Chapter 34

Hypercoagulable state after off-pump coronary artery bypass grafting

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During the past decade, there has been a dramatic resurgence in the adoption of off-pump technology in coronary artery bypass 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. However, despite abundant evidence validating safety and efficacy of off-pump coronary artery bypass surgery considerable controversy still persists regarding the long-term outcomes of this approach to myocardial revascularization. One area of concern, and even greater uncertainty, surrounds the issue of the existence of a hypercoagulable state after off-pump coronary artery bypass surgery. This chapter provides an overview of the impact of off-pump coronary artery bypass surgery on coagulation, fibrinolysis and platelet activation, discusses the issue of hypercoagulability with emphasis on the mechanisms responsible for this actual or potential hypercoagulability and explores the implications of this issue for clinical practice.

In an attempt to prevent cardiopulmonary bypass (CPB)-related morbidity and end-organ dysfunction during surgical myocardial revascularization, off-pump coronary artery bypass (OPCAB), a revascularization technique that does not require CPB, has seen resurgence in the last decade or so. OPCAB, first introduced in the late 1960s,[1] has recently become more popular. Proponents of OPCAB argue that all surgical myocardial revascularizations should be performed without the use of CPB. However, skepticism regarding the technical difficulty of OPCAB and concerns that incompleteness of revascularization with this strategy compromises patient outcomes has prevented OPCAB from being universally adopted.[2] As a result, numerous studies have been performed in an effort to address these issues.

Evidence in the form of randomized controlled trials (RCTs),[3-6] meta-analyses,[7-12] systematic reviews[13-15] and non-randomized observational studies[16,17] shows that compared to conventional surgical myocardial revascularization on CPB, OPCAB is associated with similar completeness of revascularization, similar early outcomes, shorter length of hospital stay, reduced transfusion requirements, reduced pulmonary morbidity, and fewer postoperative neurologic events. Despite abundant evidence validating safety and efficacy of OPCAB, one area of concern, and even greater uncertainty, surrounds the issue of the existence of a hypercoagulable state after OPCAB that potentially can endanger the patency of coronary anastomoses.[18] This chapter discusses in detail the controversial issue of presence of hypercoagulable state after OPCAB and its clinical implications.

Current evidence regarding hemostasis preserving effect of OPCAB

A systematic search for current best evidence on the topic retrieved eleven manuscripts comparing the impact of on-pump and off-pump coronary artery bypass grafting on preservation of hemostasis (Figure 1).[19-29] All of these were RCTs (Table 1). Majority of the studies[19,21-24,27-29] showed that on-pump CABG caused earlier and more significant generation of thrombin, however OPCAB caused a late and sustained generation of thrombin. On-pump CABG caused

intraoperative activation of fibrinolysis and fibrin degradation, however, at 24h these parameters were equally elevated in both groups. More importantly, early postoperative decrease in platelet count and increase in platelet activation occurs to a much lesser extent and does not alter bleeding time or adenosine diphosphate-induced platelet aggregation in patients undergoing OPCAB. This lack of significant effects on platelets might in part account for the potential decreased risk in bleeding and for the preserved hemostasis seen in patients undergoing OPCAB compared with those undergoing on-pump CABG.

Interestingly, the RCT by Paulitsch et al.[20] contrary to other RCTs concluded that on-pump CABG was associated with biochemical evidence of a prothrombotic state early after surgery but no greater incidence of thrombotic events was observed. They assigned patients prospectively and randomly to either on-pump (n = 41) or off-pump (n = 51). The concentrations of C-reactive protein, fibrinogen, D-dimer, and plasminogen activator inhibitor type-1 in blood were quantified before and after (1 and 24 h) surgery. Clinical events were assessed during initial hospitalization and at the end of 1 year. The results of this RCT showed that the concentrations of plasminogen activator inhibitor type-1 and D-dimer were greater compared with preoperative values 1 and 24 h after surgery in both groups, but their concentrations increased to a greater extent 24 h after surgery in the on-pump group ($P<0.01$). The concentration of C-reactive protein did not change appreciably immediately after surgery in either group but increased in a parallel manner 24 h after either on-pump or off-pump surgery ($P<0.01$). Bypass surgery in the on-pump group was associated with greater blood loss during surgery and more bleeding after surgery ($P<=0.01$). The incidence of all other complications was similar in the two groups. According to the authors the prothrombotic state might be a consequence of extracorporeal bypass, compensation in response to more bleeding, or both in patients undergoing on-pump surgery.

