The physiologic and histologic properties of the distal internal thoracic artery and its subdivisions

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Objective: We compared the flow rates, reactivity, and morphology of the distal internal thoracic artery and its branches, the superior epigastric and musculophrenic arteries, to test their applicability as possible conduits in coronary artery bypass grafting surgeries.

Methods: Skeletonized internal thoracic artery and subdivisions of patients undergoing coronary artery bypass grafting were studied intraoperatively (n = 100) for flow and length measurements and in vitro in organ baths (n = 58) for active response to norepinephrine. Quantitative microscopic analysis of the muscle density and degree of intimal hyperplasia was performed. Results were analyzed according to age, gender, risk factors, and medications.

Results: Internal thoracic artery subdivisions contributed an average extra length of 2 cm. Free flow rates were 129 ± 45 mL/min, 114 ± 41 mL/min, and 93 ± 36 mL/min in the internal thoracic artery, superior epigastric artery, and musculophrenic artery, respectively. Sternum and internal thoracic artery length and free flow rates were significantly lower in women. The subdivisions were significantly more reactive to norepinephrine than the distal internal thoracic artery ($P \sim .005$), although sensitivity to norepinephrine was similar. Patients treated with beta-blockers had significantly decreased reactivity ($P = .009$). Microscopic analysis suggests similar muscle content in the internal thoracic artery and subdivisions. Eccentric (28%) and concentric (62%) intimal hyperplasia were observed in 90% of specimens, with no evidence for atherosclerotic plaques. There was no significant difference in the degree of intimal hyperplasia between the distal internal thoracic artery and its subdivisions, and there was no correlation to risk factors.

Conclusions: Our results confirm the previous studies on the higher contractility in internal thoracic artery subdivisions, suggesting caution in the use of the bifurcation for revascularization. However, the extra length, sufficient flow, and favorable histologic properties suggest that the bifurcation may be appropriate for coronary revascularization in selected cases. (J Thorac Cardiovasc Surg 2015;149:1042-50)

See related commentary on pages 1050-1.

The internal thoracic artery (ITA) is the conduit of choice in coronary artery bypass grafting (CABG) surgeries because of its well-established superior long-term patency,

survival benefit, and freedom from reinterventions.¹⁻³ The ITA divides at the level of the sixth intercostal space into the superior epigastric (SE) and musculophrenic (MP) arteries. The need for extra length for use in different graft configurations and the recent skeletonization techniques for ITA harvesting impose the question of the applicability of the ITA's subdivisions as possible conduits. Most surgeons avoid using these vessels on the basis of several reports of increased reactivity to vasoconstrictor stimuli,⁴⁻⁷ increased muscle content, and a tendency for atherosclerosis.⁸⁻¹¹

The present study is aimed at investigating the anatomy, flow rate, active response, and microstructure of the distal ITA and its subdivisions. The influence of patients' risk factors and medications on these parameters is discussed.

MATERIALS AND METHODS

Arteries of consecutive patients undergoing CABG by various surgeons at the Rabin Medical Center were studied. A total of 158 patients participated in the 2 in vivo and in vitro phases of the study. The experimental protocol was approved by the hospital human ethics committee.

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ARB	= angiotensin receptor blocker
CABG	= coronary artery bypass grafting
ITA	= internal thoracic artery
MP	= musculophrenic
NE	= norepinephrine
SE	= superior epigastric
SMA	= smooth muscle actin
SV	= saphenous vein

Anatomy and Flow Rate

The first phase included 100 patients for whom gender, age, height, presence of risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking, peripheral vascular disease), and medications (beta- and alpha-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], nitrates, diuretics, statins, and aspirin) were extracted from the medical chart.

The ITA was harvested using the skeletonization technique. The following anatomic parameters were recorded: sternum length, length of the incision in the internal thoracic fascia, ITA length measured from its origin in the subclavian artery, and contribution of each subdivision to the total length.

