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Review

Pulmonary Embolus after Coronary Artery Bypass Surgery: A Review of the Literature

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Summary: Pulmonary embolus (PE) after cardiac bypass surgery is an uncommon complication but carries with it high morbidity and mortality. The incidence of deep vein thrombosis (DVT) and PE after cardiac bypass varies depending on postoperative thromboprophylaxis, the presence of indwelling central venous catheters in the lower extremities, and early ambulation. The clinical diagnosis of DVT remains difficult and challenging. Pulmonary embolus is often the first occurring clinical event. The safety and effectiveness of preventative pharmacologic agents, such as subcutaneous unfractionated or fractionated heparin or oral coumadin, remain largely unknown. Heparin-induced thrombocytopenia, generally associated with a high incidence of DVT and PE, occurs in approximately 3.8% of patients who have undergone cardiac surgery and are placed postoperatively on high-dose intravenous unfractionated heparin. Sequential compression devices (SCD) have not been effective in reducing the incidence of DVT in an ambulating cardiac bypass patient when added to routine elastic graded compression stockings (GCS). Very large clinical trials are necessary to prove the effectiveness of pharmacologic or mechanical preventative measures in reducing the incidence of PE after cardiac surgery above the commonly used GCS, early ambulation, and aspirin. In a nonambulating, higher-risk cardiac bypass patient with slow recovery, a more aggressive prophylaxis regimen might be necessary for optimal prevention, although further data are needed to support this hypothesis.

Key words: pulmonary embolus, cardiac bypass, heparin, platelets, graded compression stockings

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Introduction

Pulmonary embolism is a significant complication of many surgeries and remains a major source of morbidity and mortality. Annually, pulmonary embolus (PE) occurs in approximately 700,000 patients in the United States, leading to a fatal outcome in 20–40% of these cases.[1,2] The diagnosis of deep vein thrombosis (DVT) remains very challenging to the health care professional because DVT is mostly silent and lacks reliable and reproducible clinical symptoms and signs. Less than 5% of patients with DVT have obvious clinical findings,[3,4] and PE is often the first clinical event prior to the diagnosis of DVT.[5,6] Prevention of DVT probably remains the most cost-effective way to lower the incidence of PE.

The optimal prevention strategy for venous thrombosis and pulmonary embolism for several major surgeries was outlined by the Consensus Development Conference on Prevention of Venous Thrombosis and Pulmonary Embolism held by the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of Medical Applications of Research.[7] These included general, orthopedic, gynecologic-obstetric, urology, trauma, and neurosurgery. The incidence of DVT, PE, and fatal PE in these surgical subspecialties, as well as in patients with cardiac bypass is outlined in Table I. Prophylaxis regimens varied among the different surgeries and within the same surgical specialty depending on the patient's risk profile for DVT and PE. The Consensus Conference noted the lack of data from controlled trials for venous thromboembolism prophylaxis for patients undergoing coronary artery bypass surgery and issued no specific guidelines for this surgical subspecialty. Since then, a few published studies have discussed the frequency, risk factors, and mechanical prophylaxis for DVT and PE after cardiac bypass (Table II). No randomized clinical trials have yet addressed the issue of pharmacologic prophylaxis in this patient population.

Incidence and Clinical Course of DVT after Cardiac Bypass

In a study by Reis *et al.*,[3] the incidence of DVT after cardiac bypass surgery was 48.3% [95% confidence interval (CI) 30.1–66.4%] diagnosed at an average of 6.5 days after surgery by high-resolution B-mode ultrasonography with color Doppler imaging. All patients received aspirin and graded compression

TABLE I Approximate incidence of deep vein thrombosis (DVT) and fatal pulmonary embolus (PE) in different elective surgeries

Surgery/(Ref. no.)	DVT	Fatal PE
General surgery, % (7)	25	1
Orthopedic surgery, % (7)	50–70	1–6
Urology, % (7)	10–40	>1
Gynecology, % (7)	7–45	1–5
Neurosurgery, % (7)	24	1.5–3
Trauma, % (7)	20–40	1–4
Cardiac bypass, (3, 8)	23	0.3–0.7

stockings (GCS). Included in this study were 29 asymptomatic patients with cardiac bypass. Of these, 14 patients had 20 documented thromboses that were equally present in both contralateral and ipsilateral leg to the saphenous vein graft harvest site. None of these DVT's was clinically detected; 95% were limited to calf veins and were not treated with warfarin anticoagulation. Only one proximal popliteal vein thrombosis was diagnosed by ultrasonography and treated with anticoagulation. There was no association between pitting edema, incisional drainage, and tenderness of the lower legs and the presence of DVT. At 5 to 11 months follow-up, there was no clinical evidence of DVT and PE. This study was prospective but was limited by its small sample size and potential selection bias.

