The Physiologic and Histologic Properties of the Distal Internal Thoracic Artery and Its Sub-Divisions

Sahar Gideon[1*] MD, Shavit Reut[2,3,&,*] MD, Yosibash Zohar[4] DSc, Novack Lena[5] PhD, Matsa Menachem[1] MD, Medalion Benjamin[2] MD, Hochhauser Edith[3] PhD, Aravot Dan MD[2].

1-Department of cardiothoracic surgery, Soroka university medical center, Beer-Sheva, Israel

2-Department of cardiothoracic surgery, Rabin medical center, Petach-Tikva, Israel

3-Cardiac research laboratory, Felsenstein medical research center, Tel Aviv University, Israel

4-Computational mechanics laboratory, Ben Gurion University of the Negev, Beer-Sheva, Israel

5- Department of public health, Faculty of health sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

*Authors equally contributed

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Corresponding author: Dr. Reut Shavit, Department of Cardiothoracic Surgery, Rabin Medical Center-Beilinson Campus, Petach-Tikva, ISRAEL 49100 tel +972-3-9376701 fax +972-3-9240762

E. mail: reut.shavit@gmail.com

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Abstract

Objective: We compared the flow rates, reactivity and morphology of the distal Internal Thoracic Artery (ITA) and its branches, the Superior Epigastric (SE) and Musculophrenic (MP) arteries to test their applicability as possible conduits in coronary artery bypass grafting (CABG) surgeries.

Methods: Skeletonized ITA and sub-divisions of patients undergoing CABG were studied intraoperatively (n=100) for flow and length measurements and *in vitro* in organ baths (n=58) for active response to Norepinephrine (NE). Quantitative microscopic analysis of the muscle density and the degree of intimal hyperplasia was performed. Results were analyzed according to age, gender, risk factors and medications.

Results: ITA subdivisions contributed an average extra length of 2 cm. Free flow rates were 129±45, 114±41 and 93±36 ml/min in ITA, SE and MP, respectively. Sternum and ITA length and free flow rates were significantly lower in women. The sub-divisions were significantly more reactive to NE than the distal ITA (p~0.005), though sensitivity to NE was similar. Patients treated with β-blockers had significantly decreased reactivity (p=0.009). Microscopic analysis suggests similar muscle content in ITA and sub-divisions. Eccentric (28%) and concentric (62%) intimal hyperplasia was 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 ITA and its subdivisions, and there was no correlation to risk factors.

Conclusion: Our results confirm the previous studies on the higher contractility in ITA sub-divisions, suggesting caution in the use of the bifurcation for revascularization. However, the extra length, sufficient flow, and favorable histological properties suggest that the bifurcation may be appropriate for coronary revascularization in selected cases.

Ultramini abstract:

This paper investigates the distal ITA and its branches in order to assess whether or not they may be employed for distal coronary anastomoses. We found greater maximal contraction to Norepinephrine yet satisfactory free flow rates and similar degree of muscle density and intimal hyperplasia between the compared arteries.

1. Introduction

The internal thoracic artery (ITA) is the conduit of choice in coronary artery bypass grafting (CABG) surgeries due to its well established superior long term patency, survival benefit and freedom from re-interventions [1-3]. The ITA divides at the level of the sixth intercostal space into the superior epigastric (SE) and the musculophrenic (MP) arteries. The need for extra length for use in different graft configurations, combined with recent skeletonization techniques for ITA harvesting impose the question of the applicability of ITA's sub-divisions as possible conduits. Most surgeons avoid using these vessels based on 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 sub-divisions. The influence of patient's risk factors and medications on these parameters is discussed.

2. 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 two *in vivo* and *in vitro* phases of the study. The experimental protocol was approved by the hospital human ethics committee.

Anatomy and Flow rate:

The first phase included 100 patients for which: 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 inhibitors (ACEI's), Angiotensin Receptor Blockers (ARB's) , 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 sub-division to the total length.

The artery was then soaked in diluted Papaverine solution. Free flow measurements (ml/sec) from each sub-division and the distal ITA were recorded immediately prior to the anastomosis. All measurements were taken at a mean systemic blood pressure of 70mmHg.

