PROTOCOL

COLLATERAL STUDY

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Transit Time Flow measurement in coronary surgery. The mutual influence of collateral flow between different coronary territories on parameter metrics: the COLLATERAL Study.

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ABSTRACT

Transit-time flowmetry (TTFM) allows grafts quality control during coronary artery bypass surgery by measuring the flow volume through them.
To date, many studies have deeply studied the predictive role on the graft outcomes of the various flowmetry-derived parameters. One of the least investigated aspects, however, is the mutual influence that two newly realized grafts can have. This possibility would be related to the presence of a more or less developed collateral circulation between the bypassed territories.
The purpose of this study is to assess whether a graft for a territory different than that provided by the left anterior descending artery (LAD) may affect the functionality (measured through flowmetry) of the left internal mammary artery – LAD graft.
This is a prospective, observational, monocentric cohort study in which adult patients undergoing cardiac surgery of isolated aortocoronary bypass are enrolled.

BACKGROUND

When performing coronary artery bypass surgery, it is essential to verify that grafts are patent and functioning. Indeed, this has important consequences in the perioperative period and an impact on patient long-term prognosis (1,2).
Since the second half of the 1990s, this intraoperative quality control is possible thanks to the transit-time flow measurement (TTFM) that evaluates the flow volume through the grafts.
In 2009 intraoperative epicardial high-frequency ultrasound (HFUS) of the graft and coronary anastomosis was introduced.
Both these techniques are characterized by simplicity, reproducibility, reduced cost, safety and speed of learning. Once the information derived from TTFM and HFUS are integrated, the surgeon can feel confident on the good functioning of the graft and on its long-term patency.
This quality control protocol has been adopted by our department and it is routinely used for all coronary artery bypass grafting surgeries.

The evaluation of the coronary grafts by TTFM allows to acquire the following parameters:

- **Mean flow (ml/min**): it is influenced by multiple factors including the size and quality of the graft, the size and quality of the coronary target, the quality of the anastomosis, the run-off of the distal coronary vascular territory, the hemodynamic condition of the patient, the presence of competitive flow between grafts pertaining to the same territory.
According to currently guidelines, the average flow should be above 20 ml/min (3,4).

- **Pulsatility index (PI)**: calculated as [(maximum flow - minimum flow)/average flow] through 5 cardiac cycles. It represents an estimate of resistance to flow. It can be influenced by multiple factors: anastomosis quality, coronary stenosis after the anastomosis, competitive flow.
Literature data suggest that an ideal value would be < 3 (4).

- **% Backward flow (BF)**: it represents the percentage of flow directed from the native coronary artery to the graft during a cardiac cycle. It may indicate the presence of competitive flow

between the graft and the coronary target; studies that evaluated the association between %BF and angiographic patency of remote graft concluded that this parameter can be considered a predictor of patency of anastomosis with an identified cut-off of 3% of the total flow; (5) practically, a retrograde flow area >3% of the total graft flow area represents a risk factor for failure.

- **Diastolic filling (%DF)**: this is a parameter that describes the mode of flow distribution according to the phase of the cardiac cycle (systole/diastole); it provides an estimate of the diastolic flow within the graft, considering that:
1) the prevalence of diastolic flow is a distinctive feature of the left coronary circulation in which coronary resistances are higher during systole for higher transmural pressure;
2) the right coronary artery supplies the right ventricular myocardium in both systole and diastole; for this reason in this territory a DF% is accepted around 50% and it may change in case of right coronary hyper-dominance.

The correct interpretation of the TTFM requires an integration of all these parameters and their analysis also in light of the result of the intraoperative HFUS, which serves as a benchmark of patent anastomosis.

Although last European Guidelines on myocardial revascularization recommended intraoperative flowmetry and ultrasound (Class IIa, evidence level B) their use remains substantially limited, estimated at 30% of all coronary artery bypass interventions (3). Still, many evidence supporting TTFM and HFUS exist:

By studying 227 arterial and 77 venous grafts in 157 patients, Di Giammarco *et al* demonstrated a correlation between a mean flow <= 15 ml/min, PI >= 3, %BF > 3% and graft dysfunction at an average follow-up of 6.7 months (5).

Although with a shorter follow-up (3 months), similar results were reported by Tokuda *et al* (6). Kim and collaborators found an association between mean flow, PI, %BF and DF with grafts patency in 59 patients undergoing early (1.1 ± 0.4 days) bypass angiographic control (7).

