maximal contractile response. After washout of the potassium Krebs solution, arterial rings relaxed to the initial baseline tension.

Norepinephrine-induced contractions were less consistent than those caused by potassium and usually resulted in a progressive decrease in contraction with repeated stimulation. The maximal decrease in norepinephrine-induced contraction of control arterial segments averaged 24 ± 6%. Ten micromoles of norepinephrine produced a mean peak contractile of 2.835 ± 410 mg.

Vasodilator inhibition of potassium contraction. A dose-response curve for nitroprusside-induced inhibition of potassium contraction is shown in Figure 1. Nitroprusside was not potent but was more potent than nitroglycerin, which inhibited potassium-induced contraction only at high doses (100
Table 1. Relaxant Effects of Vasodilators on Potassium- and Norepinephrine-Induced Contraction of Human Mammary Artery Segments

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>EC_{50} (μM)</th>
<th>Maximal % Inhibition</th>
</tr>
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<tbody>
<tr>
<td>Nitroprusside</td>
<td>0.302 ± 0.146</td>
<td>75 ± 7%</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0.447 ± 0.300</td>
<td>71 ± 8%</td>
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Arterial segments were incubated with various concentrations of vasodilator drugs and then contracted with 70 mM KCl or 10 μM norepinephrine (NE). The mean values for effective concentration of vasodilator required for 50% inhibition of concentration (EC{50}) and maximal inhibition of contraction were calculated for nitroprusside from inhibition dose-response curves. Because nitroglycerin was not potent, only one concentration (100 μM) was tested. Each value is the mean ± 95% confidence interval for EC_{50} values or the mean ± SEM for maximal inhibition. Each mean was obtained from at least five different segments of arteries.

μM). At maximally effective doses of vasodilator, nitroprusside was slightly more effective than was nitroglycerin (55 ± 7% versus 30 ± 8%, respectively).

Vasodilator inhibition of norepinephrine contraction. The ability of sodium nitroprusside to inhibit norepinephrine contraction was similar to its ability to inhibit potassium-induced contraction. Nitroglycerin was again not a potent inhibitor of norepinephrine contraction. Both nitroprusside and nitroglycerin were more effective in inhibiting norepinephrine contraction than potassium-induced contraction (Table 1). Nitroprusside was more effective in inhibiting norepinephrine-induced contraction than was nitroglycerin (71 ± 8% versus 56 ± 5%, respectively).

In Vivo Canine Internal Mammary Artery

Hemodynamic effects of drug administration in the eight dogs are demonstrated in Table 2. Vasodilator drug effects on blood flow in the canine internal mammary artery graft and saphenous vein graft are demonstrated in Table 3.

Nitroprusside. Administration of nitroprusside at 1 μg/kg per min did not alter hemodynamic measurements. Flow decreased in the mammary artery graft from 50 ± 7 to 44 ± 7 ml/min (p < 0.005) but increased in the saphenous vein graft from 64 ± 4 to 77 ± 7 ml/min (p < 0.005) (Table 2). A -12 ± 2% decrease was seen in internal mammary artery graft flow whereas a 25 ± 8% increase was seen in saphenous vein graft flow (Fig. 3). The decrease in mammary graft flow was significantly different from the increase in saphenous graft flow (p < 0.0025).

Nitroglycerin. All variables except graft flow were unchanged with nitroglycerin infusion at 1 μg/kg per min. Variations in flow were seen in different animals, but each animal responded similarly to drug administration (Fig. 3). Flow in the internal mammary artery graft increased significantly from 42 ± 7 to 59 ± 7 ml/min (p < 0.0025) whereas flow decreased significantly in the saphenous vein graft from 69 ± 4 to 59 ± 8 ml/min (p < 0.0005). The 36 ± 13% increase in mammary artery graft flow was significantly different from the -14 ± 3% change in saphenous vein graft flow (p < 0.005) (Fig. 3).