It is important to stress that all of the RCTs comparing impact of OPCAB and on-pump CABG on activation of coagulation system have several limitations. The number of patients is rather small, so these should be considered more as pilot investigations to direct the most appropriate analyses of coagulation variables in a larger cohort. Because the small sample size precludes excluding Type II error, small differences between groups at certain time points could have been missed. In addition, the number of sampling periods is limited, so only data from these predefined sampling periods can be supplied; therefore, hemostatic abnormalities at other time points after CABG could have been missed. Second, a number of additional factors associated with the on-pump procedure that could have influenced the results varied between the RCTs. These include 1) use of dexamethasone (to mitigate the systemic inflammatory response), 2) use of moderate hypothermia, 3) use of cardioplegia to arrest the heart, and 4) use of different anticoagulation strategies (target activated coagulation time [ACT] >450 vs 250 seconds). Furthermore, several trials used a fixed protamine dosage for heparin reversal. Because ACT may be influenced by other factors, such as hypothermia and hemodilution, it may not accurately reflect the extent of anticoagulation by heparin.[30] This could have led to relative protamine overdose and therefore might have influenced the results in the immediate postoperative period.[30]

Mechanisms of hypercoagulability after OPCAB

Thrombocytopenia has been well documented in patients undergoing on-pump surgery and has been attributed to many factors, including hemodilution, mechanical disruption, adhesion to the extracorporeal circuit, and sequestration in organs.[31] Additionally, platelet dysfunction has also been shown to occur during on-pump surgery, resulting both in the prolongation of the bleeding time and the decrease in ADP-induced platelet aggregation. Similarly, enhanced platelet activation after use of CPB is a recognized phenomenon.[32] Although there is a lack of consensus

as to the pathophysiology of platelet activation, many potential explanations have been entertained. Notable among these are exposure to synthetic material of the extracorporeal circuits, generation of thrombin, and use of heparin and protamine.[33-35] These decreases in platelet counts and abnormalities of platelet function and activity have been implicated by many in the bleeding complications in the postoperative period.[36,37] The fact that these changes are less pronounced in the OPCAB patients compared with on-pump patients could partly explain the relatively "preserved hemostasis" in the former group compared with the latter cohort.

Another plausible mechanism by which OPCAB may induce hypercoagulability is via the obligatory periods of regional warm ischemia that accompany the distal anastomoses. Animal models have demonstrated an induction of thrombin production during periods of warm ischemia as little as 15 minutes.[38,39] Kon et al. in their pilot study, using transcardiac assays, illustrated that regional coagulation was enhanced after off- compared with on-pump CABG.[40]

It is also important to highlight that there are temporal differences in the activation of coagulation as seen after on-pump CABG and OPCAB. In fact two discrete phases can be distinguished: an early phase, occurring only after on-pump CABG, characterized by a sharp activation of coagulation and fibrinolysis, which may be ascribable to the use of extracorporeal circulation; and a later phase, occurring in patients undergoing either on-pump CABG or OPCAB, probably consequent to an inflammatory reaction induced by general surgical trauma.[26]

Clinical implications

Traditional on-pump CABG has established a low incidence of postoperative thrombotic events[41] that is believed to be mediated in part by the anticoagulating effect of CPB.[42] By circumventing CPB, OPCAB is widely believed to be associated with a “hypercoagulable state” akin to that described after general surgical procedures.[43] Current best available evidence from RCTs confirms that there is a tendency towards decreased activation of both coagulation and fibrinolysis with less pronounced changes in platelet counts and function after OPCAB resulting in a procoagulant state.

It important to mention that there is no consensus amongst various researchers regarding a definition for this “hypercoagulable state”. Whether activation of enzymatic component of the coagulation cascade or platelet hyperactivity is synonymous with postoperative “hypercoagulable state” remains unclear at present. One could argue that perhaps a more suitable definition for this hypercoagulability could be based on an endpoint of early failure of the coronary artery bypass graft. However, as graft patency is dependent upon multiple factors a better definition for “hypercoagulability” could perhaps be achieved by performing simple functional tests such as thromboelastography (TEG) or aggregometry which are cost-effective and can be easily performed and interpreted.

