Middle and proximal sections of the human internal mammary artery are not “passive conduits”

Recent studies have shown that blood flow through the internal mammary artery graft is inadequate for maximal exercise and that hypoperfusion may be worsened by high-dose vasopressor therapy that could further reduce arterial graft flow. Histologic studies have suggested that the human internal mammary artery is an elastic “passive conduit” along the majority of its length. However, although the pharmacologic reactivity at the distal section of the internal mammary artery has been extensively studied, this evaluation has never been done at the middle and proximal sections. It is extremely important to understand the contractility at the midsection of the internal mammary artery because, in a critical situation, any contraction may further reduce the internal mammary artery flow. The present study was designed to investigate the following: (1) Is it true that the pharmacologic reactivity of the human internal mammary artery is different among various sections? and (2) Is the human internal mammary artery a nonreactive “passive conduit” at its most important area used as the graft—the middle and the proximal sections? One hundred six human internal mammary artery ring segments taken from patients who underwent internal mammary artery grafting procedures (29 from the proximal, 38 from the middle, and 39 from the distal sections) were studied in the organ bath under a physiologic pressure. Concentration-response curves were established for norepinephrine, endothelin-1, U46619, potassium, and glyceryl trinitrate (precontracted with 10 nmol/L U46619). Contraction forces were standardized (in grams per millimeter circumference) at a pressure of 100 mm Hg. The contraction force was greater in the distal section than in other sections for norepinephrine ($p = 0.002$) and endothelin-1 ($p = 0.04$). No differences were seen for potassium, U46619, or glyceryl trinitrate, whereas the effective concentration inducing 50 % of maximal response for U46619 was 100-fold lower in the distal than in the middle section (9.06 ± 0.34 versus 7.06 ± 0.48 $-\log M$; $p = 0.01$) indicating higher sensitivity in the distal section. This study for the first time shows various reactivity along the full length of the human internal mammary artery and shows that the distal section is the most reactive part of the graft. However, although the middle and the proximal sections are less reactive to some vasoconstrictors (norepinephrine and endothelin-1), it is not a “passive conduit” and it contracts with all four vasoconstrictors tested. The contractility at the midsection should be fully appreciated because, under critical postoperative situations (hypoperfusion) or during exercise with marginal flow, the ability of these sections to contract in response to vasoconstrictors may become clinically detrimental and require pharmacologic therapy. (J THORAC CARDIOVASC SURG 1994;108:741-6)

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Although superior long-term patency rates of internal mammary artery (IMA) grafting have led to the extensive use of this arterial graft,¹⁻³ recent studies have shown that blood flow through arterial grafts (IMA grafts were used in most of the patients) is inadequate for maximal exercise⁴; it was also shown that inadequate graft flow may cause a hypoperfusion syndrome manifested by low cardiac output, left ventricular failure, rising pulmonary wedge pressure, hypotension, and cardiac arrest.⁵ Severe hypoperfusion tends to occur early in the patient's course, and this situation may be worsened by high-dose vasopressor therapy that could further reduce arterial graft flow.^{5,6} Histologic studies^{7,8} have suggested that the human IMA is an elastic "passive conduit" along most of its length. On the basis of the histologic observations and pharmacologic studies, a hypothesis that the human IMA is an artery with different reactivity along its length has been proposed.⁹ This hypothesis suggests that, at the midsection, the IMA is basically a "passive conduit," whereas it is pharmacologically reactive at the distal and the proximal sections. However, although the pharmacologic reactivity at the distal section of the IMA has been extensively studied,⁹⁻¹⁷ this analysis has never been done at the proximal and middle sections. Therefore, two questions must be answered: (1) Is it true that the pharmacologic reactivity of the human IMA is different among various sections? and (2) Is the human IMA a nonreactive "passive conduit" at its most important area used as the graft—the middle and the proximal sections? The characteristics of the IMA are extremely important in a critical situation because any contraction may further reduce the IMA flow. The present study was designed to answer these questions.

