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Transit time flow measurement in off-pump surgery: is it a functional index of the biological graft integrity?

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Abstract. – OBJECTIVE: **Transit-time flow measurement (TTFM) represents a valid tool in the assessment of the quality of the anastomosis during coronary artery bypass graft (CABG). Nevertheless, a high variability limits its standardized use, lacking univocally accepted cut-off flow values. Our study analyzes TTFM data collected from a study population that underwent off-pump CABG (OP-CABG), with the aim to differentiate into subgroups according to the presence of diabetes mellitus.**

PATIENTS AND METHODS: Patients referred to the Cardiovascular Unit of S. Michele Hospital (Caserta, Italy) for coronary artery disease (CAD) and underwent OP-CABG between January 2015 and December 2019 were enrolled, and intraoperative TTFMs data were recruited and evaluated. Mean graft flow (MGF) and pulsatility index (PI) values were collected and analyzed.

RESULTS: The study population was composed of 342 patients who underwent OP-CABG with TTFM data regarding 824 grafts. Diabetic patients shared a higher cardiovascular risk profile. The TTFM assessment showed better results for the use of the arterial grafts in diabetic patients, especially for those insulin-dependent; conversely, venous grafts showed worse data with lower MGF and higher PI values. In particular, the anastomoses of the saphenous vein graft with marginal obtuse (MO) coronary artery showed worse MGF results in the insulin-dependent rather than normoglycemic subgroup (28.66 *vs.* 38.44, *p*=0.003).

CONCLUSIONS: Diabetic patients, especially in the insulin-dependent subgroups, have demonstrated lower MGF and higher PI values collected from venous anastomoses with, conversely, inverse results from the arterial one. These results might be correlated to an altered biological adaptability caused by the effects of the diabetic endocrine disorder.

Key Words:
Transit-time flow measurement, Off-pump coronary artery bypass graft, Saphenous vein, Diabetes, Glycosylated hemoglobin.

Abbreviations

TTFM: transit-time flow measurement; OP-CABG: off-pump coronary artery bypass graft; LIMA: left internal mammary artery; RIMA: right internal mammary artery; RA: radial artery; MGF: mean graft flow; PI: pulsatility index; SVG: saphenous vein graft; CAD: coronary artery disease; Hb1Ac: glycosylated hemoglobin.

Introduction

Transit time flow measurement (TTFM) in coronary artery bypass graft (CABG) represents the most adopted technique allowing to accurately measure the quality of the graft and the coronary vessel run-off.

In the beginning, intraoperative Doppler ultrasound was validated in the assessment of coronary artery bypass graft (CABG) by the study of Simpson et al[1]. They concluded through an *in-vitro* analysis, which suggested an accurate flow estimation of the grafts. Doppler systems gradually replaced electromagnetic flowmeters and TTFM achieved satisfactory outcomes among others[2,3].

The use of a flow probe holding two ultrasonic transducers and an acoustic reflector allows for an accurate measure of blood flow volume[4]. The TTFM emerged as a recommended tool for intraoperative graft analysis and early detection of technical errors, mainly in the setting of the off-pump CABG (OP-CABG)[4-7].

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Abnormal TTFM parameters have been demonstrated[8-11] to be associated with increased postoperative mortality, myocardial infarction, and reduced graft patency in the follow-up.

Nevertheless, the extremely large inter- and intra-individual variability have limited its use: vascular resistance is inversely proportional to blood flow, in turn dependent on blood viscosity, length, and diameter of the vessel. Therefore, a fully patent anastomosis may show high resistance and low absolute blood flow[6].

Over the years, retrospective studies[8,12] have tried to define a threshold useful as an indicator of the flow pattern, achieving heterogeneous values varying due to the different surgical scenarios (on-pump *vs.* off-pump), the type of the conduit (venous *vs.* arterial grafts), and the extent of coronary artery disease (CAD) among others. In general, a mean graft flow (MGF) >20 ml/min and a pulsatile index (PI) <5 are the recommended indicative values[7].

Nevertheless, saphenous vein graft (SVG) has shown[9-11] late occlusion for values <31 ml/min of MGF measured with the TTFM technique, demonstrating better outcomes when superior to 40 ml/min.

The discordance in finding an absolute cut-off, mainly regarding SVG, may reflect the variability in the biological graft integrity and vessel adaptation.