Interestingly, despite the preservation of hemostasis and procoagulant state after OPCAB correlation between this procoagulant and clinical outcome (namely graft patency) is still a matter of debate. Vein graft failure remains a major problem after CABG. Occlusion in the first weeks is secondary to thrombosis, whereas intimal hyperplasia and eventually atherosclerotic changes with superimposed thrombus formation underlie subsequent closure.[24] There are several possible explanations for the poorer graft performance in patients operated on by the off-pump technique: the poorer coronary vessel exposure, heart movement, poor coronary visualization provoked by bleeding, all render the distal anastomosis more difficult to perform and sometimes less accurate than those made with the heart arrested. The tools used during the anastomoses (intracoronary shunts, coronary occluding stitch, carbon dioxide blower) to improve visualization may all potentially damage the coronary and graft endothelium.[44]

To date, none of the RCTs has shown a correlation between procaoagulant state and early graft occlusion. This could be attributed to variable sampling periods in these RCTs with none of the trials powered or designed to detect impact of procoagulant state on thrombotic events.
Another important issue that stems from the presence of procoagulant state after OPCAB and merits further research is the perioperative anticoagulation policy for patients undergoing OPCAB. It is important to highlight that the postoperative anticoagulation treatment may differ quite significantly between off- and on-pump patients. It is uncertain at present whether for OPCAB patients the perioperative anticoagulation should be more aggressive than that for patients undergoing conventional on-pump CABG. Furthermore, the suitable dose of heparin administered intraoperatively and the need to antagonize the heparin with protamine at the end of the procedure are potential avenues for further research.
There is evidence to suggest that there is a significant increase in platelet resistance to aspirin effect in off-pump patients with early graft thrombosis.[45] The presence of hypercoagulability after OPCAB along with aspirin resistance in the early postoperative period is extremely risky for early graft failure because of thrombosis. There arises a question whether modification or intensification of the dose regimen of aspirin or different anti-platelet strategies after off-pump and on-pump bypass surgery could lead to a more effective inhibition of platelet aggregation with a minimum influence on postoperative bleeding and thus possibly improved clinical outcomes.
Antiplatelet therapy has been shown to improve vein graft patency.[46] Study by Chesebro et al.[47] demonstrated that the combination of dipyridamol and aspirin was effective. More agressive antiplatelet therapy, including clopidogrel, could potentially increase graft patency similar to the effect on intracoronary stents. The American College of Chest Physicians (ACCP) seventh conference on antithrombotic and thrombolytic therapy published their guidelines in 2004.[48] For patients who undergo CABG for non-ST segment elevation acute coronary syndrome (ACS), they recommend that clopidogrel should be started in addition to aspirin post-surgery and continued for 9–12 months. This recommendation is based on the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study[49] and the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study.[50]
The CAPRIE study reported an 8.7% relative risk reduction in the primary composite endpoint (first occurrence of ischaemic stroke, myocardial infarction or vascular death) in favour of clopidogrel (75 mg/day) over aspirin (325 mg/day) in a multicentre RCT of 19,185 patients with a history of recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease.[49] A sub-analysis of the CAPRIE database showed that in 1480 patients with a previous history of cardiac surgery, clopidogrel was associated with a relative risk reduction of 39% for vascular death, 38% for myocardial infarction, 25% for all-cause rehospitalization, and 27% for rehospitalization for ischemia or bleeding. A major drawback of this study is the lack of information about the type of cardiac surgery previously performed in these patients.
The CURE trial randomized patients with acute coronary syndromes (n = 12,562) to treatment with clopidogrel (300 mg then 75 mg/day) or placebo in addition to aspirin (75–325 mg/day). The antiplatelet combination resulted in a 20% risk reduction relative to aspirin alone (9.3% vs. 11.4%, $p < 0.001$) in the primary endpoint of cardiovascular death, myocardial infarction or stroke over a mean nine-month treatment period.[50] The antiplatelet combination produced a 19.0% reduction relative to aspirin alone in the risk of cardiovascular death, myocardial infarction or stroke among those patients who underwent CABG surgery during the initial hospitalisation and an 11.0% relative risk reduction among patients who underwent CABG surgery at any time during the treatment period. The clinical benefits of aspirin plus clopidogrel

were mainly evident during the preoperative period with 18% relative risk reductions in the primary endpoint seen before CABG surgery compared to 3% relative risk reduction following CABG surgery relative to aspirin alone.[51] The main pitfall of the study is that patients who did not take the drug after surgery were still included in the clopidogrel group and the effect of clopidogrel was not adjusted for other risk factors.