Methods

Segments of the human IMA (either left or right) were nonselectively collected from patients undergoing IMA grafting procedures whenever available. These segments were taken from either the distal section, the proximal section (usually when a free IMA graft is used), or the midsection when an extremely short length of an IMA graft was needed or when an IMA was considered inadequate to use as a graft because of low flow measured from the free distal end. The midsection was defined in the present study as at least 4 cm from the distal bifurcation or 4 cm from the origin of the IMA from the subclavian artery. This definition was created for two reasons. First, by this definition, the length of the midportion of IMA is about 60% of the total length (19.5 ± 2.4 cm) and contains more elastic lamellae than do the proximal and the distal portions.⁷ Second, even used as a "free graft," this portion of IMA is almost always essential and therefore is the most important part as a graft. Approval to use discarded IMA tissue was given by the Human Ethics Committee of the Medical City Dallas Hospital. After sternotomy, full-length left IMA pedicle was carefully dissected from

the chest wall. The patients were then heparinized, and cardiopulmonary bypass was instituted. The left IMA was cut distally, and the length for grafting to the left anterior descending artery was carefully measured and preserved. Any discarded distal IMA segments were collected and put in a container with oxygenated physiologic solution (Krebs), maintained at 4° C, and then transferred to the laboratory immediately. The IMA was transferred into a glass dish and dissected out from its surrounding connective tissue. The IMA was then cut into 3 mm-long rings, which were then suspended on wires in organ baths.^{10,11} The Krebs solution had the following composition (in millimoles per liter): Na⁺ 144, K⁺ 5.9, Ca²⁺ 2.5, Mg²⁺ 1.2, Cl⁻ 128.7, HCO₃⁻ 25, SO₄²⁻ 1.2, H₂PO₄⁻ 1.2, and glucose 11. The solution was aerated with a gas mixture of 95% O₂-5% CO₂ at $37 \pm 0.1^\circ$ C.

Organ bath technique. A technique that allowed vascular rings to be normalized under a physiologic pressure in vitro, by establishing the individual length-tension curve for each vascular segment, was used to set the vascular rings at a pressure comparable with that at the in vivo situation. The details of the technique have been previously published.^{11,18} Because of the importance of vascular endothelium in modulating contraction or relaxation, we intentionally preserved the endothelium by cautiously dissecting and mounting the rings.^{13,18}

Protocol. After the normalization procedure, the IMA rings were equilibrated for 1 hour. The following protocols were designed for the experiments.

Contraction. Diameters of the IMA at a pressure of 100 mm Hg (D100) were recorded from the normalization procedure. The cumulative concentration-contraction curve was established for the following vasoconstrictor substances: endothelin-1 (ET), norepinephrine (NE), U46619 (a stable thromboxane A₂ mimetic), and the membrane-depolarizing agent potassium chloride (K⁺). The total contraction force and the standardized force (Fn) were used to compare the contraction among the different sections. As previously described,⁹ the standardized contraction force was calculated by the following equation: $F_n = \text{Force (grams)} / C_{100}$ (millimeters), where C_{100} is the circumference at a pressure of 100 mm Hg and $C_{100} = \pi \times D_{100}$. The meaning of Fn is the force (grams) produced by 1 mm of circumference of the vessel. Because the length of the IMA rings is equal (3 mm), the Fn represents the force produced by each millimeter of the circumference at a length of 3 mm. Therefore, comparison of Fn among arteries with different diameters is more logical in regard to test contractility.

Relaxation. The maximal relaxation induced by glyceryl trinitrate on U46619 (10 nmol/L)-induced contraction was analyzed as percentage relaxation of the precontraction. EC₅₀: Sensitivity of the IMA to vasoconstrictor (U46619, K⁺, NE, and ET) or vasodilator (glyceryl trinitrate) agents is expressed by the effective concentration which induced 50% of maximal effect (either contraction or relaxation). The EC₅₀ was determined from each concentration-contraction (or relaxation) curve by a logistic, curve-fitting equation¹⁹: $E = MA^p / (A^p + K^p)$ where E is response, M is maximal contraction (or relaxation), A is concentration, K is EC₅₀ concentration, and p is the slope parameter.