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 was immediately stored in a physiologic 4°C Krebs-Henselite (KH) solution [13]. Specimens from the distal ITA and each of its subdivisions were cut into 3mm-long rings using a double bladed knife. Any discarded tissue was kept in a 4% formaldehyde solution for later histological processing.

Ring test protocol [12-13]:

Each 3mm-long vascular ring segment was suspended between two stainless steel 0.4mm wires: the upper being attached to a load cell, whereas the lower was fixed to a micrometer (see Fig.1A).

The rings were placed into an organ bath chamber filled with 20ml of KH 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 (see Fig.1B-C). The wires were moved apart in steps every minute while the force (F [gr]) and the displacement (l [mm]) were recorded. F and l were input online in a computer program (Mathlab 7.0) to determine the theoretical lumen circumference that would have corresponded to a transmural pressure of 100mmHg. 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} M) were added to the organ bath, in 0.5log increments to create a dose-response curve (see Fig. 1).

Since the arteries were of different diameters we normalized the contraction response by the circumference at an equivalent internal pressure of 100mmHg, i.e., $E=f_A/L_{100}$ with units of grmf/mm,

where f_A is the recorded force at a given concentration level A of NE, and L_{100} is the estimated circumference of the lumen at internal pressure of 100mmHg. The maximal normalized contraction denoted by M (grmf/mm) was obtained at a concentration of 10^{-4} M 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

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

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

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

Having for each artery the values of log A and $\log\left(\frac{E}{M-E}\right)$, 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 (H&E), elastic fibers, and smooth muscle actin (SMA) immunuhistochemical stain. Each slice was photographed at four magnifications (X4, X10, X20 and X40), and analyzed by a color image analyzing system (Image Pro plus 5.1).

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 (IMR) - width of the intima at maximal intimal thickness/width of the media at maximal intima thickness, (3) luminal narrowing (%) according to the formula: $(\mathrm{IEL})^2/4\pi$, where IEL is the circumference of the internal elastic lamina (Fig. 2A-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 eight identical rectangles at angles: 0, 45. 90, 135. 180, 225 and 270 degrees at X20 magnification was calculated (muscle/ECM*100)-See Fig. 2C-D.

Data analysis:

All data were statistically analyzed by the STATA 8 program [15]. Comparisons were conducted using the student's t-test and Mann-Whitney test for continuous variables, χ^2 and Fisher exact tests for categorical variables and non-parametric 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 due to the high correlation assumed between observations belonging to the same patient. The pathological and physiological results were compared using analysis of variance (ANOVA). A 95% confidence interval level was set for all tests, with a p-value<0.05 considered significant.

3. Results

Patient's 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±1.88cm. Harvesting of the sub-division yielded significant extra length of 2.33±0.63cm, and 1.73±0.53 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 to the skeletonized ITA (p<0.01). ITA length in females was significantly smaller (p<0.0001).

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<0.0001 and p=0.02, respectively).

Average free flow rate in the left ITA was 126±44.43 ml/min and in the right 130.30±50.79 ml/min (p=0.43). A flow reduction of 24.09±20.67 ml/min between the ITA and its sub-divisions was observed (p<0.0001). Females had significantly lower flow rates in ITA and sub-divisions (p=0.0047). Predictors of a lower free flow in the linear regression model were female gender (p=0.01) and older age (p=0.02). None of the cardiovascular risk factors had a significant effect on the free flow rates (See figure 3A-D).

Physiology

Arterial segments (n=122) were collected from 58 patients (See table 1).

L_{100} was 4.99±1.77, 3.93±1.59 and 3.62±1.31 mm in ITA, SE and MP, respectively.

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

We conclude that the maximal contraction in response to NE is significantly higher in the sub-divisions, compared with the ITA (p~0.005). No statistically significant difference exists between SE and MP (p~0.283). Our results are in line with previous published data (see table 2). Though 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=0.095).

There was no statistically significant connection between the patient's risk factors and the normalized contraction, even after adjustment for medications and age. Additionally, 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=0.009). Alpha adrenergic blockers had the same effect (p=0.08), yet after adjusting to age was not statistically significant (p=0.1). The average age of patients treated with alpha blockers was 73.8±2.5, compared with 66.9±1.6 in patients not treated by alpha blockers (p=0.064).