The artery was then soaked in diluted papaverine solution. Free flow measurements (milliliters/second) from each subdivision and the distal ITA were recorded immediately before the anastomosis. All measurements were taken at a mean systemic blood pressure of 70 mm Hg.

Physiology: In Vitro Phase

Experiments were conducted on 122 skeletonized arterial segments collected from 58 patients (ITA 41, SE 47, MP 34). Before soaking in papaverine solution, the artery was trimmed to the necessary length, and the extra distal ITA and bifurcation were immediately stored in a physiologic 4°C Krebs-Henseleit solution.¹² Specimens from the distal ITA and each of its subdivisions were cut into 3-mm-long rings using a double-bladed knife. Any discarded tissue was kept in a 4% formaldehyde solution for later histologic processing.

Ring Test Protocol

Each 3-mm-long vascular ring segment was suspended between 2 stainless-steel 0.4-mm wires: The upper wire was attached to a load cell, and the lower wire was fixed to the micrometer (Figure 1, A).^{12,13}

The rings were placed into an organ bath chamber filled with 20 mL of Krebs-Henseleit solution at 37°C and bubbled with 95% O₂ + 5% CO₂. After a stabilization period of 30 minutes without tension, each ring was stretched in progressive steps to determine its own length-tension exponential curve (Figure 1, B and C). The wires were moved apart in steps every minute while the force (F [g]) and the displacement (l [mm]) were recorded. F and l were input online in a computer program (MATLAB 7.0; The MathWorks Inc, Natick, Mass) to determine the theoretic lumen circumference that would have corresponded to a transmural pressure of 100 mm Hg. This value is termed “ L_{100} .” The artery was then relaxed to a circumference equal to $0.9 L_{100}$, termed “passive tension,” kept constant throughout the remainder of the experiment. Cumulative concentrations of norepinephrine (10^{-9} to 10^{-4} mol/L) were added to the organ bath in 0.5 log increments to create a dose-response curve (Figure 1).

Because the arteries were of different diameters, we normalized the contraction response by the circumference at an equivalent internal pressure of 100 mm Hg, that is, $E = f_A/L_{100}$ with units of grmf/mm, where f_A is the recorded force at a given concentration level A of norepinephrine

(NE), and L_{100} is the estimated circumference of the lumen at internal pressure of 100 mm Hg. The maximal normalized contraction denoted by M (grmf/mm) was obtained at a concentration of 10^{-4} mol/L of NE.

The sensitivity of the arteries was estimated as the effective NE concentration that induced 50% of the maximal contraction $-EC_{50}$. According to Parker and Waud,¹⁴ the relation between the normalized contraction E and the NE concentration A is represented by fitting the equation

$$E = \frac{M \times A^p}{(A^p + EC_{50}^p)} \quad (1)$$

to experimental observations. The slope parameter p and EC_{50} can be estimated if the formula is transformed to a logarithmic representation:

$$\log A = \log(EC_{50}) + \frac{1}{p} \log \left(\frac{M}{M-E} \right) \quad (2)$$

By having the values of $\log A$ and $\log \left(\frac{E}{M-E} \right)$ for each artery, a linear regression can be performed obtaining the slope $1/p$ and the estimate of $\log(EC_{50})$.

Pathology

The discarded tissues, kept in formaldehyde, were used for pathology investigation (all also tested in vivo). Fifty specimens from different arterial segments ($n = 18$ ITA, 18 SE, 14 MP) were studied. Each piece was stained with hematoxylin-eosin, elastic fibers, and smooth muscle actin (SMA) immunohistochemical stain. Each slice was photographed at 4 magnifications ($\times 4$, $\times 10$, $\times 20$, and $\times 40$) and analyzed by a color image analyzing system (Image-Pro Plus 5.1; Media Cybernetics Inc, Rockville, Md).

Three methods were used to quantify the degree of intimal thickening¹¹: (1) intimal thickness index (ITI), intimal area/medial area; (2) intimal to medial ratio, width of the intima at maximal intimal thickness/width of the media at maximal intima thickness; (3) luminal narrowing (%) according to the following formula: $(IEL)^2/4\pi$, where IEL is the circumference of the internal elastic lamina (Figure 2, A and B).

