

# Remodeling of the right internal thoracic artery: new method of analysis using the coronary area grafted

## *Remodelamento da artéria torácica interna direita: novo método de análise pela área coronariana revascularizada*

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### *Abstract*

**Objective:** To analyze angiographic factors related to remodeling of the right internal thoracic artery (RITA) remodeling using a new quantitative technique of the target coronary grafting area.

**Method:** In the period from January 1992 to 2002, 452 consecutive patients were submitted to coronary artery bypass grafting (CABG) with the RITA "in situ" through the transverse sinus. In this sample, 32 patients were submitted to at least one postoperative coronarography study after receiving RITA grafts. The studies were analyzed by CASS II® software. The angiographic criteria assessed were the proximal and distal diameters of the RITA, coronary area irrigated by the target vessel, TIMI flow score, quantitative coronary angiography (QCA), dominant flow grade and the existence of patent lateral branches of the RITA.

**Results:** The mean follow-up period was 42 months, ranging from 6 to 204 months. The mean proximal diameter

of the RITA was  $2.639 \pm 0.09$  mm and the distal diameter was  $2.159 \pm 0.1$  mm ( $p < 0.001$ ). The coronary area irrigated by the target marginal branch presented a  $\beta$  coefficient of 0.424 ( $p=0.001$ ) and diameter of the stenosis (QCA) of the marginal branch gave a  $\beta$  coefficient of 0.55 ( $p=0.001$ ) adjusted by weight, height, time surgery/study, TIMI flow score, angina functional class and systemic hypertension. Multiple regression modeling demonstrated an adjusted  $R^2$  of 0.696 ( $p<0.0001$ ).

**Conclusion:** This study, using angiographic evaluation, demonstrated that the grafted coronary area and proximal diameter (QCA) of the marginal branch stenosis were independent factors in RITA remodeling in the postoperative period of CABG.

**Descriptors:** Internal mammary-coronary artery anastomosis. Heart catheterization. Image processing, computer-assisted.

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### Resumo

**Objetivo:** Avaliar os fatores angiográficos no remodelamento da artéria torácica interna (ATI) direita por novo método quantitativo com a área coronariana revascularizada.

**Método:** No período entre janeiro de 1992 e 2002, 452 pacientes foram submetidos à revascularização do miocárdio (RM) com ATI bilateral. Desta amostra, 32 pacientes com ponte de ATI direita “in situ” pelo seio transverso foram reestudados por meio de cineangiocoronariografia (CATE). Os filmes foram analisados na plataforma CASS II®. Quanto aos critérios angiográficos, foram medidos os diâmetros proximal e distal das ATIs, área coronariana da artéria revascularizada, pontuação pela escala de fluxo de TIMI, diâmetro de estenose proximal, dominância de fluxo e presença de ramos acessórios patentés.

**Resultados:** O período médio de acompanhamento foi de

42 meses, variando de 6 a 204 meses. As medidas da ATID proximal foram de  $2,639 \text{ mm} \pm 0,09$  e distal de  $2,159 \text{ mm} \pm 0,1$  ( $p < 0,001$ ). A variável área coronariana correspondente à artéria marginal apresentou um coeficiente de  $\beta$  de 0,424 ( $p < 0,001$ ) e o diâmetro de estenose da marginal um coeficiente de  $\beta$  de 0,55 ( $p < 0,0001$ ) ajustados por peso, altura, intervalo cirurgia/CATE, escala de fluxo de TIMI “flow”, classificação de angina e Hipertensão Arterial Sistêmica (HAS), com  $R^2$  ajustado de 0,696 ( $p < 0,0001$ ).

**Conclusão:** Na amostra estudada, por critérios angiográficos quantitativos, a área coronariana revascularizada e o diâmetro de estenose proximal apresentaram-se como fatores independentes no remodelamento da ATID, no pós-operatório de RM.

**Descritores:** Anastomose mamário-coronária. Cateterismo cardíaco. Processamento de imagem assistida por computador.

## INTRODUCTION

In 1984, Puig et al. [1,2] proposed the utilization of the right internal thoracic artery (RITA) *in situ* passing through the transverse sinus for the revascularization of the circumflex branches. In other series of patients [3-7] alternative techniques were used and subsequently the patency was analyzed demonstrating morphological and functional adaptation of the grafts, a process denominated arterial remodeling.

Despite of the evidence of variations in the patency between the left and right internal thoracic arteries [3-5], the most commonly described casual factors as predictors of occlusion were: presence of native flow in the coronary bed, quality of the distal coronary bed, presence of large-diameter accessory branches leading to flow ‘steal’ [8-13], demographic and environmental characteristics (e.g. diabetes mellitus, dyslipidemia, smoking) [12,13], progression of the atherosclerotic disease as well as problems related to the surgical technique [14-17].