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 two typical morphologies: in 72% the morphology was concentric, and in 28% the morphology was eccentric (see Fig.2E-F)

Three parameters: ITI, IMR and percent of luminal narrowing [11] 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; Intimal to medial ratio was 0.4±0.45, 0.37±0.46, 0.25±0.18 and the percent of luminal narrowing was 12.19±6.76, 15.65±14.76, 13.63±8.74 for ITA, SE and MP, respectively. There was no statistically significant difference in the level of intimal thickening between 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 (see Fig. 2G-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 few specimens (see Fig. 2I-J).

Fifty three arterial segments were immunohistochemically stained for SMA and analyzed for muscle content. Mean muscle density was 75.06±9.66%, 75.42±11.93 and 78.18±12.15 for ITA, SE and MP, respectively. There were no statistically significant differences in muscle content between ITA and SE ($p=0.69$) or MP ($p=0.43$). There was no statistically significant connection between the medial muscle density and the maximal contraction force to NE ($p=0.86$). Analysis for the normalized contraction was borderline ($p=0.09$).

4. Discussion

The anatomy, flow rate, active response and microstructure of the distal ITA and its sub-divisions 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 single arterial and SV graft [17]. Moss et al found that "no aortic touch" technique (by using in situ internal thoracic arteries) had the lowest risk for postoperative stroke among 12000 patients that underwent primary isolated CABG [18]. Harvesting the sub-divisions yields a significant extra length of approximately two centimeters, which can potentially increase the number of distal anastomoses. Arterial revascularization is feasible using in situ separate origin single or bilateral ITA [3] in different configurations still enabling the use of ITA midportion to the LAD. Bakay et al [19] have monitored 102 patients with 3-vessel coronary arteries disease that underwent arterial myocardial revascularization using bilateral in situ ITA grafts. In their study, ITA's were transected distal to their bifurcation to provide extra length and increase ITA accessibility. A single post-bifurcation branch (either SE or MP) with higher free flow and larger diameter was used. The circumflex and distal right coronary artery were revascularized sequentially with left ITA and the LAD was grafted with the right ITA. Patients were monitored for a mean period of 3 years and 75% of them underwent post-operative 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 sub-divisions. Nevertheless, mean free flow rates in the skeletonized subdivisions are approximately 100ml/min, and therefore are theoretically 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 [20]. Similar results were obtained using transit-time flowmeter and non-invasive transthoracic doppler ultrasound [21-22]. Direct application of papaverine on the skeletonized ITA and sub-divisions, 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 sub-divisions compared with the distal ITA. However, no statistically significant difference was found in the sensitivity to NE (represented by EC_{50}).

There are contradictive reports regarding the influence of different cardiovascular risk factors on ITA reactivity [23-24]. Dignan et al [25] investigated the influence of age and gender on ITA reactivity. In their study, ITA 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 between the different cardiovascular risk factors or gender to NE induced contraction. However, a careful consideration is warranted in females as ITA length and free flow are significantly lower. Moreover, we found that contractility to NE tends to decline 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 postjunctional 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 et al. [28] 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 et al. [29] demonstrated the subtype-selective up-regulation of beta-2 adrenergic receptors in the heart muscle and the Saphenous Vein (SV) by chronic beta-adrenoreceptor antagonist treatment. However, Ferro et al. [30] did not find change in beta-1 or beta-

2 reactions, nor 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 Dalaklioglu et al [33] suggested that pre-operative treatment with ACEI and statins for more than a 6-month period may influence ITA vasoreactivity by improving endothelial control of vascular tone. Use of Statins, ACEI's, as well as ARB's and nitrates proved non-significant in our study.