Comparative quantitative analysis of muscle content in the media layer of the artery was conducted on specimens dyed by SMA immunohistochemical stain. Calculations were based on the amount of color pixels in a specific area.¹⁵ The average muscle density of 8 identical rectangles at angles 0°, 45°, 90°, 135°, 180°, 225°, and 270° at $\times 20$ magnification was calculated (muscle/extracellular matrix $\times 100$) (Figure 2, C and D).

Data Analysis

All data were statistically analyzed by the Stata 8 program (StataCorp LP, College Station, Tex).¹⁶ Comparisons were conducted using the Student t test and Mann-Whitney test for continuous variables, chi-square and Fisher exact tests for categorical variables, and nonparametric tests including Friedman test and Wilcoxon signed-rank test.

The influence of risk factors and medical therapy was assessed using multivariate linear regression analysis. The clustered structure of the data was accounted for because of the high correlation assumed between observations belonging to the same patient. The pathologic and physiologic results were compared using analysis of variance. A 95% confidence interval level was set for all tests.

RESULTS

Patients' demographics and risk factors are presented in Table 1. No statistically significant differences were found between the in vivo and in vitro groups.

Anatomy and Flow Rates

Average ITA length was 19.87 ± 1.88 cm. Harvesting of the subdivision yielded a significant extra length of

FIGURE 1. Experimental protocol. A, Experimental system. B, Length-tension curve. X-axis represents the micrometer displacement. Y-axis represents the wall tension in gram force. C, Experimental protocol timeline. D, Progressive steps in the creation of a length-tension curve. E, Arterial contraction in response to the addition of NE. NE, Norepinephrine.

2.33 ± 0.63 cm and 1.73 ± 0.53 cm for SE and MP, respectively.

Incision length in the internal thoracic fascia (assumed to be identical to arterial length when separated as a pedicle) was significantly smaller compared with the skeletonized ITA ($P < .01$). The ITA length in female patients was significantly smaller ($P < .0001$).

Possible predictors for arterial length were analyzed by a linear regression model. The model included age, gender, height, and the different risk factors. We found that sternum length and gender were strongly associated with ITA length ($P < .0001$ and $P = .02$, respectively).

Average free flow rate was 126 ± 44.43 mL/min in the left ITA and 130.30 ± 50.79 mL/min in the right ITA

($P = .43$). A flow reduction of 24.09 ± 20.67 mL/min between the ITA and its subdivisions was observed ($P < .0001$). Female patients had significantly lower flow rates in the ITA and subdivisions ($P = .0047$). Predictors of a lower free flow in the linear regression model were female gender ($P = .01$) and older age ($P = .02$). None of the cardiovascular risk factors had a significant effect on the free flow rates (Figure 3, A-D).

Physiology

Arterial segments ($n = 122$) were collected from 58 patients (Table 1). L_{100} was 4.99 ± 1.77 mm, 3.93 ± 1.59 mm, and 3.62 ± 1.31 mm in the ITA, SE, and MP, respectively.

FIGURE 2. Histopathologic analysis. A and B, Measurement of intimal hyperplasia indices, hematoxylin–eosin $\times 4$. A, Intimal thickness index. B, Intimal to medial ratio. C and D, Quantitative analysis of muscle content in the media. C, SE, SMA stain, $\times 4$. D, Same specimen at $\times 20$ magnification. Red = muscle. Yellow = extracellular matrix. E and F, Typical morphologies of intimal hyperplasia, hematoxylin–eosin stain, $\times 4$ magnification. E, SE artery showing significant intimal thickening with narrowing of the arterial lumen. F, MP artery showing concentric intimal hyperplasia. G and H, Positive SMA stain in the intimal hyperplastic areas. G, ITA, hematoxylin–eosin stain, $\times 10$. H, Same specimen SMA stain, $\times 20$. I and J, Elastic fibers stain. I, MP, $\times 10$. Arrow, Internal and external elastic laminae. J, SE, $\times 10$. Defects and doubling areas in the internal elastic lamina are observed.