In principle, as was described by Gibbons et al. [18], vascular remodeling is a phenomenon present in systemic and coronary arteries responsible for a proportional increase in the caliber due to the atherosclerotic process. This is a physiopathological process of re-adaptation to flow. The vascular response to changes in flow, for example in a graft, modifies the modeling forces. Thus, the behavior of a graft in a situation of changes in flow modulates the vessel to chronically increase or decrease its diameter in order to adapt to the new conditions. Barner et al. [19] determined a positive correlation between the forces of transformation on the vessel wall, which is one of the main stimuli of positive arterial remodeling on radial artery and internal thoracic artery (ITA) grafts in the postoperative period of coronary artery bypass grafting (CABG).

Measurement of arterial remodeling is achieved through angiography assessing variations in luminal diameters and by the measurement of the blood flow through the graft. Hence, a vessel submitted to acute and chronic modifications of its flow pattern manages to adequately supply the high oxygen demands to the grafted bed (e.g. CABG) by means of remodeling its cyto-architecture to increase the flow of blood [20-22].

The availability of quantitative methods of angiographic evaluation might more precisely define the global and regional physiological repercussions between the graft interface and CABG. Previously validated quantitative angiographic criteria, such as the “TIMI” flow scale [23,24], percentage of the diameter of stenosis (QCA) [25] and flow dominance are remodeling evaluation tools of the RITA.

Using these previously validated angiographic criteria and with the new method of measuring the revascularized coronary area, the current study aims at evaluating the influence of each angiographic and clinical factor on the remodeling of the RITA.

## METHOD

### Patients

The study has a retrospective design based on coronary cineangiographic examinations made in the postoperative period of CABG performed after referral by physicians independent of this study protocol. The Scientific Commission and the Ethics Committee of InCor-HCFMUSP and the Ethics Commission for Research Project Analysis (CAPPesq) approved the project classifying it as risk-free. In a pilot study, the sample size with a  $\beta$  error of 0.2 and  $\alpha$  error of 0.05 was calculated at 30 patients.

### **Selection criteria**

#### **Inclusion criteria**

- 1 – Presence of patent RITA
- 2 – Absence of a lesion > 20% in the RITA or anastomoses
- 3 – The quality of the technique was sufficient for the analysis of the examination or for digitalization of the film
- 4 – If there were more than one examination for the same patient made at different times, which sufficiently satisfied the technical adaptation, the most recent study was used.

#### **Exclusion criteria**

- 1 – Inadequate technique for ‘a posteriori’ analysis of the film using the CASS II® or Osiris v. 11® computer systems
- 2 – Inadequate projections on the orthogonal plane for all the proposed angiographic measurements

#### **Technical standardization**

Analysis of the coronary cineangiography was achieved by two independent examiners. After the two examiners agreed on the possibility of manipulating the images, films from before 1995 were digitalized in the DICOM format. Subsequently they were analyzed by the CASS II® and Osiris v. 11® software. In respect to the angiographic criteria, the proximal and distal diameters of the ITAs, the coronary area revascularized by the graft, the score of the TIMI flow scale and the level of stenosis of the native bed were measured. Additionally, the flow dominance and the presence of accessory vessels before grafting were determined.

A Macintosh microcomputer with interface for the CASS II® platform was used for examinations directly from the internal network or after digitalization of images to TIF and DICOM formats from VHS, SVHS or 35 mm films. Calibration of the images was achieved by measuring the catheter tip without contrast. This calibration resulted in a ratio of number of pixels and the size of the catheter in millimeters. E.g. 7F Judkins-type catheter is 2.33 mm which hypothetically corresponds to 12 pixels under those conditions of penetration and depth of image. Thus, a measurement of 24 pixels would correspond to 4.66 mm. The measurements were performed on the best orthogonal plane. Delimitation of the area of interest was made by automatic demarcation. Correction of any distortions was achieved by manually overlaying the images.

#### **Angiographic criteria**

**Proximal and distal diameters:** An area of interest of between 15 and 20 mm was delimited 20 mm from the beginning of the ITA in the subclavian artery or branch and 20 mm proximal to the anastomosis between the ITA and the revascularized coronary artery. Analysis of the graph of the area was made with measurements of circular area, area of reference and diameter of reference. The diameter of

reference is the result of the mean diameter of the area of interest and corresponds to the proximal diameter.

**The revascularized coronary area:** is measured from the anastomosis between the ITA and the revascularized coronary artery, in the distal direction all the coronary surface and main branches were demarcated. In the case of retrograde flow to the anastomosis, the coronary surface was measured under the same conditions and the ratio between them considered. The measurement of the coronary area is expressed in square millimeters (Figure 1).