In a clinical study including 336 patients, Kieser *et al* described 990 arterial grafts. A PI > 5 in association with signs of ischemia (evaluated by EKG, echocardiogram and/or hemodynamic instability) led to graft revision in 2% of patients. In those patients (59) who did not receive an indicated graft revision, Authors found a significantly higher rate of MACCEs than those with normal TTFM (2).

Although the evidence supporting TTFM mainly derives from retrospective studies with a limited number of patients, there is general agreement that it can predict the outcome of a graft, especially when associated with an intraoperative ultrasound assessment (8). On the other hand, flowmetry parameters cut-offs are not universally defined.

This study aims to evaluate if different grafts could mutually have an influence on flowmetry parameters. From a pathophysiology point of view, this influence could stand on the presence and magnitude of a collateral circulation between the two myocardial territories supplied by the grafts.

In this sense it would be of interest to understand if and how a graft for a coronary vessel other than the left anterior descending artery (LAD) modifies the flow parameters of the left internal mammary artery (LIMA) to LAD graft.
Similarly, it would be important to understand if and how the LIMA-to-LAD graft modifies the flow parameters in the grafts for non-LAD coronary targets.

Excluding anatomical causes (since patency is systematically checked by HFUS), the factors that we can relate to the presence and extent of the collateral coronary circulation are:

- stenosis severity of the two bypassed coronaries (of particular interest is the case of chronic occlusions);
- type of graft used (artery vs vein) to bypass the coronary vessel;
- size of the target coronary vessel (measured by HFUS);
- size of the graft (measured by HFUS);
- anatomical position of the bypassed non-LAD coronary vessel;
- regional contractility abnormalities in the territory of the bypassed coronary vessels;
- clinical presentation: stable vs unstable.

PRIMARY OBJECTIVE

The primary aim of this study is to assess whether a graft for a non-LAD coronary target modifies the performance (measured by combined analysis of TTFM and HFUS) of the LIMA>LAD graft.

PRIMARY END-POINT

- LIMA>LAD PI modification before and after transient occlusion of other grafts for non-LAD coronary vessels, under rest conditions and after pharmacological stress.
(The choice of the PI as primary end-point derives from our preliminary experience that led us to believe that this is the parameter that most correlates to the presence of a collateral circulation)

SECONDARY OBJECTIVES

- Identify which factors (covariates) related to the presence/extent of the collateral circulation affect the performance of the LIMA>LAD graft;
- Assess whether the LIMA>LAD graft modifies the performance (measured by combined analysis of TTFM and HFUS) of non-LAD grafts;

SECONDARY END-POINTS

- LIMA>LAD mean flow change before and after transient occlusion of the other grafts for non-LAD coronary targets, under rest conditions and after pharmacological stress;
- LIMA>LAD DF change before and after transient occlusion of the other grafts for non-LAD coronary targets, under rest conditions and after pharmacological stress;
- variation of DF% on the right coronary depending on its dominance or hyperdominance;

- LIMA>LAD BF change before and after transient occlusion of the other grafts for non-LAD coronary targets, under rest conditions and after pharmacological stress;
- variation of mean flow, PI, DF and BF in the non-LAD grafts before and after transient occlusion of the LIMA>LAD graft, under rest conditions and after pharmacological stress.

TRIAL DESIGN

This is a prospective, observational, monocentric cohort study on adult patients undergoing isolated coronary artery bypass surgery.

INCLUSION CRITERIA

- age > 18 years;
- informed consent acquired and registered;
- patients who undergo coronary artery bypass grafting (with or without cardiopulmonary bypass);
- patients with stable angina, unstable angina or acute coronary syndrome without elevation of the ST tract (NSTEMI).

EXCLUSION CRITERIA

- patients unable to give informed consent;
- patients undergoing emergency surgery;
- patients in unstable haemodynamic conditions or in need of pharmacological or mechanical support;
- patients undergoing combined surgery;
- patients undergoing single aortocoronary bypass surgery;

STUDY PROCEDUREs

All patients with coronary artery disease and an indication for surgical revascularization (coronary artery bypass grafting) who meet the above-described inclusion and exclusion criteria will be enrolled by signing the informed consent the day before surgery.