We measured the contraction force for each artery at 11 different concentrations of NE. On the basis of these observations, we created a dose-response curve for NE. Estimated parameters that determine the dose-response curve, that is, $1/p$, EC_{50} , and the maximal contraction M , are summarized in Figure 4.

TABLE 1. Distribution of patient demographics and risk factors

Parameter	In vivo n = 100	In vitro n = 58	Total n = 158	P value
Age (y) mean $\pm$ SD	66.0 $\pm$ 11.4	67.5 $\pm$ 10.3	66.6 $\pm$ 11.0	.41
Gender (female)	20.0%	19.6%	19.9%	1.00
Hypertension	69.0%	67.9%	68.6%	1.00
Diabetes mellitus	37.4%	37.5%	37.4%	1.00
Dyslipidemia	70.7%	76.8%	72.9%	.46
Peripheral vascular disease	20.0%	26.8%	22.4%	.42
Smoking	37.0%	44.8%	39.9%	.87

SD, Standard deviation.

We conclude that the maximal contraction in response to NE is significantly higher in the subdivisions compared with the ITA ($P \sim .005$). No statistically significant difference exists between SE and MP ($P \sim .283$). Our results are in line with previously published data (Table 2). Although the maximal contraction was higher, there was no statistically significant difference in the sensitivity to NE between the different arteries (represented by EC_{50}). The contraction was similar in both genders and tended to decrease with age ($P = .095$). There was no statistically significant connection between the patient’s risk factors and the normalized contraction, even after adjustment for medications and age. In addition, the number of risk factors per patient did not correlate with the normalized contraction force.

Arteries from patients treated with beta-adrenergic blockers had significantly reduced contractility ($P = .009$). Alpha-adrenergic blockers had the same effect ($P = .08$),

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FIGURE 3. Anatomy and flow. A, Contribution of subdivisions to ITA length. B, Comparison of length parameters between genders. C, Free flow in ITA and subdivisions. D, Comparison of free flow rates between genders. *ITA*, Internal thoracic artery; *MP*, musculophrenic; *NS*, not significant; *SE*, superior epigastric.

but after adjusting to age this was not statistically significant ($P = .1$). The average age of patients treated with alpha-blockers was 73.8 ± 2.5 years compared with 66.9 ± 1.6 years in patients not treated by alpha-blockers ($P = .064$).

Histology

A sample of 50 arterial segments collected from 29 patients was investigated. Some degree of intimal hyperplasia was observed in 90% of specimens, with 2 typical morphologies: The morphology was concentric in 62% of patients and eccentric in 28% of patients (Figure 2, E and F).

Three parameters—ITI, intimal to medial ratio, and percent of luminal narrowing¹¹—were used to compare the degree of intimal hyperplasia. The intimal thickness index was 0.12 ± 0.08 , 0.16 ± 0.14 , and 0.13 ± 0.10 ; the intimal to medial ratio was 0.4 ± 0.45 , 0.37 ± 0.46 , and 0.25 ± 0.18 ; and the percent of luminal narrowing was $12.19\% \pm 6.76\%$, $15.65\% \pm 14.76\%$, and $13.63\% \pm 8.74\%$ for the ITA, SE, and MP, respectively. There was no statistically significant difference in the level of intimal thickening among ITA, SE, and MP.

None of the cardiovascular risk factors significantly correlated to the degree of intimal hyperplasia. An interesting finding was the positive staining of cells in the intimal hyperplastic areas for SMA (Figure 2, G and H).

We performed an elastic fibers stain in a small sample of specimens, all of which contained scarce elastic fibers in the media. The intimal hyperplastic areas were negative for elastic fibers. Defects and doubling of the internal elastic lamina were observed in a few specimens (Figure 2, I and J).

