D-dimer is associated with arterial and venous coronary artery bypass graft occlusion

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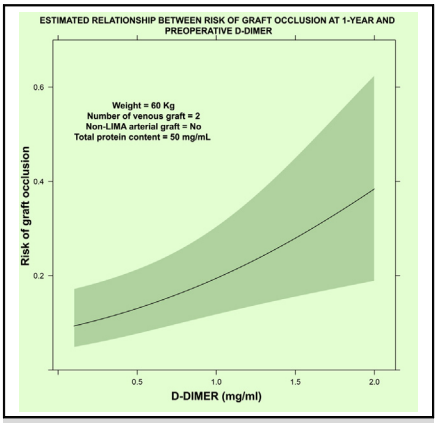
ABSTRACT

Objective: In this observational prospective study, we assessed the role of clinical variables and circulating biomarkers in graft occlusion at 18 months to identify a signature for graft occlusion.

Methods: A total of 330 patients undergoing primary elective coronary artery bypass grafting were enrolled. Blood collection for biomarker assessment was performed before surgery and discharge. Patients were then scheduled to undergo coronary computed tomography angiography at 18 months follow-up, and 179 patients underwent coronary computed tomography angiography 18 ± 2 months postoperatively.

Results: There were 46 of 503 (9.1%) occluded grafts; of these, 29 (63%) were venous and 17 (37%) were arterial grafts; overall, 43 of 179 patients (24%) had at least 1 occluded graft. Logistic mixed effects model assessing independent factors associated with graft occlusion identified that lower D-dimer levels at baseline (odds ratio [OR], 2.58; 95% confidence interval [CI], 1.36-4.89; $P = .00$) and total protein content at discharge (OR, 1.09; 95% CI, 1.01-1.19; $P = .028$) were related to overall graft occlusion at follow-up, along with an arterial graft other than the left internal thoracic artery (OR, 2.92; 95% CI, 1.24-6.9; $P = .078$); moreover, a venous graft emerged was possibly associated with graft occlusion (OR, 1.51; 95% CI, 0.95-2.39; $P = .078$). By separately analyzing saphenous vein and arterial grafts, D-dimer levels (OR, 2.67; 95% CI, 1.15-6.2; $P = .022$ and OR, 2.5; 95% CI, 1.01-7.0; $P = .05$ for venous and arterial graft, respectively) were still associated with arterial and venous graft occlusion at follow-up.

Conclusions: We identified D-dimer as a biomarker associated with arterial and venous grafts occlusion. This may help stratify patients at risk of graft failure and identify new molecular targets to prevent this complication. (J Thorac Cardiovasc Surg 2017;■:1-8)



The estimated relationship between risk of graft occlusion at 1 year and preoperative D-dimer.

Central Message

We identified D-dimer as a biomarker associated with arterial and venous graft occlusion after CABG.

Perspective

The long-term success of CABG depends on graft patency. With this observational prospective study, we identified D-dimer as a biomarker associated with graft occlusion. This may help to stratify patients at risk of graft failure, identify new molecular targets to prevent this complication, and improve coronary artery disease therapy.

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CCTA = computed tomography angiography
CI = confidence interval
OR = odds ratio

Scanning this QR code will take you to the appendices and supplemental tables for this article.

Graft patency at follow-up represents a major concern after coronary artery bypass grafting (CABG) because it influences outcomes and can lead to increased rates of rehospitalization. Occluded venous grafts have been demonstrated in up to 40% of patients within 12 and 18 months, whereas occlusion of internal thoracic artery graft has been shown in 9% of patients.[1,2] Several factors can be related to reduced graft patency, although there is not a complete comprehension on the causes and mechanisms that lead to graft occlusion. Off-pump CABG has resulted in a significantly lower patency of arterial and saphenous grafts in randomized and observational studies,[3-6] and the debate on the more appropriate surgical strategy is still open. Except for potential technical issues, early vein graft failure almost exclusively is due to thrombotic occlusion, and the high incidence of early thrombotic graft failure with established antiplatelet regimens calls for a deeper knowledge of prothrombotic responses related to surgery and further improvement of preventive strategy.