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated the short-term benefits of combined aspirin and clopidogrel pre-treatment and the long-term benefits of sustained therapy in the setting of percutaneous coronary intervention (PCI) in an RCT of 2116 patients. After one year of treatment, patients receiving clopidogrel (75 mg/day) plus aspirin (81–325 mg/day) had a significant 26.9% relative risk reduction in the combined endpoint of death, myocardial infarction or stroke.[52] A subgroup analysis of patients who underwent CABG without PCI had a modest reduction of 1-year events (risk reduction rate = 16.7%) with clopidogrel.[53] But this was a post hoc analysis and the number of patients in this group was small.

With regard to the other high risk group of patients, namely patients post PCI having CABG, at present there are no studies that report the outcome of stent patency post-CABG. The ACCP guidelines[54] recommend clopidogrel in addition to aspirin for all patients post PCI for 9–12 months. A small study by Kaluza et al.[55] demonstrated that there was an instent thrombosis rate of around 20% with a similar mortality in patients having surgery of any type shortly post PCI. Therefore, if the stent is not covered by a graft intraoperatively then it would seem reasonable to follow the ACCP guideline with 9–12 months of clopidogrel. However, if the stent is covered by a graft more distally, there is no evidence to support continuation of clopidogrel. Gao et al.[56] in their study, of one-hundred and ninety-seven selected patients undergoing CABG, assigned the patients to two groups according to antiplatelet drug: the clopidogrel group of 102 patients who received clopidogrel (75 mg) daily; and the combination group of 95 patients who received clopidogrel (75 mg) plus aspirin (100 mg) daily. Multislice computed tomography angiography was performed to evaluate graft patency at 1 month and 12 months after CABG. At 1 month and 12 months after CABG graft patency rates of clopidogrel group were, respectively, 99.0% and 96.9% for the left internal mammary artery (LIMA) and 98.1% and 93.5% for the saphenous vein grafts; those of the combination group were, respectively, 98.9% and 97.8% for LIMA, and 98.2% and 96.3% for saphenous vein grafts. There were no significant differences in graft patency between the two groups ($p > 0.05$). On the other hand, an RCT[57] to evaluate the effect of aspirin plus clopidogrel versus aspirin alone on SVG occlusion at 3 months after CABG showed that SVG patency was 91.6% (219 of 239) in the dual antiplatelet therapy group versus 85.7% (198 of 231) in the aspirin alone group ($p = 0.043$). In multivariate analysis, combined antiplatelet therapy independently increased venous graft patency ($p = 0.045$). Multislice computed tomography angiography was used to evaluate graft patency in this RCT. Similar conclusions were reached by Sun et al.[58] in their RCT which showed a high rate of graft occlusion after CABG surgery and suggested that the addition of clopidogrel to aspirin is feasible and safe.

Interestingly, the CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial[59] undertaken to evaluate whether the addition of clopidogrel to aspirin inhibits saphenous vein graft (SVG) disease after CABG, as assessed at 1 year by intravascular ultrasound, concluded that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia 1 year after CABG.

The published evidence for the use of dual antiplatelet therapy after OPCAB is extremely scant at present unlike that for on-pump CABG. Nielsen et al.[60] randomly assigned twenty nine patients to receive aspirin alone or clopidogrel and aspirin until 30 days after OPCAB. The follow-up time was 2 months including standard blood samples and TEG with a specific platelet inhibition assay. In both groups a significant increase in TEG maximum amplitude was found 5 days after surgery. Platelet inhibition showed great variations but was significantly increased in the clopidogrel group (34.1%) vs. control group (11.0%) after 1 month. This study showed that hypercoagulability was seen 5 days after OPCAB and could not be demonstrated after 1 month. An observational study by Gurbuz et al.[61] showed that clopidogrel therapy with aspirin was independently associated with decreased symptom recurrence and adverse cardiac events following OPCAB. However, extending clopidogrel use beyond 30 days did not have a significant effect on defined end points. A small recently published RCT[62] recruiting twenty patients undergoing OPCAB concluded that early administration of a combined regimen of clopidogrel and aspirin after OPCAB grafting is not associated with increased postoperative bleeding or other major complications. Despite the small number of patients in this study and small number of examined grafts, the results of this RCT suggest that the addition of clopidogrel may increase graft patency after OPCAB grafting.