A total of 53 arterial segments were immunohistochemically stained for SMA and analyzed for muscle content. Mean muscle density was $75.06\% \pm 9.66\%$, $75.42\% \pm 11.93\%$, and $78.18\% \pm 12.15\%$ for the ITA, SE, and MP, respectively. There were no statistically significant differences in muscle content between ITA and SE ($P = .69$) or MP ($P = .43$). There was no statistically significant connection between the medial muscle density and the maximal contraction force to NE ($P = .86$). Analysis for the normalized contraction was borderline ($P = .09$).

FIGURE 4. Dose-response relationships for NE. A, Dose-response curve for NE. The relation is presented for the ITA, SE, and MP arteries based on a least mean square estimate of $1/p$ and EC_{50} (3 curves), and the experimental results (*bars*). B, Contraction and sensitivity to NE in different arterial segments determined by least mean square from experiments. The higher contractility in ITA subdivisions, suggesting caution in the use of the bifurcation for revascularization, is demonstrated. However, the extra length, sufficient flow, and favorable histologic properties suggest that the bifurcation may be appropriate for coronary revascularization in selected cases. ITA, Internal thoracic artery; LMS, least mean square; MP, musculophrenic; NE, norepinephrine; SE, superior epigastric; SEM, standard error of the mean; EC_{50} , effective concentration that induces 50% of the maximal contraction force.

DISCUSSION

The anatomy, flow rate, active response, and microstructure of the distal ITA and its subdivisions were investigated to test their applicability as possible conduits in CABG surgeries.

Current studies advocate the use of a second arterial graft and total arterial revascularization. A recently published large multicenter study on 3774 patients found that total arterial revascularization is associated with improved long-term survival compared with the use of a single arterial and saphenous vein (SV) graft.¹⁸ Moss and colleagues¹⁹ found that the “no aortic touch” technique (by using in situ internal thoracic arteries) had the lowest risk for postoperative stroke in 12,000 patients who underwent primary isolated CABG. Harvesting the subdivisions yields a significant extra length of approximately 2 cm, which can potentially increase the number of distal anastomoses. Arterial revascularization is feasible using in situ separate origin single or bilateral ITA³ in different configurations still enabling the

use of ITA midportion to the left anterior descending. Bakay and colleagues²⁰ have monitored 102 patients with 3-vessel coronary artery disease who underwent arterial myocardial revascularization using bilateral in situ ITA grafts. In their study, ITAs were transected distal to their bifurcation to provide extra length and increase ITA accessibility. A single post-bifurcation branch (SE or MP) with higher free flow and larger diameter was used. The circumflex and distal right coronary artery were revascularized sequentially with the left ITA, and the left anterior descending was grafted with the right ITA. Patients were monitored for a mean period of 3 years, and 75% of them underwent postoperative coronary imaging. The overall patency rates were 97%, and no cardiac deaths occurred during follow-up.

Free flow rate is one of the parameters used by surgeons to decide on graft quality. We found a decrease in free flow rate between the ITA and its subdivisions. Nevertheless, mean free flow rates in the skeletonized subdivisions are approximately 100 mL/min, and therefore are theoretically

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TABLE 2. Maximal contraction and effective concentration that induces 50% of the maximal contraction force to norepinephrine in different studies

	Artery	Sample size	Normalized contraction $\pm$ SEM (g/mm)	$EC_{50} \pm$ SEM ($-\log M$)
Our study	ITA	41	0.56 ± 0.05	6.44 ± 0.09
	SE	47	0.92 ± 0.07	6.08 ± 0.09
	MP	34	1.02 ± 0.1	6.22 ± 0.12
He et al ⁵	ITA	7	0.54 ± 0.1	6.3 ± 0.2
	BIF	8	0.82 ± 0.06	5.78 ± 0.13
He et al ⁶	Proximal ITA	6	0.29 ± 0.08	6.25 ± 0.27
	Mid-ITA	8	0.25 ± 0.07	6.19 ± 0.17
	Distal ITA	7	0.73 ± 0.11	5.91 ± 0.16
He ⁴	ITA	26	0.6 ± 0.1	6.42 ± 0.1
Dignan et al ¹⁷	Male ITA	18	—	6.98 ± 0.2
	Female ITA	8	—	7.2 ± 0.02