CABG has been demonstrated to evoke a wide systemic inflammation response, evidenced by markedly elevated plasma levels of inflammatory mediators, which may regulate inflammatory and prothrombotic responses. Moreover, CABG may evoke activation and interaction of platelets, leukocytes, and vessel wall cells, which are all involved in the pathogenesis of graft failure. This protracted activation of hemostasis and inflammation, as well as increased oxidative stress and unfavorable endothelial milieu, persists for days and even weeks after surgery.[7-12] Although some biomarkers have been demonstrated to be associated with the CABG inflammatory response and the relationship between prothrombotic/inflammatory responses and graft occlusion has been disclosed, few data on potential clinical and biological variables associated with graft thrombosis are available. This prospective study was carried out to identify which clinical data and biomarkers can be associated with coronary bypass graft occlusion at 1.5 years.[5,9,10,12]

MATERIALS AND METHODS

Study Design

The CoronAry bypass grafting: factors related to late events and Graft patEncy study is a prospective observational study that enrolled 330 white patients scheduled for elective CABG at a single university hospital. Inclusion criteria were age 18 to 89 years, elective primary CABG surgery, and signing a consent form. Exclusion criteria were concomitant surgery, major end-organ dysfunction, serious undercurrent illness or infection, known coagulation disorders, serum creatinine level greater than 2 mg/dL, and atrial fibrillation.

On enrollment, patients underwent clinical assessment and blood collection. Saphenous vein and radial and internal thoracic artery grafts were implanted according to the routine techniques of staff surgeons; in all cases, saphenous veins were harvested pedicled with a no-touch technique, whereas arterial grafts were harvested with their pedicle including satellite veins. Radial grafts were used only in case of greater than 90% target vessel stenosis (Table E1 shows the target anastomoses). Single or sequential distal anastomoses were performed at the surgeon's discretion. After surgery, all patients received aspirin 100 mg/day, whereas dual antiplatelet therapy was given to patients with a previous coronary stent implanted less than 12 months before surgery. Calcium channel blockers were used postoperatively in patients who received radial artery grafts, and statin therapy followed current guidelines.

All patients were then contacted to undergo computed tomography angiography (CCTA), which was performed 15 to 21 months after surgery. The primary end point was to identify clinical variables and circulating biomarkers associated with graft occlusion. Our Institutional Review Board and Ethical Committee approved the study, and all subjects gave written informed consent on enrollment. The trial was registered on ClinicalTrials.gov (Identifier: NCT00755248).

Sample Collection and Biochemical Assays

Blood collection was performed 1 to 3 days before surgery (baseline) and at patient discharge (discharge), usually between postoperative days 6 and 9, from a peripheral vein; plasma was prepared by centrifugation at 1500*g* for 20 minutes at 4°C within 30 minutes from venipuncture, divided into aliquots, and frozen at –80°C until assayed. Samples were frozen and thawed only once. Immunoenzymatic assays determination is described in the Supplemental Methods.[1]

Follow-up and Coronary Computed Tomography Scan

Patients who agreed to undergo coronary CCTA (Figure 1) underwent follow-up visit at the time of CCTA, including blood tests. CCTAs were performed with a 64-slice computed tomography scanner (VCT; GE Medical System, Milwaukee, Wis) with 64 × 0.625-mm collimation, 330-ms gantry rotation time. Dose modulation was attained with "electrocardiographic gating" for a maximum gantry delivery between 40% and 80% during the R-R interval. The "smart prep" scanning was performed to obtain a 4-chamber projection. A bolus of 80 mL of high-concentration contrast medium (Iomeron 400 mg/mL; Bracco, Milan, Italy) was administered intravenously at 5 mL/s, followed by 50 mL of saline injected at the same infusion rate. The scan was initiated according to the bolus-tracking technique. Graft occlusion was defined as the identification of a graft stump on computed tomography (body of graft without intraluminal contrast enhancement).[13,14]

Statistical Analysis

The distribution of variables was evaluated using the Shapiro–Wilk test. Continuous data were expressed as mean ± standard deviation or as median and interquartile range. Categoric data were reported as number and percentage. If continuous data were normally distributed, comparison between 2 groups was performed with the Student *t* test for (un)paired samples, as