Type 2 diabetes, besides the increased extent of CAD, produces a negative impact on SVG patency and may alter the biological properties of the bypass graft conduits, with an inverse correlation between SVG intimal abnormalities and metabolic control[13,14].

Fibromuscular hyperplasia may affect SVG at the time of CABG in diabetic patients, accelerating post-operative atherosclerotic changes, responsible for poor outcomes in the prognosis of surgical revascularization[14].

Our study aims to retrospectively analyze the TTFM values in patients who underwent OP-CABG, differentiating between the use of arterial and venous conduits and focusing on the difference associated with the presence of type 2 diabetes.

Patients and Methods

Patients referred to the Cardiovascular Unit of S. Michele Hospital (Caserta, Italy) for CAD who underwent OP-CABG between January 2015 and December 2019 were enrolled, and intraoperative TTFM data were recruited and evaluated. The study population was differentiated according to the presence of type 2 diabetes, including its categorization into anti-diabetic oral therapy and insulin-dependent groups.

Study Design

The study is a retrospective, observational analysis of the data. Data were collected and analyzed anonymously, and the design did not involve direct interaction with any human subjects.

Surgical Technique

After median sternotomy and conduit harvesting, in a pedicled fashion for mammary and radial arteries, the pericardium was opened, and pericardial stay sutures were placed. Modified Lima stitches (invented by Dr. Ricardo Lima, Recife, Brazil) were used to improve lateral exposure of the heart. The safe construction of the anastomosis was achieved through the stabilization of coronary arteries using Octopus™ Evolution AS Tissue Stabilizer and the Starfish™ Evo Heart Positioner (Medtronic, Dublin, Ireland). The suction devices, attached to the epicardium and connected to the operating table rail, allowed optimal coronary target exposure. Intracoronary shunting of the involved coronary artery branches was always used according to proper arterial size. The distal anastomoses were performed with a 7-0 prolene running suture. The proximal anastomoses were performed with a 5-0 prolene running suture on a partially excluded ascending aorta with a side clamp. Intravenous beta-blocker agents and vasodilators were rarely used during surgical procedures.

TTFM Assessment

The TTFM device MiraQ (Medistim BF 2004, Medistim, Oslo, Norway) was used to obtain flow curves and flow values at the end of every single anastomosis. When necessary, mammary and radial arteries were skeletonized in a small segment to improve probe contact with the vessel. The flow probe holds the graft perpendicularly to its components, two ultrasound transducers, and a fixed acoustic reflector. The ultrasound signals are transmitted and propagated through the vessel and the blood flow. The analysis of the integrated signal travel time between the two transducers is used to provide the flow measurement. The MGF, calculated by the analysis of the flow waveform, is expressed in mL/min; the PI is a derivative parameter obtained by dividing for the mean flow the difference between the maximum and the minimum flow, and it is expressed as an absolute number. PI and MGF are evaluated to correctly interpret TTFM findings.

Statistical Analysis

Continuous variables were expressed as means±SD, median with interquartile range, and comparison between groups used the *t*-test. Categorical variables were compared using the Chi-square test. Statistical analyses were performed using Excel (Microsoft Corporation, Albuquerque, New Mexico, USA) and Stata 17.0 (StataCorp, College Station, TX, USA). A *p*-value <0.05 was considered to be statistically significant.

Results

Pre-Operative Features

Three hundred forty-two patients underwent OP-CABG, for a total of 824 grafts harvested. TTFM assessment was performed for each single anastomose. The pre-operative clinical characteristics of the study population are reported in Table I.

The mean age of the study population was 65.07±9.59 years; 78.07% (267 of 342) were male. CAD was associated with high cardiovascular risk profiles; 75.15% (257 of 342) had hypertension and 32.46% (111 of 342) of patients smoked. Type II diabetes affected 44.15% (151 of 342) of the patients, including 54.30% who were insulin-dependent and 45.70% who took anti-diabetic oral therapy. Previous myocardial infarction (MI) was documented in 28.66% (98 of 342) of the population and previous PCI in 22.81% (78 of 342) of the cases.

Extracardiac arteriopathy was present in almost one-fifth of the patients with a prevalence of 21.05% (72 of 342); 76.39% were affected by carotid stenosis, and the remaining by peripheral abdominal disease (18.06%, 13 of 342).