Norepinephrine is a potent vasoconstrictor that participates in peri-operative endogenic physiologic processes and is a common vasopressor used in the early post-operative period. However, the previous suggestions cautioning the use of the bifurcation are based on the higher contractile response to various vasoconstrictors. Other possible spasmogenic agent are endothelin-1, Thromboxane A2, Prostaglandin F2α, 5-HT, angiotensin II vasopressin and Potassium Chloride [4-6]. Therefore the present study is limited by the fact that only one 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 quantitative [11] studies. Nataf et al [34] studied the morphometric and metabolic profile of the distal ITA segments and also found intimal proliferative changes. Although there was no histological evidence of atherosclerotic plaque, the enzyme-histochemical profile of this intimal thickening was favorable to cell proliferation and lipid accumulation.

Similarly to our study, no correlation was found between cardiovascular risk factors and the degree of intimal thickening.

Microscopic observations on ITAs harvested from patients that died from non-cardiac 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, while the proximal and distal segments are elasto-muscular. The amount of elastic fibers decreases distally, while the muscle content increases. Our study did not demonstrate differences in muscle content between ITA, SE and MP using quantitative analysis. Moreover, no correlation was found between the muscle content and the contraction force.

Interestingly, the intimal hyperplastic cells stained positive for smooth muscle actin-a pathognomonic sign of smooth muscle (see Fig. 2H). 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 cells migration and neo-intimal 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.

5. Conclusions

Our results confirm the previously published data on the higher contractility in ITA sub-divisions, suggesting caution in the use of the bifurcation for revascularization. However, the extra length gained by harvesting the sub-divisions (increasing arterial anastomoses options and use of in situ grafts), sufficient mean flow rates and favorable histological 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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Table 1-Patients Demographics and Risk Factors Distribution

Parameter	In Vivo *n=100*	In vitro *n=58*	Total *n=158*	*p-value*
Age (years) Mean±SD	66.0±11.4	67.5±10.3	66.6±11.0	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%	0.46
Peripheral vascular disease	20.0%	26.8%	22.4%	0.42
Smoking	37.0%	44.8%	39.9%	0.87

Table 2-Maximal contraction and EC_{50} to NE in Different Studies

	Artery	Sample size	Normalized contraction ± SEM [gr/mm]	EC50± 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]	Prox ITA	6	0.29±0.08	6.25±0.27
	mid ITA	8	0.25±0.07	6.19±0.17
	dist ITA	7	0.73±0.11	5.91±0.16
He et al [4]	ITA	26	0.6±0.1	6.42±0.1
Dignan et al [25]	male ITA	18	-----	6.98±0.2
	female ITA	8	-----	7.2±0.02

ITA-internal Thoracic Artery, SE-Superior Epigastric artery, MP-Musculophrenic artery, SEM-Standard Error of the Mean, EC_{50}-Effective concentration that induces 50% of the maximal contraction force, NE-Norepinephrine

400

Figures legend:

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

Fig. 2: Histopathological Analysis. A+B-measurement of intimal hyperplasia indices, H&E X4. A-Intimal thickness index, B-Intimal to medial ratio. C-D: Quantitative analysis of muscle content in the media. C-SE, SMA stain, X4. D- Same specimen at X20 magnification. Red-muscle, Yellow-ECM. E+F: Typical morphologies of intimal hyperplasia, H&E stain, X4 magnification. E-SE artery showing significant intimal thickening with narrowing of the arterial lumen. F-MP artery showing concentric intimal hyperplasia. G+H: Positive SMA stain in the intimal hyperplastic areas. G-ITA, H&E stain, X10 Arrow-The internal elastic lamina. H-Same specimen SMA stain, X20. I+J: Elastic fibers stain. I-MP, X10. Arrow-internal and external elastic laminae. J-SE, X10. Defects and doubling areas in the internal elastic lamina are observed.

Fig. 3: Anatomy and flow. A-Contribution of sub-divisions to ITA length. B-Comparison of length parameters between genders. C-Free flow in ITA and sub-divisions. D-Comparison of free flow rates between genders.

Fig. 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 (LMS) estimate of *1/p* and EC_{50} (three curves), and the experimental results (bars). B-Contraction and sensitivity to NE in different arterial segments determined by LMS from experiments. The higher contractility in ITA sub-divisions, suggesting caution in the use of the bifurcation for revascularization, is demonstrated. However, the extra

length, sufficient flow, and favorable histological properties suggest that the bifurcation may be appropriate for coronary revascularization in selected cases.