Discussion

Myocardial revascularization is a common and effective treatment of coronary artery disease. Although the saphenous vein is usually used for grafting (10,11), the internal mammary artery has recently gained recognition as a conduit (1-3). The artery is less prone to develop arteriosclerosis (12) and has demonstrated superior long-term patency (1-3). Some investigators (4,5) have also claimed that it results in better patient survival. Techniques have recently been described (13,14) to revascularize large areas of myocardium with the mammary artery to expand its utilization as a conduit. Accordingly, the internal mammary artery is currently the preferred conduit for myocardial revascularization.

Role of spasm in the internal mammary artery. The internal mammary artery is a vasoactive vessel (15,16). Recent studies (8,15,17) have suggested that the artery can enlarge with time to meet the demands of the coronary vascular bed. Vasospasm of the internal mammary artery during its isolation from the chest wall is frequently seen (6,7). In addition, vasospasm has been seen postoperatively (8). Treatment of vasospasm not only may influence the decision regarding use

Table 2. Hemodynamic Effects of Vasodilator Drug Administration in Eight Dogs

<table>
<thead>
<tr>
<th>Measurement</th>
<th>AoP (mm Hg)</th>
<th>AoF (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>dP/dt (mm Hg/s)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>116 (6) ± 42</td>
<td>81 ± 1</td>
<td>108.5 ± 3/1</td>
<td>6 ± 1</td>
<td>135 ± 13</td>
<td>166 ± 10</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>114 (6) ± 42</td>
<td>82 ± 1</td>
<td>108.5 ± 3/1</td>
<td>6 ± 1</td>
<td>135 ± 13</td>
<td>166 ± 10</td>
</tr>
<tr>
<td>Control</td>
<td>118 (4) ± 41</td>
<td>81 ± 1</td>
<td>1104 ± 4/1</td>
<td>5 ± 1</td>
<td>1345 ± 120</td>
<td>165 ± 9</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>116 (6) ± 32</td>
<td>82 ± 1</td>
<td>1084 ± 3/1</td>
<td>5 ± 1</td>
<td>1338 ± 110</td>
<td>164 ± 10</td>
</tr>
</tbody>
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Values are mean ± SEM. AoP = mean aortic pressure; AoF = mean aortic flow; dP/dt = maximal rise of left ventricular pressure with respect to time; HR = heart rate; LAP = mean left atrial pressure; LVP = mean left ventricular pressure.
of the artery as a graft, but also may improve flow through this graft postoperatively. Some studies (6,7) have used mechanical dilation of the internal mammary artery to reverse vasospasm (6,7); however, mechanical dilation can cause intimal damage, which may lead to thrombosis or obstruction to flow in the graft, or both (6,18). In addition, endothelial cell damage may enhance arterial spasm or constriction of the internal mammary artery by reducing the formation of endothelial derived relaxing factors (19). Topical papaverine has been used to reverse mammary artery spasm (6,18), but other vasodilators have not been investigated.

Our in vitro method was chosen to evaluate the ability of two commonly used vasodilators to inhibit contraction of the human internal mammary artery. Because the mechanisms of spasm of this artery are not known, two agents were used to induce contraction by different mechanisms with both extracellular and intracellular calcium pools. Potassium contracts vascular smooth muscle by direct membrane depolarization, resulting in an influx of extracellular calcium (20,21), whereas norepinephrine is thought to cause contraction of vascular smooth muscle by stimulating alpha-adrenergic receptors, which cause release of intracellular calcium (20,21) and some influx of extracellular calcium through receptor-operated calcium channels (21). Both agents were used in this study to evaluate both mechanisms of arterial contraction.

Table 3. Graft Blood Flow in Eight Dogs

<table>
<thead>
<tr>
<th>Vasodilator (1 μg/kg per min)</th>
<th>Internal Mammary Artery Graft</th>
<th>Saphenous Vein Graft</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control (mL/min)</td>
<td>Drug (mL/min)</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>50 ± 7</td>
<td>44 ± 7*</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>47 ± 7</td>
<td>59 ± 7*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *p < 0.05 compared with control; **p < 0.05 compared with internal mammary artery; ***p < 0.05 compared with nitroprusside.

