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 a 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% O_2 + 5% CO_2. 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 (×4, ×10, ×20, and ×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 thickening[11]: (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 ×20 magnification was calculated (muscle/extracellular matrix × 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 categoric 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

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