EC_{50} , Effective concentration that induces 50% of the maximal contraction force; ITA, internal thoracic artery; MP, musculophrenic; SE, superior epigastric artery; SEM, standard error of the mean; BIF, bifurcation.

capable of supplying any coronary artery, with no risk for hypoperfusion. Our institute uses skeletonization as the sole method for ITA separation. Various studies have demonstrated that skeletonized ITAs have significantly higher free flow capacity than pedicled grafts.²¹ Similar results were obtained using transit-time flowmeter and noninvasive transthoracic Doppler ultrasound.^{22,23} Direct application of papaverine on the skeletonized ITA and subdivisions, denuded from the perivascular tissue, may further increase the flow rates.

Analysis of the various reactivity profiles along the full length of the ITA showed that the distal section is the most reactive part of the graft.^{4,5} However, although the middle and proximal sections are less reactive to some vasoconstrictors, it is not a passive conduit.⁶ We found significantly greater contractility to NE in the subdivisions compared with the distal ITA. However, no statistically significant difference was found in the sensitivity to NE (represented by EC_{50}).

There are contradictory reports regarding the influence of different cardiovascular risk factors on ITA reactivity.^{24,25} Dignan and colleagues¹⁷ investigated the influence of age and gender on ITA reactivity. In their study, ITAs from female and male had equal strength of contraction to NE, and there was no correlation between age and arterial reactivity. We did not find a correlation among the different cardiovascular risk factors or gender to NE-induced contraction. However, careful consideration is warranted in female patients because ITA length and free flow are significantly lower. Moreover, we found that contractility to NE tends to decrease with age. A possible explanation to this observation may originate from increased arterial stiffness, as demonstrated in studies on the aorta and other big arterial vessels starting from the seventh decade of life.²⁶

Arteries from patients treated with beta-adrenergic blockers were significantly less reactive to NE. The post-junctional adrenoreceptors in the ITA are predominantly of the alpha-1 subtype.²⁷ Therefore, we expect that treatment with beta-blockers would not significantly alter the arterial reactivity and might even increase the alpha-1 adrenergic effect. A possible explanation for decreased contractility in patients treated with beta-blockers is the up-regulation of beta 2 receptors that induce arterial vasodilatation. Nevertheless, He and colleagues²⁸ found only moderate arterial relaxation in response to isoproterenol (beta 1 and 2 adrenergic agonist) and concluded that beta-adrenoreceptors would contribute little to the reactivity of the human ITA graft to sympathomimetic drugs. Brodde and colleagues²⁹ demonstrated the subtype-selective up-regulation of beta-2 adrenergic receptors in the heart muscle and the SV by chronic beta-adrenoreceptor antagonist treatment. However, Ferro and colleagues³⁰ did not find a change in beta-1 or beta-2 reactions, or the alpha-1 adrenergic reaction in ITA and SV segments from patients chronically treated with beta-blockers.

Some reports indicate that calcium channel blockers may inhibit the effect of various vasoconstrictors on ITA reactivity.^{31,32} Treatment with calcium channel blockers did not alter ITA, SE, and MP response to NE in our patient cohort. A recently published small sample ($n = 22$) in vitro study by Dalakoglu and colleagues³³ suggested that preoperative treatment with ACE inhibitors and statins for more than a 6-month period may influence ITA vaso-reactivity by improving endothelial control of vascular tone. Use of statins, ACE inhibitors, ARBs, and nitrates proved nonsignificant in our study.

NE is a potent vasoconstrictor that participates in perioperative endogenous physiologic processes and is a common vasopressor used in the early postoperative period. However, the previous suggestions cautioning the use of the bifurcation are based on the higher contractile response to various vasoconstrictors. Other possible spasmogenic agents are endothelin-1, thromboxane A2, prostaglandin F2 α , 5-HT, angiotensin II vasopressin, and potassium chloride.⁴⁻⁶ Therefore, the present study is limited by the fact that only 1 vasoconstrictor was investigated.