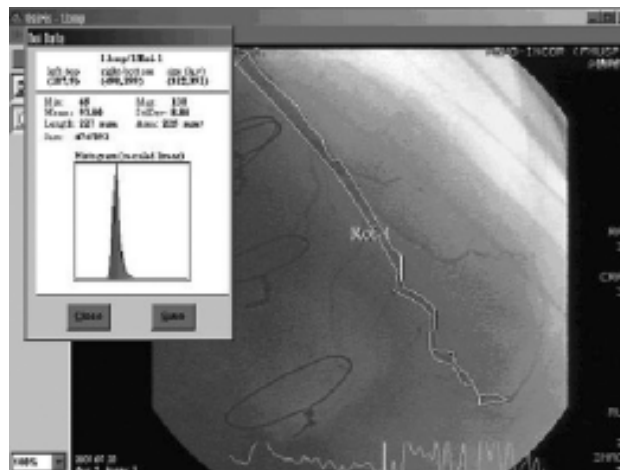


Fig 1 - Delimitation of the coronary area of the interventricular anterior branch, in histogram annex on the area of interest

**TIMI flow:** According to the criteria of TIMI, on a scale of 0 to 3, the flow through the distal coronary bed was scored and the highest number was considered, whether by injection to the native bed or by the ITA (TIMI 0 – without flow; TIMI 1 – flow without perfusion; TIMI 2 – slow flow and TIMI 3 – normal flow).

**Flow dominance:** The dominance of the flow by the revascularized coronary bed can be balanced, native bed dominant and dominant through the ITA (0 – native coronary bed; 1 – balanced; 2 – ITA graft dominant).

**Diameter of the stenosis of the revascularized coronary bed:** Using the QCA method, the site of stenosis in the revascularized coronary bed was delimited. Hence, the reference diameter results from the mean proximal and distal diameters of the atherosclerotic plaque. Measurement expressed as a percentage of stenosis (0-100%).

**Presence of ITA accessory branches:** Determination of patent accessory branches mainly corresponding to the costal-lateral, pericardio-phrantic and intercostal branches. A diameter greater than 1 mm was considered significant (0 – absent; 1 – present).

**Statistical analysis**

Statistical analysis was achieved in two phases. In the first phase, the variables were categorized in respect to the distribution frequency. The distal diameter of the ITA was considered as a dependent variable. The independent parameters were submitted to the Student t-test. Non-parametric variables were evaluated using the Spearman correlation, Chi squared and Mann-Whitney tests. In the second phase, variables which presented with a p-value < 0.01 were submitted to a multiple linear regression model. The level of statistical significance was set with a p-value < 0.05.

**RESULTS**

In the analyzed period, 452 patients submitted to CABG using both ITAs were identified. Of these, 32 patients with *in situ* RITA grafts through the transverse sinus were studied by coronary cineangiography. The mean follow-up time was 42 months ranging from 1 to 204 months, between the surgery and the angiographic re-evaluation.

The clinical and demographic characteristics of the participants are illustrated in Table 1. The distal diameter of the RITA graft was compared to test the hypothesis between the demographic and angiographic characteristics (Table 2).

Table 1. Demographic characteristics

Characteristics	
Age (years)	63.1±1.5* (42-79)**
Weight (kg)	73.8 ± 7.9 (58-92)
Height (m)	1.66±0.08 (1.35-1.82)
Gender - male	26 (81.6%)*
Dyslipidemia	14 (43.8%)
Diabetes mellitus	6 (18.8%)
Systemic arterial hypertension	19 (59.4%)
Smokers	8 (25%)
Classification of angina	
stable	12 (37.5%)
Instable	14 (43.8%)
Asymptomatic	6 (18.8%)
NYHA Functional class	
I	9 (28.1%)
II	9 (28.1%)
III	2 (6.3%)
IV	0

\*Mean ± standard deviation

\*\* minimum and maximum values

\*\*\*n (relative percentage)

The continuous independent or ordinal variables correlated to the distal diameter of the RITA are shown in Table 3.

The weight, height, the grafted coronary area, interval between surgery and coronary cineangiography, diameter of proximal stenosis, TIMI, classification of angina and systemic arterial hypertension variables were statistically significant in the univariant analysis (Tables 2 and 3).

These eight independent variables were included in the multiple linear regression model. The coronary area corresponding to the marginal artery presented a β coefficient of 0.424 (p-value < 0.001) and the diameter of the marginal stenosis, a β coefficient of 0.55 (p-value < 0.0001). This model presented with R = 0.846 and the adjusted R2 = 0.696 with a p-value < 0.0001.