The similar protocol was used for the rings taken from the proximal, middle, or distal sections of the IMA. Analysis of variance and the Scheffé test (as the post-hoc test) were used to compare the Fn for each vasoconstrictor, the percentage relax-

Fig. 1. Mean concentration ($-\log M$) – contraction ($Force, g$) curves for norpinephrine (NE) at the proximal ($\circ$ Pro, $n = 6$), middle ($\bullet$ Mid, $n = 8$), and distal (Δ Dis, $n = 7$) sections of IMA. Symbols represent data averaged from a group of IMA rings. Horizontal bars are placed on EC_{50} values (± 1 standard error of the mean), averaged from logistic, fitted curves from each ring. Vertical bars are 1 standard error of the mean at the maximum response.

Fig. 2. Mean concentration ($-\log M$) – contraction curves for endothelin (ET) at the proximal ($\circ$ Pro, $n = 5$), middle ($\bullet$ Mid, $n = 7$), and distal (Δ Dis, $n = 11$) sections of the IMA. Symbols represent data averaged from a group of IMA rings. Horizontal bars are placed on EC_{50} values (± 1 standard error of the mean), averaged from logistic, fitted curves from each ring. Vertical bars are 1 standard error of the mean at the maximum response.

ation to vasodilator glyceryl trinitrate, and the EC_{50} s; $p < 0.05$ was considered significant.

Drugs. Drugs used in this study and their resources were as follows: NE (Sigma, St. Louis, Mo.); U46619 (Cayman Chemical, Ann Arbor, Mich.); ET (Peptides International, Louisville, Ky.); glyceryl trinitrate (Roussel Canada Inc., Montreal, Canada). Stock solution of NE was freshly made each day. Stock solution of ET was held frozen until required.

Results

One hundred and six IMA rings were studied. These included 29 rings taken from the proximal, 38 from the middle, and 39 from the distal sections. The diameter at a pressure of 100 mm Hg^{11,18} was 2.76 ± 0.16 mm for the proximal, 2.35 ± 0.12 mm for the middle, and 1.85 ± 0.08 mm for the distal section of the IMA ($p < 0.0001$).

Figures 1 to 4 show concentration-contraction curves for the four vasoconstrictors. Table I gives the standardized F_n and the EC_{50} for vasoconstrictor substances (NE , ET , U46619, and K^+) in the rings taken from the proximal, middle, and distal sections of the IMA. The F_n was greater in the distal than in the proximal ($p = 0.01$, Scheffé test) and the middle section ($p = 0.0036$, Scheffé test) for NE . Similarly, the F_n induced by ET was greater in the distal section ($p = 0.04$, analysis of variance), and this difference was mainly between the distal and middle sections ($p = 0.04$, Scheffé test). No differences were seen for K^+ and U46619 with regard to F_n . However, the EC_{50} for U46619 was 100-fold lower in the dis-

Fig. 3. Mean concentration ($-\log M$) – contraction ($Force, g$) curves for U46619 at the proximal ($\circ$ Pro, $n = 6$), middle ($\bullet$ Mid, $n = 10$), and distal (Δ Dis, $n = 7$) sections of the IMA. Symbols represent data averaged from a group of IMA rings. Horizontal bars are placed on EC_{50} values (± 1 standard error of the mean), averaged from logistic, fitted curves from each ring. Vertical bars are 1 standard error of the mean at the maximum response.

tal section than in the mid section of the IMA (9.72 ± 0.61 versus $7.06 \pm 0.48 -\log M$; $p = 0.016$, Scheffé test) indicating a much higher sensitivity to this vasoconstrictor in the distal section than in the midsection of the IMA. No statistical difference was found between the proximal

