

Is there a hypercoagulable state after off-pump coronary artery bypass surgery? What do we know and what can we do?

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Coronary artery bypass graft (CABG) surgery on a beating heart was introduced with suture techniques and local stabilization by Kolessov in 1967.¹ However, cardiopulmonary bypass and cardioplegic arrest, with their ability to provide a quiet bloodless field for the construction of precise and delicate surgical anastomoses, offered compelling advantages compared with the off-pump approach and rapidly became more widely accepted.² With the dramatic reduction of operative mortality throughout the ensuing decades, surgeons began to focus their attention on decreasing operative morbidity, especially conditions associated with neurologic and systemic inflammatory influences after CABG surgery. Traditionally, many of these sequelae have been ascribed to the use of cardiopulmonary bypass.

During the past decade, there has been a dramatic resurgence in the application of off-pump technology in CABG surgery. This has inspired remarkable advances in the techniques of localized tissue stabilization and a greater understanding of the physiology of beating heart mobilization and exposure. An avalanche of reports in the literature has demonstrated the early safety and efficacy of the procedure.³ More than 20% of CABG procedures performed nationwide apply off-pump technology. However, considerable controversy remains regarding the relative merits and long-term outcomes of this approach to coronary revascularization.⁴

One area of concern, and even greater uncertainty, surrounds the issue of the existence of a hypercoagulable state after off-pump CABG surgery. Are patients undergoing off-pump CABG surgery relatively more hypercoagulable postoperatively than their counterparts undergoing on-pump CABG surgery? Such a hypothesis is indeed reasonable in view of the acute phase activation of clotting factors that follow off-pump CABG surgery (as well as surgery in general) and the lack of platelet, fibrinolytic, and other abnormalities related to the heart-lung machine. However, there was no evidence to indicate a clinical problem associated with the procedure until Mariani and colleagues⁵ awakened our concern with their report in 1999. They reviewed 22 consecutive off-pump cases and found a postoperative increase in procoagulant activity, represented by prothrombin factor 1 and 2, which was also accompanied by an increase in von Willebrand factor (endothelial activation) and fibrinolysis. Although Mariani and colleagues⁵ demonstrated no clinical sequelae during their brief follow-up of this limited series of patients with internal thoracic artery (ITA) grafts, they recommended the institution of an aggressive perioperative anticoagulant regimen in all off-pump CABG cases.

What is the major concern? Clearly, a pattern of deep venous thrombosis, pulmonary embolism, or arterial thrombosis would be a source of serious concern to the cardiac surgeon. However, the already extensive clinical experience fails to demonstrate such a pattern. Perhaps a less apparent concern would be the occurrence of acute graft closure. Careful evaluation of the current body of knowledge would indicate just the opposite, with acute graft patency rates exceeding 90% in virtually all cases reviewed. The information in Table 1 summarizes the results of a series of angiographic patency studies after off-pump CABG surgery.⁶⁻¹⁵ Even accounting for extensive variability in patient selection, operative technique, and heparin and

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TABLE 1. Angiographic patency after off-pump coronary bypass surgery

Author	Year	Operation	Patients	Angio timing	Conduit	Patency	
Mack and colleagues ⁶	1999	MIDCAB	100/103 (97)	96 h	LITA	99/100 (99) 91/100 (91)	A*
Izzat and colleagues ⁷	1999	OPCAB	24/24 (100)	Intraoperative	LITA	22/24 (92)	Before revision
Diegler and colleagues ⁸	1999	MIDCAB	221/271 (82)	2-6 postoperative days	SVG LITA	18/18 (100) 218/221 (99) 195/221 (89) 23/221 (10) 3/221 (1)	A* B* C*
Akpinar and colleagues ⁹	2000	OPCAB	71/126 (56)	Before discharge	LITA	71/71 (100)	
Omeroglu and colleagues ¹⁰	2000	OPCAB	70/696 (10)	24-61 mo	All types LITA RITA	143/150 (95) 65/68 (96) 1/1 (100)	
Zehr and colleagues ¹¹	2000	OPCAB	Random 50/50 (100)	<48 h	SVG LITA RA SVG	82/103 (80) 46/51 (90) 15/17 (88) 73/76 (96)	
Amano and colleagues ¹²	2001	MIDCAB/OPCAB	80/194 (41)	Before discharge	All types	201/203 (99)	
Bull and colleagues ¹³	2001	OPCAB	40/40 (100)	<48 h	All types	105/108 (97)	
Kim and colleagues ¹⁴	2001	OPCAB	112/122 (92)	<96 h	ITA	139/145 (96) 130/145 (90) RA RGEA SVG	
			90/122	1 y	ITA RA RGEA SVG	114/117 (97) 101/117 (86) 8/8 (100) 7/7 (100) 106/156 (68)	A* A*
Puskas and colleagues ¹⁵	2001	OPCAB	167/200	Before discharge	LITA RITA RA SVG	158/158 (100) 143/158 (91) 4/4 (100) 24/24 (100) 22/24 (92) 208/213 (98) 203/213 (95)	A* A* A* A*

Numbers in parentheses are percentages. *MIDCAB*, Minimally invasive direct coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *LITA*, left internal thoracic artery; *RITA*, right internal thoracic artery; *RA*, radial artery; *RGEA*, right gastroepiploic artery; *SVG*, saphenous vein graft; A,* B,* C,* Fitzgibbon classification.

antiplatelet regimens in these studies, it does not seem that acute graft closure secondary to a hypercoagulable state is a valid clinical concern.