Hence, additional studies are needed to address the need for dual anti-platelet therapy after OPCAB particularly when it is known that clopidogrel, unlike aspirin, inhibits not only platelet aggregation but also P-selectin expression.[21]

Conclusion

Cardiopulmonary bypass induces clotting disorders and platelet dysfunction. However, such an effect on hemostasis, which increases postoperative bleeding and is usually considered as adverse, also has a desirable effect in protecting anastomosis patency. An impaired hemostasis is thought to prevent thrombosis of the coronary grafts, presumably until a full postoperative regimen of antiplatelet therapy is established. Avoidance of CPB preserves hemostasis which may result in a hypercoagulable state after OPCAB surgery. At present however, it is not clear whether this hypercoagulable state translates into increased graft occlusion or adverse outcomes after OPCAB. It is expected that future laboratory and clinical research will provide greater insight into the mechanisms of this hypercoagulable state after OPCAB and its impact on clinical outcomes of relevance (graft patency and thrombotic events). Furthermore, any future research in this area will hopefully provide important information regarding the routine adoption of dual anti-platelet therapy and appropriate perioperative anticoagulation protocols to allay the anxiety attributed to presence of hypercoagulable state after OPCAB.

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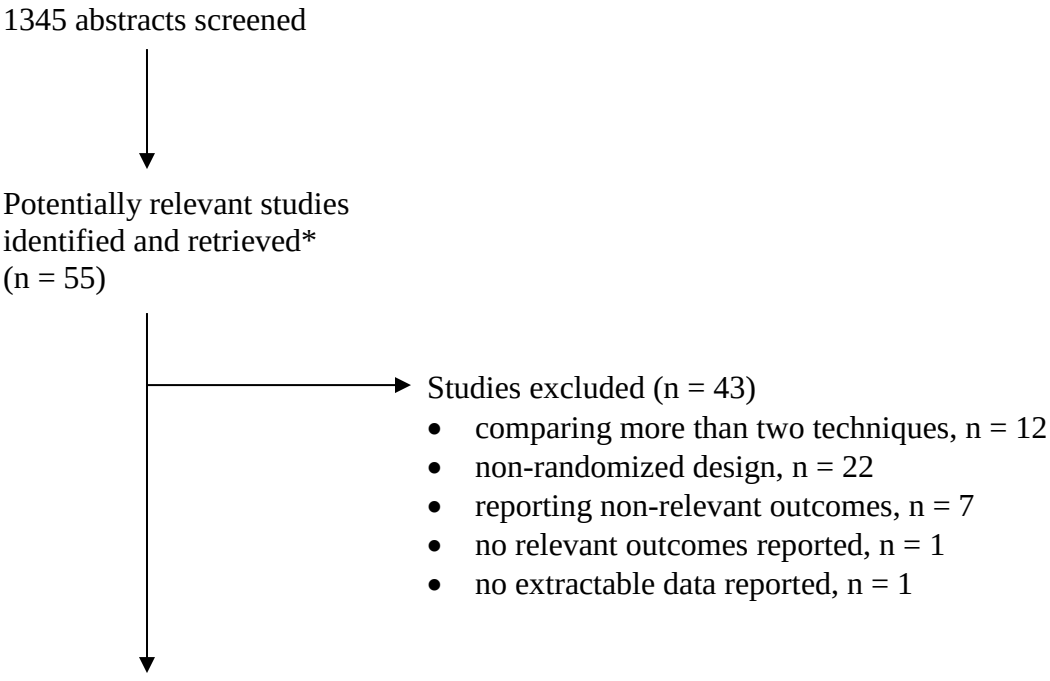

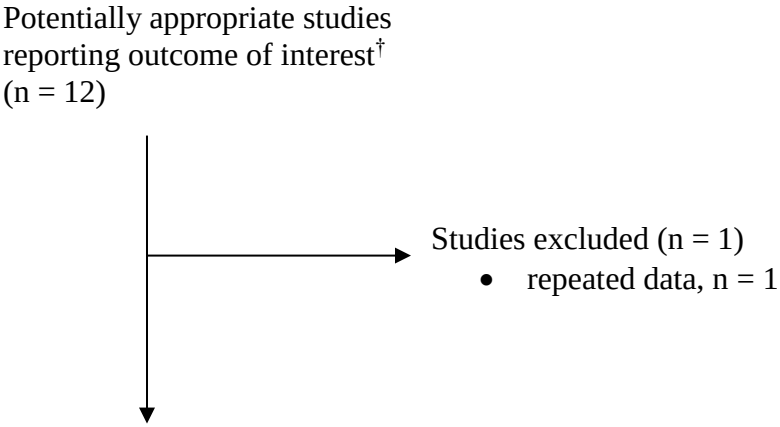

Figure 1. Identification of eligible studies.
* Randomized controlled trials
CABG = coronary artery bypass grafting; OPCAB = off-pump coronary artery bypass
† Coagulation, hemostasis, fibrinolysis or platelet activation