Table 2. Student t-test or Mann-Whitney test between the means of diameters

	Right internal thoracic artery		
	Present	Absent	p-value
Gender –female	2.055 ± 0.152 (n=6)	2.0 ± 0.108 (n=26)	0.82
Accessory branches	1.937 ± 0.181 (n=8)	2.035 ± 0.107 (n=24)	0.65
Dyslipidemia	2.072 ± 0.137 (n=14)	1.962 ± 0.124 (n=18)	0.55
Diabetes Mellitus	1.951 ± 0.29 (n=6)	2.024 ± 0.094 (n=26)	0.76
Systemic arterial hypertension	1.886 ± 0.122 (n=19)	2.192 ± 0.126 (n=13)	0.10
Prior AMI	1.887 ± 0.103 (n=15)	2.119 ± 0.144 (n=17)	0.21
Smoker	1.817 ± 0.223 (n=8)	2.075 ± 0.096 (n=24)	0.22

Distal diameter of the right internal thoracic artery with the independent variables; \* mean ± 2 standard deviations; AMI: acute myocardial infarction

Table 3. Spearman correlation between mean of the distal diameter of the right internal thoracic arteries and independent variables

	correlation Coefficient (rho)	Two-tailed significance
weight	-0.35	0.05
height	-0.16	0.03
age	-0.06	0.74
Coronary area	0.67	< 0.0001
Interval surgery/CATE	0.29	0.1
Diameter of proximal stenosis	0.32	0.08
Criteria of flow TIMI	0.35	0.05
Flow dominance	-0.21	0.24
NYHA Functional class	-0.19	0.29
Classification of Angina	-0.35	0.05

## DISCUSSION

Analysis of the angiographic factors in the evaluation of arterial graft remodeling is based on *in vivo* morphometric studies. By morphometric analysis, the present study focused on validated angiographic criteria [23-25], factors with a direct influence on the ITA graft [9-16] and an assessment of the distal coronary bed using a measurement of the revascularized area.

In the univariate analysis, the coronary area of the marginal branch of the circumflex artery, the time in months between surgery and re-evaluation by coronary cineangiography and the diameter of stenosis of the marginal branch presented moderate positive correlations with the diameter of the RITA. Other variables were included in the regression model, despite being considered possible confounding factors serving to adjust the proposed model. Notably, with the adjusted model, variables with little or no influence, such as the presence of patent collateral branches, previously correlated with negative remodeling [9-13] and flow 'steal' did not demonstrate statistically significant correlations.

The influence of the distal native flow assessed by the area of the revascularized marginal artery on the positive remodeling of the RITA is well-known. This measurement has a positive regression coefficient with moderate importance and independent of other possible confounding variables such as height, weight, age and gender. In respect to the  $\beta$  coefficients, these are the final results of a statistical model based on multiple linear regression. Thus, they can be interpreted as independent factors correlated to the analyzed outcome. Hence, in this study the distal diameter of the RITA, considered as a dependent variable, was associated to the influence of the revascularized coronary artery in 0.42 ( $p$ -value  $< 0.001$ ) and to the diameter of stenosis of the marginal artery in 0.55 ( $p$ -value  $< 0.0001$ ). The application of these coefficients demonstrated a predictive value of the RITA, that is, we can determine the capacity and magnitude of the alteration of the diameter of the RITA in isolation.

This model presented with an adjusted  $R = 0.696$  and  $p$ -value  $< 0.0001$ . This denotes a probability of 69.6% that this statistical model, using the final coefficients, can predict the measurement of the diameter of the RITA graft. Many variables initially inserted into the model were only statistically significant in the univariate analysis.

Other authors [19-21] also observed positive correlations between the diameter of the stenosis and the diameter of the graft. The presence of stenosis in the native bed, to a greater or lesser magnitude, influences the flow dominance through the distal bed (graft flow versus native coronary flow) and consecutively in stimulating arterial remodeling.

The mean follow up time of 42 months can demonstrate that remodeling is a dynamic and continuous phenomenon.

It is possible to infer that the most evident functional substrate is the evolution of the atherosclerotic disease in the native bed itself.

As this is a transversal study, there are limitations due to the presence of bias that may influence the external validity. It is particularly important to mention the selection bias due to the non-selective indication for re-evaluation by coronary cineangiography and the size of the sample. Additional to these, the rigorous exclusion and selective factors were important.

We should note that in other studies [16, 17,21] there was also loss of patients during the follow-up period. Even so, the proposed study brought a new perspective in the analysis of the regional influences between the revascularized coronary bed and the diameter of the RITA.

## CONCLUSION

In conclusion, based on the angiographic measurements in the postoperative period of CABG, the RITA, continuously submitted to forces of transformation, presents with positive remodeling.

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