In Table II, the pre-operative characteristics are reported, dividing the study population by the presence of type II diabetes. Diabetic patients share a higher cardiovascular risk profile than normoglycemic patients, with a great prevalence of hypertension, previous CAD with more MI events, and recurrence of PCI. Similarly, and not surprisingly, extracardiac arteriopathy and previous cerebrovascular disease were observed more in the diabetic group. The differences between the studied populations have not shown statistical significance ($p>0.05$). Conversely, chronic kidney disease affected 12.58% of diabetics, with a statistical difference when compared with normoglycemic (5.24%) ($p=0.0205$). The magnitude of CAD has been evaluated through a coronary angiogram, with the three-vessel disease more frequently found (21.86%), followed by two-vessel disease (13.72%), one- and four-vessel, respectively. The left main disease was documented in 13.14% of the cases. A pre-operative echocardiographic exam showed a preserved left ventricle ejection fraction in most of the study population (Table I). Regarding angiographic and echocardiographic data, no significant differences were found between diabetic and normoglycemic patients (Table II).

Intra-Operative Features

Tables III and IV summarize intra-operative data. Surgery was urgent in 4.39% of the cases, with no significant difference between diabetic and normoglycemic patients (Table IV).

Considering the total population, 835 grafts were performed, with a mean of 2.44 grafts for every single patient. In half of the cases (48.54%), two grafts were used to bypass the coronary vessels, three grafts in 41.81%, and rarely one and four grafts, respectively in 5.26% and 4.09%.

The most frequently used conduit was the left internal mammary artery (LIMA) in 94.44% of the cases, followed by the saphenous vein (SV) (92.11%); in selected cases (2.34%), bilateral internal mammary artery (BIMA) and radial artery (RA) have been harvested and used. In 46.78% of the cases, surgical revascularization was predominately venous; the same distribution between venous and arterial graft was reported in 42.11%, the majority of arterial in 11.11%, and total arterial revascularization in 7.89% of cases.

Most of the anastomosis was performed with the graft on a single target vessel (79.24%); twenty (20%) of the anastomosis included grafts bypassing two vessels, respectively, in the 12.28% and 8.48%, sequentially or as y-graft technique. The use of this latter allows us to avoid aortic manipulation in the context of the aortic no-touch technique, used in 8.77% of cases in our series. The mean time of surgery was 222.56±55.44 minutes. In Table IV, the same intra-operative data are reported according to the two different subgroups of the population (diabetics and normoglycemic) without a significant difference between the observed features.

TTFM Assessment

The assessment of every single anastomosis was performed, and the values of the MGF and PI

Table I. Pre-operative features of the population study.

Cardiovascular risk profile, n (%)	*Total population n=342 (100)*
Age, years	65.07±9.59
Gender	
•Male	267 (78.07)
•Female	75 (21.93)
Diabetes	151 (44.15)
•ADO	69 (45.70)
•Insulin	82 (54.30)
Smoking	111 (32.46)
Hypertension	257 (75.15)
Previous MI	98 (28.66)
Previous PCI	78 (22.81)
Atrial fibrillation	18 (5.27)
• NOAC	15 (83.33)
Extracardiac arteriopathy, n (%)	
Vascular disease	72 (21.05)
• Carotid stenosis	55 (76.39)
• Peripheral abdominal disease	13 (18.06)
• Concomitant carotid and abdominal	4 (0.05)
Previous cerebrovascular disease	22 (6.43)
• Stroke	9 (40.91)
• TIA	2 (9.09)
• Carotid Interventions	11 (50)
Multiple organ dysfunction, n (%)	
Chronic lung disease	185 (54.09)
Chronic kidney disease	29 (8.48)
• Yes	21 (72.41)
• Severe (Clearence <50 ml/m^2)	5 (17.24)
• Dialysis	3 (10.35
Angiographic and echocardiographic findings, n (%)	**Total population n=342 (100)**
Number of vessels disease	Total vessels affected by CAD n=860 (100)
• One-vessel	20 (2.33)
• Two-vessel	118 (13.72)
• Three-vessel	188 (21.86)
• Four-vessel	10 (1.16)
Left Main disease	113 (13.14)
Left ventricle ejection fraction, EF %	
• >50	242 (70.76)
• 45-50	23 (6.72)
• 30-44	30 (8.77)
• <30	1 (0.29)

ADO: anti-diabetic oral therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention; NOAC: novel oral anticoagulant; TIA: transient ischemic attack; EF: ejection fraction; CAD: coronary artery disease.

were collected. None of the anastomosis assessed using TTFM was revised according to the surgeon's integrated analysis of the flow values.