Abbreviated Legend for the Central Picture- The higher contractility in ITA sub-divisions, suggesting caution in the use of the bifurcation for revascularization, is demonstrated. However, the extra length, sufficient flow, and favorable histological properties suggest that the bifurcation may be appropriate for coronary revascularization in selected cases.

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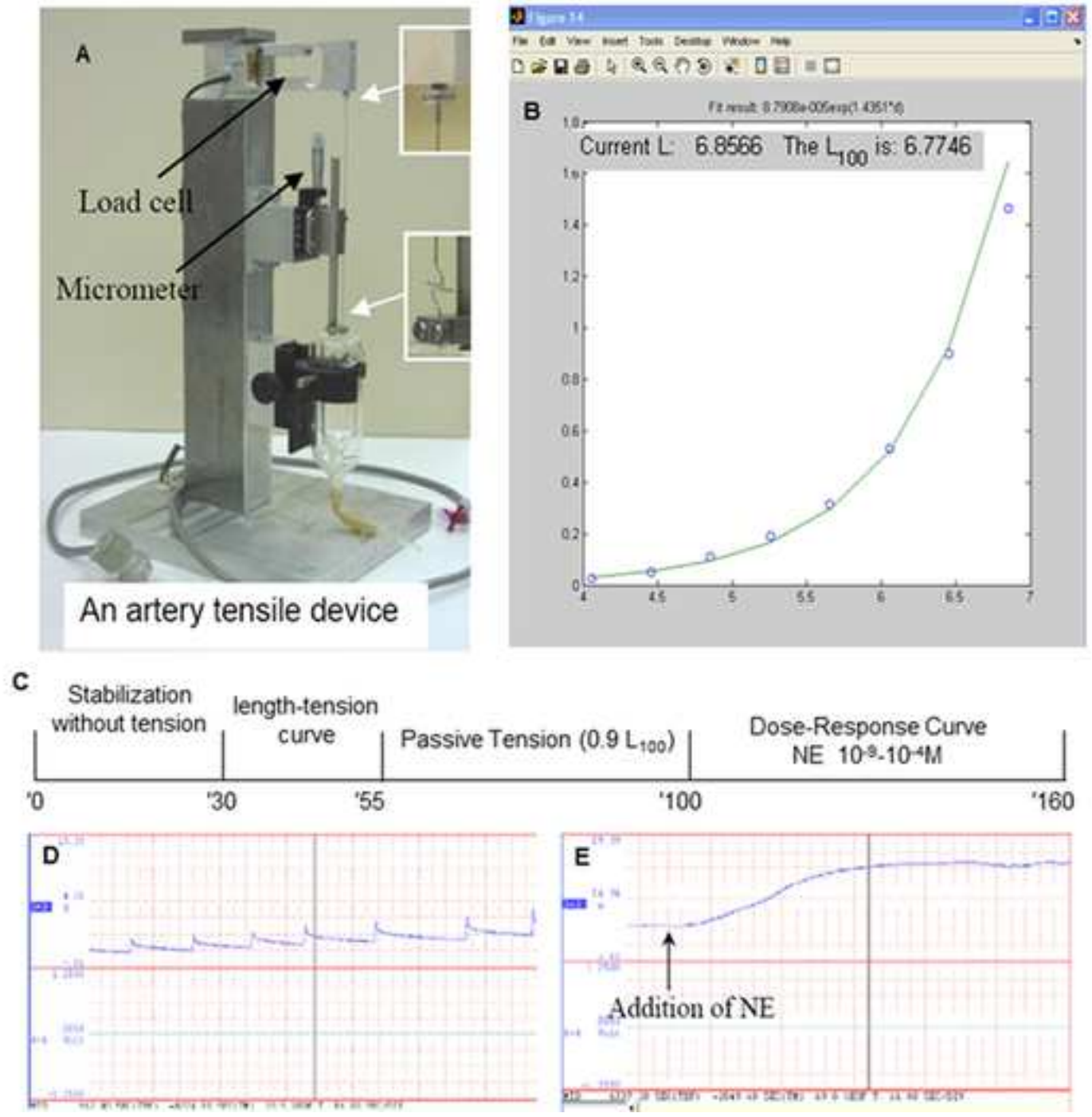
Fig 1