The role of the endothelium in arterial contraction has recently been emphasized (22,23). Our study utilized a method of tissue preparation that preserves the integrity of the endothelium. Although we did not specifically test for the presence of endothelium, other studies utilizing an identical method of tissue preparation have demonstrated its presence (9,22,24). In addition, the nitrates have been found to be endothelium-independent vasodilators (22,25,26). The presence or absence of endothelium should therefore not affect our results with the vasodilators used.

Inhibition of mammary artery contraction by vasodilators. Nitroprusside and nitroglycerin relax various smooth muscles including vascular, uterine, gastrointestinal and bronchial. The mechanism of action of these drugs on vascular smooth muscle appears to require reaction with a sulfhydryl group, which results in the lowering of intracellular calcium (27). Recent studies (26,28) have found increased intracellular levels of cyclic guanosine monophosphate (GMP) induced by nitroprusside and nitroglycerin, which may be responsible for their vasodilator effect. Our study found nitroprusside to be more potent and more effective than nitroglycerin in inhibiting contraction of the human internal mammary artery. Nitroprusside had inhibited potassium and norepinephrine contraction at similar dose levels. Both

Figure 2. Vasodilator drug effect on blood flow in internal mammary artery (IMA) graft in eight dogs. Individual flows are depicted by lines and mean flow ± SEM is represented by circles or triangles. Although there are wide variations in flow among different animals, each animal responded similarly to vasodilator administration. Nitroprusside (triangles) decreased internal mammary artery flow whereas nitroglycerin (circles) significantly increased it.

Figure 3. The percent change in graft blood flow compared with control is demonstrated. The internal mammary artery (IMA) is represented by open bars and the saphenous vein graft (SVG) is represented by crossed bars. The opposite effect of nitroglycerin and nitroprusside on graft flow blood can be appreciated.
nitroprusside and nitroglycerin were more effective in inhibiting norepinephrine-induced than potassium-induced contraction. Previous studies (29) have also shown that nitroprusside is more effective in relaxing norepinephrine-contracted arteries, probably because its vasodilator mechanism of action depends more on intracellular than on extracellular calcium.

Effects of vasodilators on mammary artery and saphenous vein graft flow. The next portion of this study assessed whether inhibition of contraction of the mammary artery by vasodilators studied in vitro could be correlated with alterations in blood flow in canine mammary artery grafts studied in vivo. We selected our in vivo canine model instead of an in vivo human model to more effectively maintain constant systemic hemodynamic variables. Prior studies (30-32) have evaluated internal mammary artery graft flow, but our study more effectively isolated the local effect of the drugs from their systemic effects. In this model, graft flow is dependent not only on the effect of the drug on the conduit (mammary artery and saphenous vein), but also on the effect of the drug on the associated regional vasculature: coronary as well as subclavian. The saphenous vein was chosen as a conduit as well because it is most commonly used for grafting and should be less vasoreactive than the mammary artery (33).

Nitroprusside versus nitroglycerin effects. Nitroprusside decreased graft flow in the canine internal mammary artery whereas it increased graft flow in the saphenous vein. Nitroprusside is mainly an arteriolar vasodilator and has less effect on collateral vessels (34) and large coronary arteries (35,36). The coronary arteriolar vasodilation resulted in an increase in saphenous vein graft flow. Other studies (37) have similarly demonstrated increased saphenous vein graft flow with nitroprusside administration. Decreased flow in the internal mammary artery was unexpected and was perhaps due to peripheral arteriolar vasodilation of the respective subclavian and brachial arteries. This would have shunted blood flow away from the mammary branch of the subclavian artery and thereby resulted in a decrease in mammary artery flow. Alternatively, with marked coronary vasodilation, the resultant decrease in pressure along the mammary artery might have resulted in an increased conduit resistance, thereby reducing mammary artery flow. Nitroprusside administration after coronary artery surgery has also been associated with a decrease in myocardial lactate extraction, which may represent regional myocardial ischemia (38).