In Table V, arterial and venous bypass grafts are grouped in a composite fashion to analyze the flow curves and values in the study population and those affected by diabetes, including the insulin-dependent subgroup.

In the entire study population, better results with higher MGF and lower PI characterize ar-

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terial rather than venous bypass grafts with an MGF of 37.06 *vs.* 33.72 (p=0.0217) and a mean PI value of 2.01 *vs.* 2.23 (p=0.0009), respectively. In particular, the arterial grafts demonstrated better results in the diabetic group with higher MGF and lower PI values, especially in the insulin-dependent subgroup, rather than in normoglycemic.

On the contrary, SVGs show an inverse and worse trend with lower MGF and higher PI in the diabetic group, particularly in the insulin-dependent subgroup; indeed, the MGF of the normoglycemic patients is significantly better compared to the diabetics (35.16 *vs.* 30.38, respectively, p=0.0368).

All collected and analyzed data from the more frequent anastomosis, LIMA-left anterior descending (LAD) coronary artery, SVG-marginal obtuse (MO) coronary artery, and SVG-posterior descending coronary artery (PDA) are shown in Table VI. The values of the MGF and PI, as well as for Table

Table II. Pre-operative features of the population divided according the presence of diabetes mellitus.

Cardiovascular risk profile, n (%)	**Normoglycemic n=191 (100)**	**Diabetic n=151 (100)**
Age, years	64.68±10.12	65.57±8.88
Gender		
• Male	150 (78.53)	117 (77.48)
• Female	41 (21.47)	34 (22.52)
Smoking	74 (38.74)	37 (24.50)
Hypertension	128 (67.02)	129 (85.43)
Previous MI	52 (27.23)	46 (30.46)
Previous PCI	41 (21.47)	37 (24.50)
Atrial fibrillation	12 (6.28)	6 (3.97)
• NOACs	10 (83.33)	5 (83.33)
Extracardiac arteriopathy, n (%)		
Vascular disease	33 (17.28)	39 (25.83)
• Carotid stenosis	27 (81.81)	28 (71.80)
• Peripheral abdominal disease	5 (15.15)	8 (20.51)
• Concomitant carotid and abdominal	1 (3.03)	3 (7.69)
Previous cerebrovascular disease	10 (5.24)	12 (7.95)
• Stroke	4 (40)	5 (41.67)
• TIA	2 (20)	0 (0)
• Carotid Interventions	4 (40)	7 (48.33)
Multiple organ dysfunction, n (%)		
Chronic lung disease	111 (58.12)	74 (49.01)
Chronic kidney disease	10 (5.24)	19 (12.58)
• Yes	6 (60)	15 (78.95)
• Severe (Clearence <50 ml/m^2)	2 (20)	3 (15.79)
• Dialysis	2 (20)	1 (5.26)
Angiographic and echocardiographic findings, n (%)	**Normoglycemic n=191 (100)**	**Diabetic n=151 (100)**
Number of vessels disease	Total vessels n=465	Total vessels n=395
• One-vessel	15 (7.85)	5 (3.31)
• Two-vessel	69 (36.13)	49 (32.45)
• Three-vessel	100 (52.36)	88 (58.28)
• Four-vessel	3 (1.57)	7 (4.64)
Left Main disease	71 (37.17)	42 (27.82)
Left ventricle ejection fraction, EF %		
• >50	118 (61.78)	124 (82.12)
• 45-50	14 (7.33)	9 (5.96)
• 30-44	25 (13.09)	5 (3.31)
• <30	0 (0)	1 (0.66)

MI: myocardial infarction; PCI: percutaneous coronary intervention; NOAC: novel oral anticoagulant; TIA: transient ischemic attack; EF: ejection fraction.

Table III. The intra-operative features of the population study.

Intraoperative characteristics, n (%)	*Total population n=342 (100)*
Surgery status	
• Elective	327 (95.61)
• Urgent	15 (4.39)
Number of grafts	Total: 835
• 1	18 (5.26)
• 2	166 (48.54)
• 3	143 (41.81)
• 4	14 (4.09)
Choice of the conduit	
• SV	315 (92.11)
• LIMA/RIMA	323 (94.44)
• BIMA	8 (2.34)
• Radial artery	8 (2.34)
Graft	
• Majority venous	160 (46.78)
• Majority arterial	38 (11.11)
• Same	144 (42.11)
Total arterial revascularization	27 (7.89)
Type of the bypass graft	
• Single	271 (79.24)
• Sequential	42 (12.28)
• Composite	29 (8.48)
Aortic no touch technique	30 (8.77)
Time of surgery	222.56±55.44

SV: saphenous vein; LIMA: left internal mammary artery; RIMA: right internal mammary artery; BIMA: bilateral internal mammary artery.