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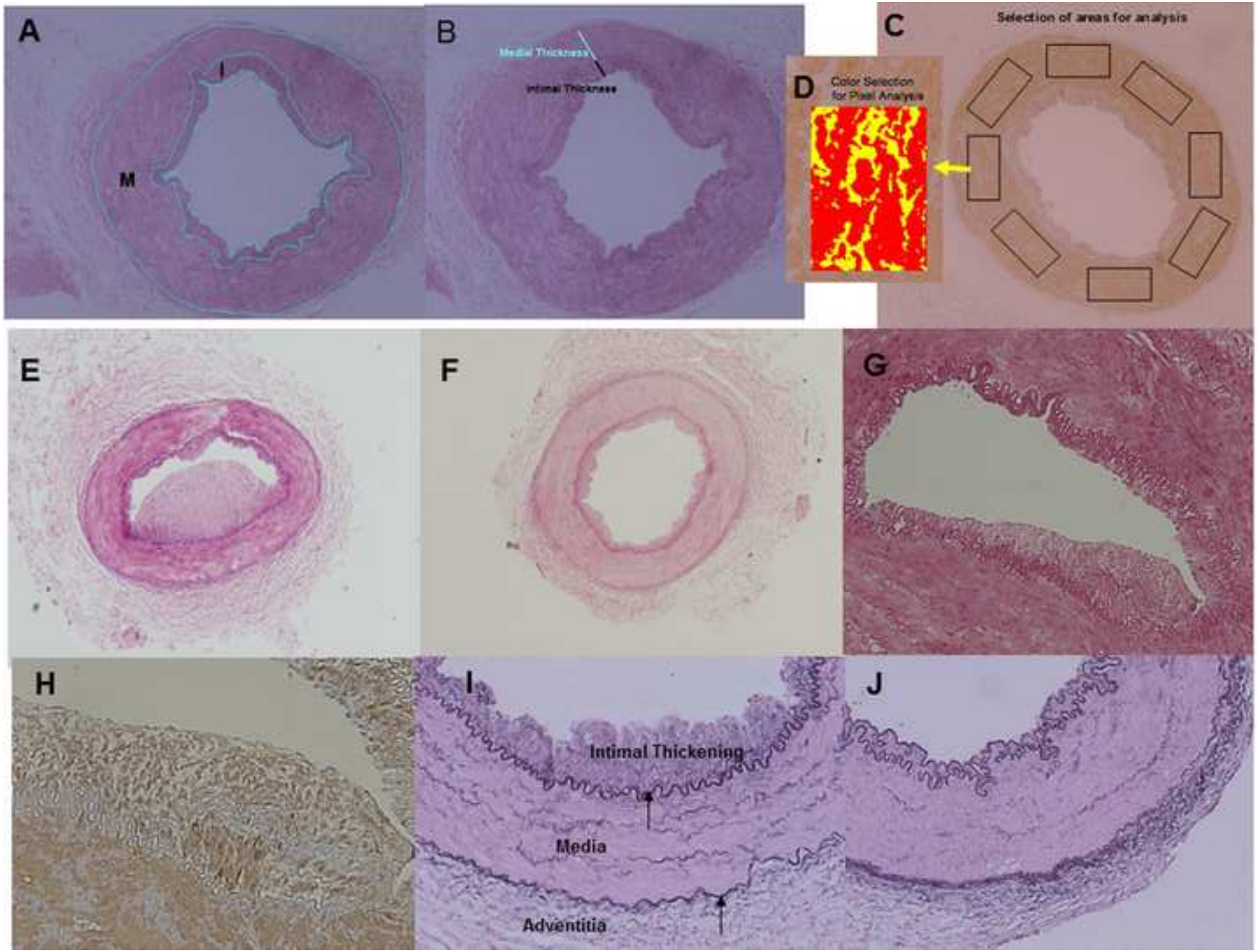