Fig. 4. Mean concentration (*mM*) – contraction (*force, g*) curves for potassium (*K*) at the proximal (*Pro*, *n* = 6), middle (*Mid*, *n* = 8), and distal (*Dis*, *n* = 7) sections of the IMA. Symbols represent data averaged from a group of IMA rings. Horizontal bars are placed on EC_{50} values (± 1 standard error of the mean), averaged from logistic, fitted curves from each ring. Vertical bars are 1 standard error of the mean at the maximum response.

and the middle sections with regard to the F_n or EC_{50} for the all four vasoconstrictors.

Table II and Figure 5 show the maximum relaxation induced by glyceryl trinitrate in U46619-precontracted rings of the proximal, middle, and distal sections of the IMA. No difference was found either in the maximum relaxation or in the EC_{50} .

Discussion

In the present study, we were able to, for the first time, show that the reactivity of the human IMA is variable along its full length and that the distal section of this artery has the highest reactivity. We tested four potential spasmogens for the human IMA. Thromboxane A_2 , represented by its stable analog U46619, is released from platelets and has been shown to be the most potent vasoconstrictor in the human IMA.^{10, 17} ET, a vasoconstrictor substance derived from endothelial cells, has been suggested in general as the most powerful vasoconstrictor for blood vessels^{20, 21} and measured with an increased release during cardiopulmonary bypass for coronary artery bypass grafting.²² α -Adrenoceptor agonists are generally considered to be causes of vasospasm,²³ and the α_1 -adrenoceptor has been shown to be predominant in the human IMA.^{10, 12-14} Apart from these receptor stimuli, potassium ion was also chosen because it depolarizes cellular membrane and therefore opens voltage-dependent calcium channels to cause calcium influx and finally con-

Fig. 5. Mean concentration ($-\log M$) – relaxation (% of pre-contraction) curves for glyceryl trinitrate (*GTN*) at the proximal (*Pro*, *n* = 6), middle (*Mid*, *n* = 5), and distal (*Dis*, *n* = 7) section of the IMA. Symbols represent data averaged from a group of IMA rings. The precontraction was induced by U46619 (10 nM). Vertical bars are 1 standard error of the mean of the response at each concentration.

tract smooth muscle cells.¹⁰ The present study shows that the distal section is more contractable to two receptor agonists—NE and ET. With regard to thromboxane A_2 -mediated contraction, although no evidence was found showing that the distal section was more contractable to this receptor agonist, the sensitivity to this vasoconstrictor was higher at this section as indicated by the lower EC_{50} at this part of IMA. In fact, the EC_{50} was as much as 100-fold lower in the distal section compared with the midsection, and this disparity represents a much higher sensitivity in this part of the IMA. In general, a contractility is indicated by F_n and sensitivity. A greater contraction force and a higher sensitivity (lower EC_{50}) usually mean a greater contractility. Therefore, the present study shows a greater contractility of the distal section compared with that of the middle and proximal sections of IMA. Physiologically, this difference may be important because the distal end of the IMA, possibly the proximal portion as well, regulates blood flow in this artery and thus may shut down when other parts of the body, particularly vital organs, need better perfusion.

On the other hand, the middle and proximal sections of the IMA are not completely passive conduits. Although histologic studies have suggested that the human IMA is a passive conduit,^{7, 8} on the basis of the fact that this artery contains more elastic lamellae than other arteries, such an artery is not necessarily a completely passive conduit because there are still smooth muscle cells in the arterial

Table I. Comparison of standardized contraction force and EC₅₀ for four vasoconstrictors between various sections of the human IMA