V, are reported for the different subgroups of the total population. The anastomosis of the LIMA to LAD surprisingly shows better results with higher MGF and lower values of PI in diabetic and specifically in insulin-dependent subgroups (38.04 *vs.* 39.57; 1.99 *vs.* 1.96, respectively), even in the absence of statistical significance. An inverse result is obtained from SVG-MO and SVG-PDA flow analysis, where diabetic and insulin-dependent subgroups show lower MGF and higher values of PI, with a significant difference in the MGF between normoglycemic and diabetic/insulin-dependent in SVG-MO anastomosis (38.44 *vs.* 31.19, p=0.0089; 38.44 *vs.* 28.66, p=0.003).

Post-Operative Features

Table VII reports the prevalence of postoperative complications. The subgroups did not show any statistical difference in the observed rates. Sternal wound infection affected almost 5% of the total population, more in diabetic patients (6.62%), in the absence of a statistical significance. Postoperative acute kidney failure was more developed in the group diabetes with 4.64% *vs.* 1.09% in the normoglycemic one, without any statistical difference. The other major complications did not achieve a prevalence of 2% in the series, with a similar distribution in the two subgroups.

The length of hospital and intensive care unit stays was 14 and 2 days, respectively, with a longer stay for the diabetic subgroup. In the whole series, 3 patients of the 342 total population died, with a thirty-day/in-hospital mortality of 0.88%, representing 1.32% (2 of 151) in the diabetic series.

Discussion

The intraoperative graft verification using TTFM integrates the analysis of the MGF and the PI. The latter is a good indicative parameter mirroring the flow curve and, consequently, the quality of the anastomosis, which predicts outcomes15. Higher values of the PI have been observed[6] to

Table IV. The intra-operative features of the population, divided according to the presence of diabetes mellitus.

Intraoperative characteristic, n (%)	Normoglycemic n=191 (100)	Diabetic n=151 (100)
Surgery status		
• Elective	182 (95.29)	145 (96.03)
• Urgent	9 (4.71)	6 (3.97)
Number of grafts	Total: 465	Total: 370
• 1	12 (6.28)	6 (3.97)
• 2	94 (49.22)	72 (47.68)
• 3	75 (39.27)	68 (45.03)
• 4	10 (5.24)	4 (2.65)
Choice of the conduit		
• SV	178 (93.19)	137 (90.73)
• LIMA/RIMA	175 (91.62)	148 (98.01)
• BIMA	3 (1.57)	148 (98.01)
• Radial artery	2 (1.05)	6 (3.97)
Graft		
• Majority venous	89 (46.6)	71 (47.02)
• Majority arterial	21 (11)	17 (11.26)
• Same	81 (42.2)	63 (41.72)
	13 (6.81)	14 (9.27)
Total arterial revascularization		
Type of the bypass graft		
• Single	157 (82.2)	19 (9.95)
• Sequential	19 (9.95)	23 (15.23)
• Composite	15 (7.85)	14 (9.27)
Aortic no touch technique	17 (8.9)	13 (8.61)
Time of surgery	225.48±52.80	218.28±59.24

SV: saphenous vein; LIMA: left internal mammary artery; RIMA: right internal mammary artery; BIMA: bilateral internal mammary artery.

Table V. Composite Transit-time flow measurement (TTFM) data from arterial and venous grafts referred to the study population and of the different subgroups related to the presence of diabetes mellitus.

Type of the bypass graft	Total population N=342	Normoglycemic N=191	Diabetes N=151	Insulin N=82	*p*-value[1]	*p*-value[2]
Arterial						
• MGF	37.06±20.55	35.75±20.29	38.21±21.23	39.67±23.21	0.2811	0.1330
• PI	2.01±0.68	2.02±0.68	1.99±0.68	1.93±0.61	0.6942	0.4123
Venous						
• MGF	33.72±18.94	35.16±19.18	31.84±18.51	30.38±17.26	0.0784	0.0368
• PI	2.23±1.05	2.19±1.02	2.28±1.08	2.25±1.18	0.2377	0.6145

MGF: mean graft flow; PI: pulsatility index. [1]Comparison between the normoglycemic and diabetes group. [2]Comparison between the normoglycemic and insulin group.

correlate to technical errors in the anastomosis. The integrated use of both these two parameters allows us to reduce the high variability associated with the TTFM assessment.