Patient data (personal data, anthropometric data, cardiovascular risk factors, co-patologies, cardiac history, blood tests, drug therapy, electrocardiogram, echocardiogram, angiography) will be recorded in a dedicated database. All data recorded in the database are commonly acquired for all patients undergoing this type of surgery and no further examinations will be performed for patients included in the trial.

During surgery, every graft will be evaluated through transit time flowmetry (TTFM) and intraoperative ultrasound control (HFUS).
In details, the ultrasound control is carried out through a dedicated sterile ultrasound probe connected to a machine (MiraQ - MEDISTIM) as soon as each anastomosis is completed. The result of the evaluation is recorded together with surgery data. This evaluation is intended to confirm the correct realization of the anastomosis and provides a proof of its patency.

The TTFM evaluation, which is carried out through a specific sterile device connected to the same machine (MiraQ - MEDISTIM), will be performed once the patient has been weaned from the

cardiopulmonary bypass and before protamine administration. This recording is performed under EKG and pressure-controlled conditions. Although there is no general agreement on the optimal mean arterial pressure at which the measurement has to be recorded, we will adopt the standard used in the REQUEST study protocol [9], that is an average pressure of 80 mmHg.

The measurement procedure will be as follows: (1) recording of the above-described parameters (mean flow, PI, DF, %BF) of the LIMA>LAD graft with all other grafts occluded by an appropriate vascular clamp; (2) recording of the same LIMA>LAD graft TTFM parameters after having alternately and sequentially opened the grafts for non-LAD coronary targets; (3) recording of TTFM parameters on non-LAD grafts before and after occluding the LIMA>LAD graft; (4) finally, we will repeat steps (1), (2) and (3) also after pharmacological stress (administration of dobutamine bolus 20 mcg/Kg).

These perioperative information, laboratory, instrumental and clinical postoperative data will be recorded in the dedicated database according to clinical practice. The trial will not include clinical or instrumental follow-up.

STATISTICAL ANALYSIS and SAMPLE SIZE CALCULATION

As we have previously disclosed, we will investigate if a graft to the inferior, lateral or antero-lateral myocardial walls (non-LAD coronary targets) could affect the performance of the LIMA>LAD graft as evaluated by TTFM. Basically, the effects of a given non-LAD graft will be assessed independently of any other possible graft for non-LAD territories.

So, for each non-LAD graft, patients will be divided into two groups: in group A LIMA-LAD flowmetry is measured with the non-LAD graft closed, while in group B LIMA-LAD flowmetry is measured with the same non-LAD graft opened.

On the basis of our preliminary experience, we consider that the TTFM parameter most affected by the presence/extent of a collateral coronary circulation is the pulsatility index (PI).
We assume from the literature [5,8,10] that the mean PI measured on the LIMA-LAD graft is 2.5 ± 0.5. With that in mind, we expect a graft for a non-LAD coronary target to increase this average PI by 20%.

As mentioned above, the comparison will be made for each non-LAD myocardial territory (i.e. diagonal branch, obtuse marginal and right coronary). In each comparison, 45 patients per group will be needed, in order to have a power of 90% to identify a 20% increase of the mean PI through the left internal mammary artery, with an alpha of 0.05.

As a result, the MINIMUM sample size will be 90 patients (if all patients will receive a graft for all the non-LAD myocardial territories); the MAXIMUM sample size will be 135 patients (if all patients received only one graft for the non-LAD myocardial territories explored).

Continuous variables will be described as mean ± standard deviation if distributed normally or with median (interquartile range), otherwise. Categorical variables will be reassumed as absolute (percentage). Kolmogorov-Smirnov test will be used to check the normality/skewness of continuous variables before further analysis. Groups will be compared using the Fisher's exact test or λ^2 test for

categorical variables, as appropriate. Instead, continuous variables will be compared using independent samples t-test or Mann Whitney U tests, as appropriate. All tests will be two-sided.

ENROLLMENT DURATION

In our center, we perform approximately from 5 to 10 coronary surgery per week. Considering the above inclusion and exclusion criteria and the possibility that some patients do not provide their informed consent, we consider an average enrollment of 4 patients/week.
The minimum time to reach the number of samples will therefore be 22 weeks (5/6 months). The maximum time will be 34 weeks (8 months).

TRIAL DURATION

Considering the duration of the enrollment, the trial could be considered completed within 18 months.