Table 1. Impact of off-pump coronary artery bypass surgery on coagulation, fibrinolysis & platelet activation

Author Year	Study type Level of Evidence	No of patients OPCAB	No of patients CABG	Outcomes	Key result	Hypercoagulable state OPCAB	Hypercoagulable state CABG	Ref.
Vallely et al. 2009	RCT (level 1b)	10	10	Tissue factor pathway-factor VIIa, von Willebrand Factor antigen, prothrombin fragments FI+II, D-Dimer, platelet counts & soluble P-selectin quantified upto 24 hrs post-operatively	Late thrombin generation, reduced fibrinolysis & intact functioning platelets after OPCAB	Yes	No	[19]
Paulitsch et al. 2009	RCT (level 1b)	51	41	CRP, fibrinogen, D-Dimer & plasminogen activator inhibitor type-1 quantified before (1 hr) & after (24 hr) surgery Clinical events assessed during initial hospitalization & after 1 yr	Significantly greater increase in plasminogen activator inhibitor type-1 & D-dimer concentrations after CABG ($P < 0.01$) No greater incidence of thrombotic events	No	Yes	[20]
Bednar et al. 2008	RCT (level 1b)	40	40	Platelet activity assessed by P-selectin expression Aspirin efficacy assessed by AA-induced platelet aggregation before operation, immediately after surgery, on days 1, 2, 5 & 30	Markedly increased P-selectin expression in OPCAB group on day 2 & day 5 Similar P-selectin expression at day 30 AA-induced platelet aggregation increased in OPCAB group on day 2	Yes	No	[21]
Jares et al. 2007	RCT (level 1b)	10	10	roTEG results obtained pre-op, at 15 min after sternotomy, completion of anastomoses & at the end of surgey D-dimer levels before operation, at the end of surgery& 24 hrs later	Slightly greater activation of fibrinolysis after CABG	Yes	No	[22]
Ballotta et al.	RCT	30	30	Platelet count & function assessed	Significant decrease in platelet	Yes	No	[23]

2007	(level 1b)			2 hr before and after surgery	count & increase in platelet activation after CABG			
Paparella et al. 2006	RCT (level 1b)	16	16	Activation of coagulation & fibrinolysis & platelet function assessed at 7 times up to day 6 post-operatively	Normally functioning platelets & weak activation of fibrinolytic sytem	Yes	No	[24]
Parolari et al. 2005	RCT (level 1b)	15	15	Plasma, monocyte-bound & platelet-bound tissue factor expression Platelet & soluble P-selectin expression assessed before surgery, after protamine administration & 4, 8 & 30 days after surgery	Similar tissue factor & P-selectin expression after CABG & OPCAB	Yes	Yes	[25]
Parolari et al. 2005	RCT (level 1b)	17	18	Prothrombin fragment F1.2, thrombin-antitrombin complex, D-dimer, vWF & VCAM1 levels measured before surgery & 1 month after surgery	Similar rise in markers of activation of coagulation, fibrinolysis & endothelium after CABG & OPCAB	Yes	Yes	[26]
Vedin et al. 2005	RCT (level 1b)	17	14	Fibrin D-dimer, prothrombin fragment 1.2, α-2macroglobulin, protein C1 esterase inhibitor, fibronectin & vWF levels assessed up to 24 hrs after surgery	Less activation of fibrinolysis & coagulation after OPCAB	Yes	No	[27]
Lo et al. 2004	RCT (level 1b)	20	20	Platelet count, fibrin D-dimer, prothrombin fragment 1.2, soluble fibrin, P-selectin & vWF levels measured up to day 4 after surgery	OPCAB group had delayed activation of hemostasis & it became equivalent to CABG group in the later post-operative period (20-96 hrs)	Yes	No	[28]
Møller et al. 2003	RCT (level 1b)	15	15	Platelet function assessed pre-op, immediate post-op, 4 hr post-op & 1 day postop	Significant increase in PAF-induced platelet aggregation after OPCAB compared to CABG	Yes	No	[29]

AA = arachidonic acid; CABG = on-pump coronary artery bypass grafting; CRP = C-reactive protein; OPCAB = off-pump coronary artery bypass; PAF = platelet activating factor; RCT = Randomized controlled trial; roTEG = rotation thromboelastography; VCAM = vascular cell adhesion molecule; vWF = von Willebrand factor