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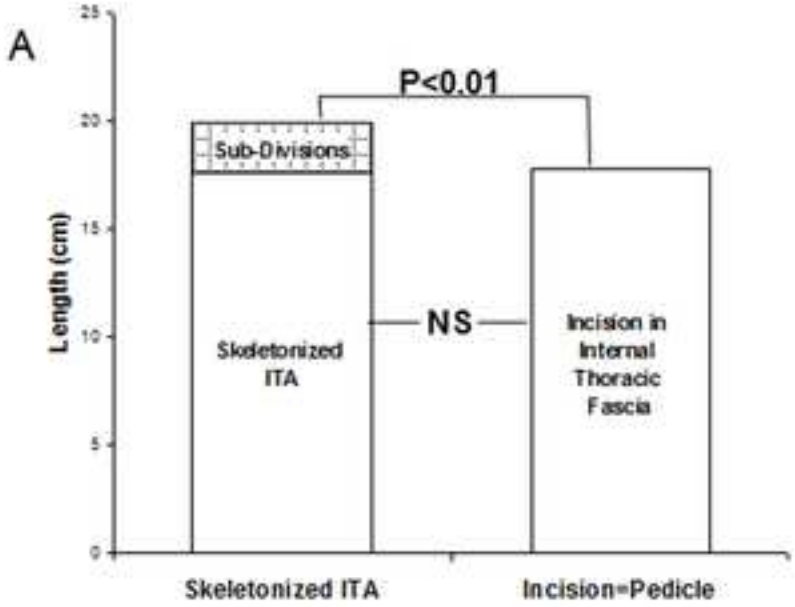