In a large meta-analysis published by Thuijs et al[8], including 8,943 CABG patients for a total of 15,673 grafts, values of MGF lower than 15 and 20 ml/min, respectively, for venous and arterial grafts, with a value of PI superior to 5, have been identified as criteria to define abnormal grafts. The rate of graft revisions in this paper was 4.3%, showing kinking or twisting of the graft, anasto-

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motic stenosis/thrombosis, and graft or coronary dissection as causes of early graft failure. Nevertheless, revised grafts represented only 25% of the grafts considered abnormal with TTFM assessment, achieving a low overall sensitivity rate, ranging from 0.205 to 0.457[8].

Besides its intraoperative use in graft verification, the follow-up analysis has demonstrated encouraging predictive results. Lenhert et al[9] reported at 1 year an increase of 4% in the rate of the venous graft failure for every 1 ml/min decrease, with an estimated optimal MGF cut-off of 20 ml/min. Une et al[11] identified for SVG the value of 31 ml/min as an advisable MGF cut-off. Differently by the arterial grafts, in which the MGF cut-off is largely estimated as 20 ml/min, the higher and variable cut-off for the venous grafts may reflect the bigger diameter of the vessels[15].

Therefore, what emerges is the necessity to improve our knowledge regarding inter- and intra-individual variability of the flow curves and values to better understand the predictive role of TTFM[16,17]. The evaluation of TTFM in the Coronary Artery Disease Surgery (EFCAD) registry has confirmed the association between inadequate flow on LAD anastomosis and worse post-operative outcomes[18].

In this context, in our study, we report and analyze TTFM data of a study population undergoing OP-CABG, focusing on the flow values of subgroups of diabetic and normoglycemic patients. The surgical OP-CABG scenario removes the potential bias associated conversely with the on-pump CABG setting. Indeed, higher MGF values have been collected in this latter rather than OP-CABG mainly due to the systemic response following extracorporeal circulation and aortic cross-clamp; the systemic vasodilatation caused by increased release of immune system mediators in the context of the systemic inflammatory response syndrome and the reactive hyperemia after aortic cross-clamp release cause the fall in the vascular resistance and an increased coronary blood flow[16,19].

The extent of CAD in patients affected by diabetes influences the whole natural history of the disease, with multivessel disease and frequent left main involvement at diagnosis, worse long-term mortality, and post-operative course after CABG[20,13]. Indeed, in our series, the diabetic group shows a major prevalence of coronary vessels and left main involvement, the cardiovascular risk profile is worse, and extracardiac arteriopathy and chronic kidney disease have been more frequently observed.

Considering this more complex expression of the CAD and in concordance with the literature, reduced flow values during TTFM for the diabetic subgroups compared to non-diabetic were expected.

Interestingly, our data show a substantial difference when considering the flow values obtained from arterial and venous conduits. Table V, unifying in a composite fashion the measurements collected from these two types of conduits, highlights better values in terms of MGF and PI for the use of arterial grafts in diabetic patients, particularly in the insulin-dependent group, even in the absence of a statistical significance probably due to the small sample. An inverse correlation is reported for the venous grafts (SVG), with MGF values significantly reduced for insulin-dependent patients *vs.* normoglycemic (30.38 *vs.* 35.16, respectively; p=0.0368).

We analyzed the more frequent anastomoses in our series, grouping data from LIMA-LAD, SVG-MO, and SVG-PDA. Confirming the findings, LIMA-LAD shows higher MGF and lower PI values in the diabetic group, especially for the insulin-dependent subgroup; conversely, considering the anastomoses with SVGs to MO and PDA, diabetic and, in particular, insulin-dependent patients show worse values in terms of MGF and PI (Table VI).

These data allow us to draw some considerations, hypothesizing that, based on the difference in terms of flow achieved in diabetic patients, the graft is associated with a different adaptability due to the intrinsic alteration caused by diabetes.

The different biological adaptability to the coronary vessel for the venous and arterial grafts is largely known, with the venous conduit less prone to the physiologic arterial setting. Nevertheless, the demonstrated variability of the flow values in the analyzed groups could be potentially explained by an altered composition of the vessels in the patients affected by diabetes from a pathophysiologic point of view.