Goldhaber *et al.*[8] demonstrated a significantly lower incidence of DVT in a similar but significantly larger study after coronary artery bypass surgery. In this prospective study, 344 patients (all on aspirin) were randomized to GCS or combination sequential compression device (SCD) and GCS. Of these, 330 (96%) patients underwent bilateral duplex venous ultrasound examination on or after postoperative Day 4. Overall incidence of DVT was 20% (95% CI 16–25%) with no statistical difference between the two prophylaxis groups. Similar to the data by Reis *et al.*,[3] DVT was found equally in both contralateral and ipsilateral leg to the saphenous vein graft harvest

TABLE II Summary of major published studies of venous thromboembolism after cardiac bypass and/or valve surgery

Surgery First author Year/Ref. no	Total no. of patients in the study	No. of patients with DVT by screening US	Documented DVT by US & clinically detected	No. of patients with proximal DVT	No. of patients with pulmonary emboli (%) [days]	No. of patients with fatal pulmonary emboli (%)	Prophylaxis regimens
CABG							
Rao, 1975 (9)	231	?	?	?	22/231 (9.5) [?]	4/231 (1.73)	DA, GCS, no ASA[b]
Rao, 1975 (9)	450	?	?	?	13/450 (2.9) [?]	0/450 (9)	EA, Dipyridamole[c]
Wisoff, 1975 (10)	200	?	?	?	7/200 (3.5) [?]	0/200 (0)	Subcutaneous heparin
Reis, 1991 (3)	29	14/29	0/14	1/14	0/29 (0)	0/29 (0)	EA, GCS, ASA
Josa, 1993 (5)	819	?	?	?	32/819 (3.9) [13]	6/819 (0.73)	EA, ASA
Goldhaber, 1995 (8)	344	67/330	1/67	11/67	2/344 (0.6) [8]	1/344 (0.29)	GCS and/or SCD, ASA, EA
Pouplard, 1999 (12)	156	?	?	?	0/156 (0)	0/156 (0)	96% Dalteparin
Subtotal (%)	2,229	81 (22.6)	1 (1.2)	12 (14.8)	76 (3.4) [12.7]	11 (0.49)	
CABG + valve							
DeLaria, 1991 (6)	10,638	?	?	?	41 (0.4) [9.9]	6 (0.06)	ASA, Dip, Coumadin[a]
Gillinov, 1992 (11)	5,694	?	?	?	32 (0.6) [13]	11 (0.19)	ASA, Dip, Coumadin[a]
Subtotal (%)	16,332	?	?	?	73 (0.45) [11.3]	17 (0.1)	
Valve surgery							
Josa, 1993 (5)	120	?	?	?	0/120 (0)	0/120 (0)	Coumadin
Pouplard, 1999 (12)	137	?	?	?	1/131 (0.8) [?]	1/131 (0.76)	High-dose UFH
Subtotal (%)	257	?	?	?	1 (0.4)	1/ (0.4)	
Total (%)	18,818	81 (22.6)	1 (1.2)	12 (14.8)	150 (0.8) [12]	29 (0.15)	

[a] For valve patients only.

[b] Patients had lower extremity long venous catheters for 2–3 days and were kept bed rest 2–3 days.

[c] Patients with early ambulation, no GCS, no venous catheters.

Abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolus, US = ultra sound, CABG = coronary artery bypass surgery, ASA = aspirin, GCS = graded compression stocking, SCD = sequential compression device, LMWH = low molecular weight heparin, UFH = unfractionated heparin, Dip = dipyridamole, [days] = average time of occurrence of pulmonary embolus in days, EA = early ambulation, DA = delayed ambulation.

site, suggesting that trauma to the ipsilateral leg cannot explain the high DVT rate after cardiac bypass surgery. Among the 67 patients who had DVT in this study, 11 (16.4%) had proximal DVT and 56 (83.6%) had isolated calf DVT. Despite the higher incidence of proximal DVT than reported by Reis *et al.*,[3] only one (1.5%) patient with proximal DVT was symptomatic, emphasizing the silent nature of this complication after bypass surgery. The study by Goldhaber *et al.*[8] was prospective and randomized and included a large number of patients. Also, 96% of enrolled patients underwent predischarge venous ultrasound examination, lending validity to the data. It should be noted that the studies by Reis *et al.*[3] and Goldhaber *et al.*[8] were conducted at the same institution with many of the same investigators (Brigham and Women's Hospital, Harvard Medical School). Goldhaber *et al.* concluded that the decline rate of DVT in their later trial may be at least partially explained by earlier mobilization.