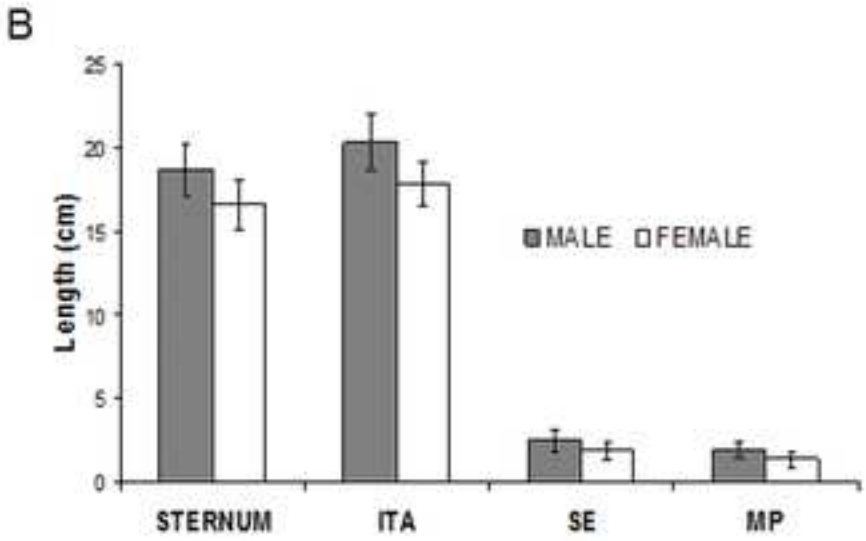

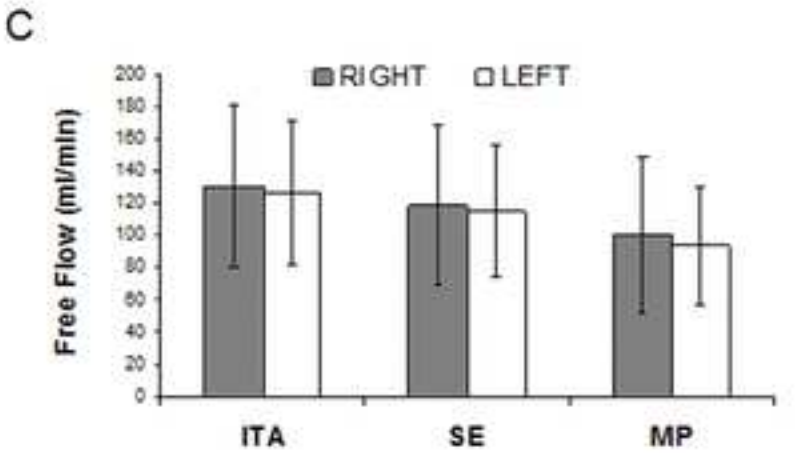

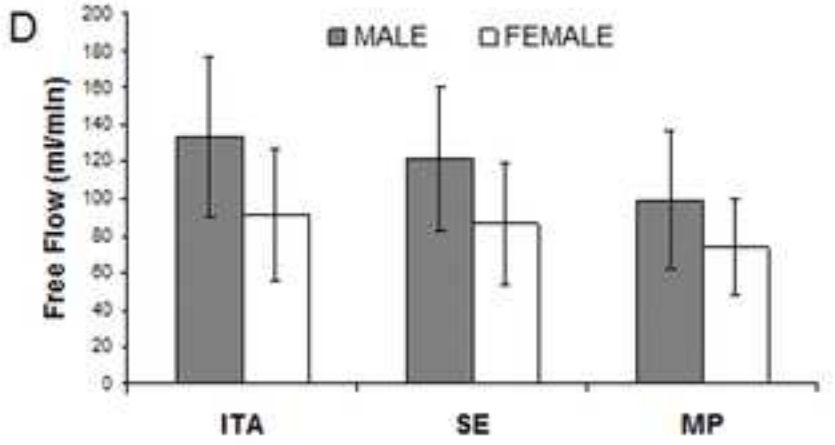

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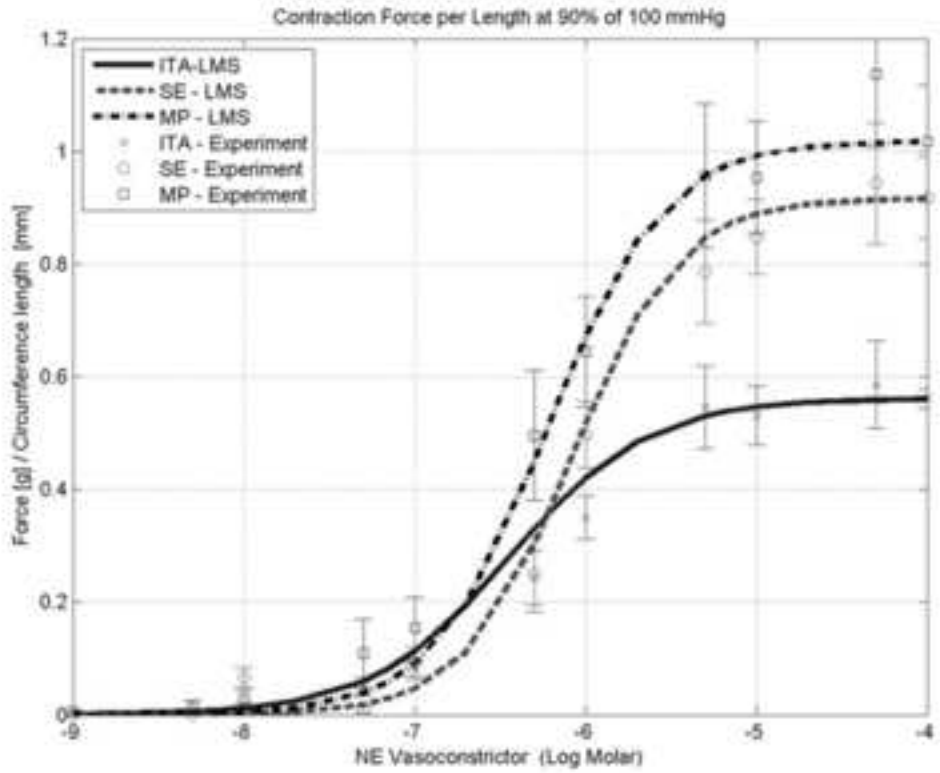
A



B

Artery	Log(EC_{50})± SEM	1/p±SEM	M (grf/mm)±SEM	R^2	No. of clusters
ITA	-6.44±0.09	0.93±0.07	0.56±0.05	0.67	39
SE	-6.08±0.09	0.72±0.05	0.92±0.07	0.64	42
MP	-6.22±0.12	0.77±0.05	1.02±0.1	0.62	29

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