Nitroglycerin produced results opposite to those seen with nitroprusside. Graft flow increased in the internal mammary artery but decreased in the saphenous vein graft with nitroglycerin administration. Nitroglycerin has been shown to be a potent venodilator and a mild arteriolar vasodilator (39). It acts mainly on the larger conductive arteries and collateral vessels (34-36,40,41). Nitroglycerin decreases vascular resistance in coronary, cutaneous and muscular arteries (42). The internal mammary artery conduit has more resistance to flow than does the saphenous vein (33), as demonstrated by its lower control blood flow. Any vasodilation of the mammary artery would therefore result in an increase in graft flow, which was evidenced. A decrease in saphenous vein graft flow has also been observed with nitroglycerin in some clinical studies (43,44). The diminished graft flow probably results from nitroglycerin-induced increase in collateral coronary blood flow to the area perfused by the graft (45) resulting in competing flow to that area with decrease in vein graft flow. The vasodilation of the mammary artery evidently was greater than its competitive collateral flow and thereby resulted in a net increase in graft flow. Although saphenous vein graft flow was decreased by nitroglycerin, myocardial blood flow to the area might have increased. Favorable effects on myocardial metabolism with nitroglycerin administration have been observed after aorto-coronary bypass operations (38). Only graft flow was measured in this study, but regional myocardial blood flow to the area supplied by the graft merits investigation.

In vitro human data versus canine graft data. These divergent results with the in vitro human data and in vivo canine data are surprising. The most effective agent in inhibiting internal mammary artery contraction would have been expected to cause a greater increase in arterial flow. Close correlation between in vitro and in vivo vascular reactivity has been shown in response to some drugs but not to others (46). These unexpected data may have resulted from the effect of the drug on the associated regional vasculature: coronary and collateral versus subclavian and brachial arteries. More marked vasodilation by nitroprusside, as seen in human in vitro studies, may have resulted in brachial or subclavian vasodilatation with a steal away from the internal mammary artery and a resultant decrease in canine in vivo mammary artery blood flow. In addition, divergent results between in vitro and in vivo studies have been seen possibly as a result of blood-borne factors or experimental conditions (47,48).

An alternative explanation for the divergent in vitro and in vivo results may be species variation (49). Most of the reported species variations have occurred with contractile agents (50). Thus, acetylcholine was reported (51) to contract human coronary arteries but to relax canine coronary arteries with intact endothelium; species differences with vasodilators have not been mentioned. A maximal percent inhibition of potassium and norepinephrine contraction in canine renal arteries (29) similar to that of our data of human mammary arteries has been reported. It is therefore unlikely that species variations between the human and canine mammary artery account for our results. Our study utilized the canine model in vivo to more effectively isolate the effect of the vasodilators on graft flow independent of systemic and cardiac hemodynamics. However, in vivo studies in canine vessels do not necessarily predict the in vivo response of
human vessels. To directly apply the canine in vivo data to humans, similar in vitro studies need to be performed on canine mammary arteries; these are currently in progress.

Conclusions. Our results demonstrate that, although sodium nitroprusside is more effective in inhibiting internal mammary artery contraction in vitro, it decreased mammary artery graft flow measured in vivo. Nitroglycerin had the opposite effect with an increase in mammary artery graft flow. Vasodilator drug effects on flow in saphenous vein grafts were different from those in internal mammary artery grafts; saphenous vein graft flow increased with nitroprusside but decreased with nitroglycerin. The vascular reactivity of the internal mammary artery and regional vasculature must therefore be considered when vasodilator drugs are used after coronary revascularization.

References