Agents	Fn				EC ₅₀ (−log M)			
	Proximal	Middle	Distal	p Value	Proximal	Middle	Distal	p Value
NE	0.29 ± 0.08* (n = 6)	0.25 ± 0.07* (n = 8)	0.73 ± 0.11 (n = 7)	0.002	6.25 ± 0.27	6.19 ± 0.17	5.91 ± 0.16	0.42
ET	0.59 ± 0.3 (n = 5)	0.44 ± 0.08* (n = 7)	0.74 ± 0.06 (n = 11)	0.04	8.11 ± 0.04	7.92 ± 0.24	8.31 ± 0.07	0.14
U46619	0.45 ± 0.15 (n = 6)	0.8 ± 0.17 (n = 10)	0.95 ± 0.14 (n = 7)	0.16	8.15 ± 0.44	7.06 ± 0.48*	9.06 ± 0.34	0.01
K ⁺	0.45 ± 0.17 (n = 6)	0.65 ± 0.17 (n = 8)	0.84 ± 0.13 (n = 7)	0.28	21.27 ± 5.35†	22.51 ± 2.57†	20.94 ± 1.99†	0.94

Fn, Contraction force (in grams) standardized by circumference at a pressure of 100 mm Hg.
*p < 0.05 in comparison to the distal section (Scheffé test).
†EC₅₀ for K⁺ in millimoles per liter.

Table II. Relaxation induced by glyceryl trinitrate

	Maximum relaxation (%)				EC ₅₀			
	Proximal	Middle	Distal	p Value	Proximal	Middle	Distal	p Value
Glyceryl trinitrate	98.45 ± 1.09 (n = 6)	100 (n = 5)	95.54 ± 2.21 (n = 7)	0.18	7.40 ± 0.22	7.99 ± 0.18	7.73 ± 0.09	0.08

The maximal relaxation is expressed as percentage of precontraction induced by U46619 (10 nmol/L). n, Number of ring segments.

wall. Previous pharmacologic studies have shown that the human IMA at the distal section is a pharmacologically reactive artery,⁹⁻¹⁷ which is in accordance with clinical reports.^{24, 25} A recent histologic study is in accordance with our pharmacologic studies.²⁶ A clinical trial on the pharmacologic dilatation of the IMA during surgical procedures has shown that the IMA flow significantly increases when intraluminal injection of pharmacologic agents is used,²⁷ and our present study is in accordance with the clinical trial. From the present study, the midsection of the IMA contracts with all four vasoconstrictors tested to a certain extent, which suggests that even this part of the IMA is still a reactive conduit despite the fact that there are fewer smooth muscle cells at the midsection than at other sections. Alternative evidence, implicating the reactive characteristic of the middle and the proximal sections of the IMA, is that these two sections react to vasoconstrictor thromboxane A₂ (U46619) and K⁺ to the same extent as does the distal section (Table I). Because the reactivity (to NE and ET) of the middle and proximal sections is significantly less than that of the distal section and, also, because these sections are significantly larger in diameter than the distal section, vasospasm is usually more frequently encountered in the smaller and more reactive distal end rather than in the middle and the proximal sections of the IMA. However, the contractility at the middle and proximal sections

needs to be fully appreciated because the contraction at these sections in response to vasoconstrictors may reduce the diameter and the flow in the IMA graft and therefore produce detrimental effects. Under a marginal situation, such as postoperative hypoperfusion, this factor may be critical.

In this study, we did not detect any difference among the different sections with regard to the relaxation induced by glyceryl trinitrate. This finding may imply that the difference along the full length of IMA only involves the contractile but not the relaxing property.

In summary, the present study has shown for the first time that the distal section of the human IMA has the greatest contractility compared with the middle and proximal sections. This finding suggests that the distal section of the IMA is the part where vasospasm may develop and requires the greatest care. However, although the middle and the proximal sections are less pharmacologically reactive than the distal section to some vasoconstrictors, these sections are not completely nonreactive passive conduits because they contract with various vasoconstrictors. This finding may have important postoperative implications. In particular, under critical postoperative situations (hypoperfusion) or during exercise with marginal flow, the ability of these sections to contract in response to vasoconstrictors may become clinically detrimental and require pharmacologic therapy.

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