The difficulty in diagnosing DVT clinically was also emphasized by Josa *et al.*[5] In a retrospective study of 1,033 cardiac surgical patients, PE developed in 33 patients within 2 weeks of surgery. The clinical diagnosis of DVT was established in only one patient before PE occurred, a recognition rate of approximately 3% prior to the embolic event. Also, DeLaria and Hunter[6] noted an incidence of 0.7% of clinically recognized DVT in 10,638 patients who underwent cardiac surgery at Rush-Presbyterian-St Luke's Medical Center in Chicago. The true rate of DVT in these retrospective studies is unknown because venous duplex ultrasound is not routinely performed on the lower extremities after bypass surgery. As in the studies of Reis *et al.*[3] and Goldhaber *et al.*,[8] DVT occurred equally in either leg. Similar to cardiac patients, Stulberg *et al.*[4] demonstrated that only 5% of orthopedic surgical patients have clinical findings of DVT. The actual rate of DVT in their study of 638 patients with knee arthroplasty was 46.2%, as confirmed by venography. Of all these DVTs, 96.8% were located in the ipsilateral leg to the site of knee surgery, in contrast to patients who had undergone cardiac surgery and in whom DVT occurred equally in both ipsilateral and contralateral legs, suggesting different pathophysiologic mechanisms for DVT formation between the two surgical populations.

In summary, DVT occurs in approximately 23% (Table II) of ambulating cardiac bypass surgery patients treated with GCS and aspirin. Clinically, DVT after cardiac surgery is very difficult to recognize, with < 2% of patients identified (Table II). Deep vein thrombosis after cardiac bypass is mostly silent and did not correlate with physical findings in the lower extremities.

Incidence and Clinical Course of PE after Cardiac Bypass

Pulmonary embolus occurred in 0.4 to 9.5% (average of 3.4%) of published studies after bypass surgery (Table II). It was fatal in 0.3 to 1.7% (average 0.5%) of cases. The wide difference in PE and fatal PE rates in these studies is probably related to various postoperative thromboprophylaxis regimens, the presence of indwelling central venous catheters in the lower extremities, and early or delayed ambulation. More recent thromboprophylaxis management after cardiac bypass surgery consisted of early ambulation and treatment with antiplatelets and GCS. With these measures, the rate of fatal PE was reported to be in the range of 0 to 0.7%.[3, 5, 8] This incidence appears to be lower than that reported for general surgery (0.8–1%), orthopedic surgery (1–6%), neurosurgery (1–5%), and trauma patients (1–4%).[7]

In the prospective study by Goldhaber *et al.*,[8] PE occurred in 0.6% of patients with bypass and fatal massive PE in 0.3% (1 of 344 patients on Day 8 post surgery). There was no weight or age exclusion for enrollment in this study. Patients with a prior history of DVT or PE, peripheral vascular disease, intraaortic balloon pump insertion, or planned postoperative anticoagulation were excluded. All patients had DVT prophylaxis with GCS or combined SCD and GCS, and all were on aspirin. A strategy of early mobilization was adopted. Furthermore, patients with silent proximal DVT identified on routine ultrasonography were treated with warfarin at an average of 6.5 days post surgery. All these factors have probably led to the very low incidence of PE and fatal PE in this patient population. In contrast to the above data, Josa *et al.*[5] reported an incidence of PE and fatal PE of 3.9 and 0.7%, respectively, after cardiac bypass surgery. The higher incidence of PE in their series is probably related to lack of DVT prophylaxis with GCS. In addition, a large percentage of their patients had delayed postoperative recovery. In fact 17.9% of all, 54.5% with PE and 83% with fatal PE, met the authors' definition of slow recovery as "unable to complete level III activities on postoperative Day 6." Furthermore, venous ultrasonography was not routinely performed postoperatively since it is not a standard routine screening test after cardiac surgery.

Rao *et al.*[9] reported a 9.5% incidence of PE after cardiac bypass in 1974. Fatal outcome was observed in four (1.7%) patients in their series. This exceptionally high rate of PE and fatal PE was attributed to lack of antiplatelet use postoperatively and indwelling long lower extremities venous catheters kept for 2–3 days after surgery and subsequent prolonged bed rest. When dipyridamole, early ambulation, and removal of venous catheters (GCS not utilized) were applied, PE and fatal PE rates were reduced to 2.9 and 0%, respectively. Wisoff *et al.*[10] also reported a 2.9% incidence of PE in 200 consecutive patients with bypass on low-dose subcutaneous heparin (GCS not utilized). Subcutaneous heparin alone did not seem to have a lower incidence of PE than other thromboprophylaxis preventative methods.

Cardiac patients undergoing both coronary bypass and valve surgery had a combined incidence of 0.8 and 0.15% PE and fatal PE, respectively (Table II). This low incidence is accounted for by the routine use of coumadin in patients with valve surgery. The incidence of PE was 0.6% as demonstrated in a study by Gillinov *et al.*[11] when patients with valve surgery are pooled with those who underwent coronary artery bypass. Of 5,694 patients undergoing cardiac surgery at Johns Hopkins Hospital, 32 had PE within 60 days of operation. Pulmonary embolus occurred on average on postoperative Day 13.