Careful analysis of the data exposes a more menacing problem. Kim and associates¹⁴ conducted a 3-group study that compared a cohort of patients undergoing off-pump CABG surgery, a group of patients undergoing on-pump CABG surgery, and a similar group of patients undergoing on-pump CABG surgery whose grafts were constructed on the beating heart during the pre-off-pump CABG learning phase. At 1-year follow-up, ITA patency was similar among the groups. Saphenous vein graft (SVG) patency was 88% in patients undergoing CABG surgery, 87% in patients undergoing on-pump beating heart surgery, and 68% in patients undergoing off-pump surgery ($P < .01$).¹⁴ There

are many questions that can be raised about a retrospective study of nonconcurrent groups of patients who underwent operations at different points during the learning curve and with variable follow-up. The major underlying issue is more subtle and one that must be addressed.

It has been learned from multiple pathologic and clinical studies that vein graft disease takes many forms: thrombosis (acute), intimal hyperplasia (subacute), and graft atherosclerosis (chronic).¹⁶ Although intimal hyperplasia may take months to occur, and atherosclerosis 1 year or more to develop, the initiating events (intimal injury, platelet activation, thrombus formation, macrophage infiltration, and smooth muscle cell activation) all occur in the acute postoperative period of SVG (but not during ITA) healing. Therefore, during the early postoperative period, even in the

absence of any clinically manifest adverse events, the groundwork may be laid for the occurrence of multiple late events, thus adversely impairing long-term graft patency. In short, have we, in our enthusiasm to reduce perioperative morbidity, created a sleeping giant of late graft closure?

Casati and colleagues¹⁷ compared multiple hematologic variables in patients undergoing off-pump versus on-pump CABG surgery. They documented that a decrease in platelet count and activation of fibrinolysis were more profound in on-pump surgery, whereas the activation of fibrinogen and other acute phase reactants (consistent with the deposition of thrombus at surgical sites of injury) seemed to be more evident during the first postoperative day in patients undergoing off-pump CABG surgery. Therefore, patients undergoing off-pump coronary artery bypass surgery might well be expected to be more prone to graft closure. As disconcerting as these findings may seem, a comparative analysis of perioperative hemostatic function in patients who did and did not experience SVG occlusion within 3 months of surgery found an increase in plasma plasminogen activator inhibitor-1 activity to be the only postoperative hemostatic measurement predictive of subsequent SVG closure.¹⁸ Notably, the classic atherosclerotic risk factors were found to be more powerful predictors than the hemostatic factors, a finding corroborated by the Cleveland Clinic experience.¹⁹

The emergence of long-term comparative studies demonstrating the clinical equivalence of on-pump and off-pump CABG surgery has been most encouraging.²⁰ However, in the absence of convincing data, there is currently extreme variability in the management of anticoagulation and antiplatelet agents in off-pump CABG surgery.²¹

In the presence of a well-founded concern for the impact of a relatively hypercoagulable state after off-pump CABG surgery on long-term graft patency, and in the absence of valid data indicating appropriate guidelines, what reasonable recommendations can be offered at this time? First, arterial conduits, especially in situ ITA grafts, have been demonstrated to be less prone to the pathogenesis of late graft closure than SVG grafts and are considered to be the conduit of choice in myocardial revascularization. As a result, off-pump CABG surgery may prove to be an even stronger indication for the use of arterial grafting than conventional on-pump surgery.

Second, risk factor modification is known to affect the course of both graft and native coronary disease in all patients undergoing CABG surgery, and patients undergoing off-pump CABG surgery are no exception. Therefore, careful attention to risk factor modification may prove critical in maintaining graft patency and improving long-term clinical results.

Third, in view of the lower incidence of bleeding complications after off-pump CABG surgery, consideration

should be given to limiting the reversal of heparin intraoperatively.²²

Fourth, in view of the well-documented and common unresponsiveness to aspirin,²³ as well as the considerable effectiveness of thienopyridines (ticlopidine and its safer successor clopidogrel) reported in both the cardiology²⁴ and cardiac surgical literature,²⁵ serious consideration should be given to the perioperative (and perhaps the prolonged postoperative) use of clopidogrel.

Fifth, the recent success of drug-eluting stents²⁶ raises serious concerns regarding the use of SVGs in stentable vessels. These data, although still early, pose a theoretical issue in the use of combined procedures for patients unable to receive all-arterial conduits.

Sixth, gene therapy may have a dramatic impact on arresting the progression of SVG disease,²⁷ and advances in this area may have particular relevance to patients undergoing off-pump coronary artery bypass surgery.

Perhaps the most helpful recommendation would be to direct research efforts toward managing the perioperative hypercoagulable state and its long-term impact on graft patency in patients undergoing off-pump coronary revascularization.

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