Ninety percent of arterial segments in our study demonstrated some degree of intimal thickening. In most cases, there was only mild hyperplastic thickening with no significant narrowing of the arterial lumen and no hemodynamic significance. We did not find advanced atherosclerotic lesions, fatty streaks, or foam cells in the intimal hyperplastic areas. There was no difference in the degree of intimal hyperplasia between the pre- and post-bifurcation segments, and no correlation between the cardiovascular risk factors and the degree of intimal hyperplasia.

Our findings are in line with several qualitative^{9,10} and quantitative¹¹ studies. Nataf and colleagues³⁴ studied the

morphometric and metabolic profile of the distal ITA segments and also found intimal proliferative changes. Although there was no histologic evidence of atherosclerotic plaque, the enzyme–histochemical profile of this intimal thickening was favorable to cell proliferation and lipid accumulation. Similar to our study, no correlation was found between cardiovascular risk factors and the degree of intimal thickening.

Microscopic observations on ITAs harvested from patients who died of noncardiac causes suggest that the media layer composition changes in the different ITA segments.⁸ The middle part of the artery is rich with elastic fibers, whereas the proximal and distal segments are elastomuscular. The amount of elastic fibers decreases distally, whereas the muscle content increases. Our study did not demonstrate differences in muscle content among ITA, SE, and MP using quantitative analysis. Moreover, no correlation was found between the muscle content and the contraction force.

Of note, the intimal hyperplastic cells stained positive for SMA-A pathognomonic sign of smooth muscle (Figure 2, H). Most of the cells that compose the healthy media layer are smooth muscle cells with contractile properties. Damage to the arterial wall that comprises the integrity of the internal elastic lamina enables penetration of proliferating smooth muscle cells from the media into the intima. These cells lose their contractile myofilament structure, continue to proliferate, and secrete extracellular matrix.⁸ Smooth muscle cell migration and neointimal proliferation may be precursors for accelerated graft atherosclerosis.³⁵ Further studies are warranted to better understand the characteristics and influence of these intimal hyperplastic changes.

CONCLUSIONS

Our results confirm the previously published data on the higher contractility in ITA subdivisions, suggesting caution in the use of the bifurcation for revascularization. However, the extra length gained by harvesting the subdivisions (increasing arterial anastomoses options and use of in situ grafts), sufficient mean flow rates, and favorable histologic properties suggest that they may be appropriate for coronary revascularization in selected cases. Prospective clinical studies with long-term clinical and angiographic follow-up are warranted to investigate the long-term patency rates, freedom from disease, and influence on survival.

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EDITORIAL COMMENTARY

Cautions on use of distal internal thoracic artery and its bifurcations

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See related article on pages 1042-50.

The reactivity, particularly the pharmacologic reactivity, of the internal thoracic artery (ITA) at the distal end, including its bifurcations, is an important clinical issue. This is due to the fact that ITA grafting often requires enough length to graft onto the distal left anterior descending artery (LAD). On the other hand, the distal section of the ITA (approximately 3 cm proximal to the bifurcation) is more pharmacologically

FIGURE 1. The contractility of the internal thoracic artery (IMA) is higher at the distal section and bifurcation. At the distal section, the contractility is inversely correlated to the diameter. Reproduced with permission.¹

responsive to vasoconstrictor agents than is its midsection. With the knowledge that ITA spasm happens sometimes at this section, I designed a study¹ that demonstrated that the contractility of the distal section of the ITA is inversely correlated to the diameter; that is, the smaller the diameter, the greater the tendency for spasm to develop (Figure 1).

Further, under certain circumstances, such as when both the LAD and the diagonal branch require grafts, the distal bifurcation of the ITA is used for Y grafting.^{2,3} Despite the convenient use of this part of the ITA, an early report

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