Endocrine disorders influence the vasoreactivity and the morphologic structure of venous grafts; altered glucose metabolism impacts the integrity of biological grafts, leading to histological and functional modifications. The deep influence of diabetes on SVG biological properties has been demonstrated[14,21], with signs of the "arterialization process" before the anastomoses with coronary arteries. The endothelium, representing the key of the antiatherogenic process, was found dysfunctional in diabetic patients due to structural derangement, with an increased rate of intimal

Table VI. Flow and pulsatility index check after off-pump coronary artery bypass graft in the population study and patients affected by diabetes.

Anastomoses	Total population N=342	Normoglycemic N=191	Diabetes N=151	Insulin N=82	*p*-value[1]	*p*-value[2]
LIMA-LAD						
• Flow	36.84±20.52	35.86±20.08	38.04±21.06	39.57±22.78	0.3607	0.2072
• PI	2.02±0.66	2.05±0.69	1.99±0.62	1.96±0.64	0.4306	0.3675
SVG-MO						
• Flow	35.33±17.88	38.44±18.25	31.19±16.71	28.66±12.86	0.0089	0.0030
• PI	2.19±0.92	2.08±0.92	2.34±0.91	2.18±0.69	0.0690	0.5574
SVG-PDA						
• Flow	30.47±17.89	32.13±19.43	28.34±15.61	27.15±13.65	0.23649	0.1875
• PI	2.40±1.41	2.4±1.39	2.41±1.43	2.55±1.64	0.97736	0.6254

LIMA-LAD: left internal mammary artery-left anterior descending; SVG-MO: saphenous vein graft-marginal obtuse; SVG-PDA: saphenous vein graft-posterior descending artery. [1]Comparison between the normoglycemic and diabetes group. [2]Comparison between the normoglycemic and insulin group.

fibrosis and sclerosis of the medial muscular layer at the histopathological evaluation. The morphological changes reflect a dysregulated vasomotor response with significantly reduced expression of endothelial nitric oxide synthase (eNOS)[14,21].

Preexisting endothelial cell dysfunction with advanced intimal hyperplasia may significantly contribute to graft failure following coronary implantation. Besides the endothelial dysfunction, an increased expression of the matrix metallopeptidase and smooth muscle cell deposition, leading to a higher incidence of atherosclerotic calcified plaque, describe the pro-inflammatory environment of diabetic SVGs[14,22].

In contrast, preserved vasoreactivity and the absence of ultrastructural abnormalities have been found[14,23] when the histopathological evaluation was performed for diabetic arterial grafts, left internal mammary, and radial arteries. The biological integrity, the contractile, and the vasodilative responses were preserved regardless of the glucose metabolism control, explaining the excellent patency rate of the arterial grafts[14,23].

Conversely, the existing direct correlation between poor glycemic control and SVG intimal hyperplasia should be considered a crucial factor in predicting outcomes after CABG in diabetic patients.

The FREEDOM (Future REvascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial[24] demonstrated the superiority of CABG compared with percutaneous coronary intervention (PCI) in diabetic patients with multivessel disease.

Therefore, the huge burden of diabetic patients affected by CAD needs a careful stratification to properly choose grafts for CABG, ensuring the long-term success of the procedure.

Elevated glycosylated hemoglobin (HbA1c), reflecting poor glycemic control, is associated with unsatisfactory outcomes for patients undergoing CABG and PCI[25,26]. Zhu et al[27] have found, as sub-analysis of the Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) trial, an interesting inverse correlation between HbA1c level and the graft patency of SVG at 1-year after CABG in more than 400 patients and almost 1,200 SVGs[28]. They failed to find any correlation between HbA1c and arterial graft patency rate. Furthermore, they observed superior benefits from the associated use of ticagrelor and aspirin compared with aspirin alone in preventing graft failure at 1-year[28].

HbA1c might represent a very important tool for predicting pre-operatively the extent of the altered biological integrity of SVG and the consequent risk of early graft failure. The growing interest in total arterial revascularization and the multiple arterial graft concepts with useful published algorithms for the choice of the conduits[29], still in the absence of a standardized use, should be integrated by predictive parameters regarding the functional status of the grafts. The unsatisfactory patency rate associated with the use of venous graft in diabetic patients should move toward a univocal consensus in choosing, always, at least a second arterial graft, even as a free graft.

Table VII. Post-operative period features of the study population and of the different subgroups related to the presence of diabetes mellitus.

Postoperative period	Total population N=342	Normoglycemic N=191	Diabetes N=151
Laboratory test result, median (interquartile range)			
Platelets count, mcL	224,500 (186,250; 318,500)	241,500 (192,500; 320,750)	246,500 (183,000; 314,000)
Hemoglobin, g/dL	9.5 (8.8; 10.4)	9.7 (8.9; 10.5)	9.3 (8.7; 10.2)
CPK, UI	100.5 (58; 207)	107 (54; 197)	98 (62; 213)
CPK-MB, UI	13 (11; 17)	12 (11; 17)	13 (11; 17.25)
GOT, UI	23 (17; 33)	24 (19; 36.5)	20 (15; 27)
GPT, UI	23.5 (15; 41)	30 (18; 46.5)	20 (13; 28)
Crea, mg/dL	0.83 (0.7; 1.04)	0.81 (0.7; 1)	0.84 (0.69; 1.1)
Complication, n (%)			
Reopening (bleeding)	4 (1.17)	2 (1.05)	2 (1.32)
Peri MI	1 (0.29)	1 (0.52)	0 (0)
Low cardiac output	1 (0.29)	1 (0.52)	0 (0)
Prolonged intubation	7 (2.05)	4 (1.09)	3 (1.99)
Respiratory failure	4 (1.17)	1 (0.52)	3 (1.99)
Neurological injury	3 (0.88)	2 (1.05)	1 (0.66)
Gastrointestinal injury	1 (0.29)	1 (0.52)	0 (0)
Acute kidney failure	11 (3.22)	4 (1.09)	7 (4.64)
Sternal wound infection	17 (4.97)	7 (3.66)	10 (6.62)
ECMO	1 (0.29)	1 (0.52)	0 (0)
PMK	1 (0.29)	1 (0.52)	0 (0)
New onset of AF	2 (0.58)	2 (1.05)	0 (0)
Outcome, n (%)			
30 day/in-hospital mortality	3 (0.88)	1 (0.52)	2 (1.32)
Length of stay, (media±standard deviation)			
ICU stays	2.11±1.32	2.06±1.09	2.18±1.58
Hospital stays	14.06±4.32	13.92±4.34	14.25±4.31

ECMO: extracorporeal membrane oxygenation; PMK: pacemaker; AF: atrial fibrillation; ICU: intensive care unit; MI: myocardial infarctio; CPK: creatin kinase; CPK-MB: creatin kinase isoenzyme MB; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase.

Limitations

The retrospective and observational nature of the study may have led to selection bias that could influence the study outcome. The study population was divided into groups in an unequal and not randomized manner. Moreover, the study was also limited by the small sample.

Conclusions

The intra-operative graft verification using TTFM allows the surgeon to avoid early graft failure due to technical errors. The analysis of the flow curve and values might be further useful to assess the functional status of the grafts. In our series, diabetic patients, especially insulin-dependent subgroups, have demonstrated lower MGF and higher PI values collected from venous anastomoses with, conversely, inverse results from arterial ones. Excluding potential bias associated with the surgical technique and the pre-existing extent of the coronary disease, these results may identify the preoperative biological integrity of the graft as a possible mechanism responsible for the intraoperative reduced flow. The diabetic endocrine disorder alters the vasoreactivity and the morphology of the venous graft, leading to altered biological adaptability of the coronary vessels.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

Ethics approval is not applicable due to the study's design. Clinical data were collected anonymously and did not involve any direct interaction with human subjects or animals. Therefore, no ethical clearance was required.

Informed Consent

Informed consent is not applicable to this study due to its retrospective nature.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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Authors' Contributions

All authors contributed significantly to this work and read and approved the final version of the manuscript. Ernesto Greco and Mattia Vinciguerra performed the conception and design of the study and revised it critically, Mattia Vinciguerra and Mizar D'Abramo performed the design of the study and wrote the manuscript, Sara Iuliano, Francesco Arlotta, Francesco Baldascino, Massimo Cioffi, Ludovico Fimiani, Rosa Alba Mozzillo, Valeria Sganga, Andrea Spadafora, Eduardo Vitagliano, Giuseppe Sepolvere, Antonio De Bellis, and Carlo Gaudio revised it critically for important intellectual content.

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