Twenty (62%) patients had PE while in hospital. The incidence of fatal PE among all patients who underwent cardiac surgery was 0.2%. These findings were consistent with data published by DeLaria and Hunter[6] who found a 0.4% incidence of PE in 10,638 cardiac patients undergoing surgery at Rush-Presbyterian-St Luke's Medical Center in Chicago. Pulmonary embolus occurred on an average of 9.9 days postoperatively in their series; fatal PE occurred in 0.1%. Patients with isolated valve surgery are generally on warfarin and had no demonstrable fatal PE, as shown by Josa *et al.*[5] When high-dose unfractionated heparin was utilized after valve surgery instead of coumadin, the rate of fatal PE was 0.8%. We can, therefore, conclude that the low incidence of PE and fatal PE in the studies of Gillinov *et al.*[11] and DeLaria and Hunter[6] is probably secondary to the inclusion of patients undergoing cardiac valve surgery and treated with warfarin in their analysis. Unfractionated heparin did not appear to have the same protection as coumadin after valve surgery, probably because of a high incidence (3.8%) of heparin-induced thrombocytopenia (HIT) and subsequent thrombosis.[12] Randomized studies are needed to confirm this observation.

Pulmonary embolus after bypass surgery appears to have a high rate of recurrence after the diagnosis is made and despite adequate intravenous heparin and/or coumadin treatment. DeLaria and Hunter[6] noted a recurrence rate of fatal PE in six (25%) patients with diagnosed PE on intravenous anticoagulation with heparin. Given the high rate of recurrent fatal PE with iliac and inferior vena cava thrombosis, early caval interruption and anticoagulation were recommended in their series. In fact, 17 (41.5%) patients with diagnosed PE in their study underwent caval interruption for three reasons: (1) contraindication to anticoagulation, (2) recurrent pulmonary embolus despite anticoagulation, and (3) prevention of a second PE in patients with large proximal DVT. None of these patients with caval interruption died from a recurrent PE.

Based on the available data, it appears that fatal PE is an uncommon complication after cardiac bypass, with an approximate incidence of 0.5%. The timing of PE appears mostly in the first 2 weeks postoperatively at an average of 12.7 days (Table II). Patients with slow postoperative recovery, indwelling central venous catheters, and receiving no DVT prophylaxis with GCS or antiplatelets may have a higher rate of fatal PE. Despite anticoagulation, PE has a high rate of fatal recurrence (25%), and, in a patient with cardiac bypass with PE and documented iliac and inferior vena cava clots, caval interruption in addition to anticoagulation should be considered.

The incidence of DVT and fatal PE appears to be lower than in other major surgical specialties, particularly orthopedic, gynecology, neurosurgery, and trauma (Table I). The reasons for this are unknown but probably multifactorial. Generally, patients with bypass surgery receive a large amount of heparin intraoperatively in the range of 40,000 to 50,000 U to keep an activated clotting time of >450 s, probably preventing significant clotting from forming during the several hours of surgery. In addition, routine antiplatelet therapy with aspirin is administered after bypass surgery. Although this therapy is not sufficient in itself to prevent DVT, it was shown by the Antiplatelet Trialist's Collaboration[13] to be is a very useful adjunctive therapy to other methods of thromboprophylaxis. In a review of 53 randomized trials, a few weeks of therapy with antiplatelet agents significantly reduced the incidence of DVT. In fact, for every 1,000 patients treated with antiplatelets, 90 were prevented from forming DVT ($2\ p < 0.00001$). Pulmonary emboli, fatal and nonfatal, were also reduced significantly with adjunctive antiplatelets use. The risk of DVT and PE was roughly halved by antiplatelet use after high-risk surgeries. There are no randomized antiplatelet trials for DVT and PE prophylaxis after bypass surgery since it is standard of care to have patients with cardiac bypass on aspirin daily to prevent graft thrombosis. It is probable that the large amounts of heparin administered intraoperatively, along with thrombocytopenia and hemodilution associated with cardiopulmonary bypass, and the routine use of antiplatelets and early ambulation postoperatively, offer some protection against DVT and PE.

The initial clinical presentation of PE in the majority of patients undergoing cardiac surgery has been generally catastrophic. In a study of Josa *et al.*,[5] 22 (67%) patients presented with massive PE and 11 (33%) had submassive PE. Massive PE was defined in their study as an embolus involving ≥40% of the pulmonary vasculature. Similarly, DeLaria and Hunter[6] demonstrated that 61% of patients who developed a PE after cardiac surgery had no known DVT despite an aggressive clinical monitoring program for thromboembolism. Eleven (27%) patients had a cardiac arrest as their first clinical manifestation. Furthermore, eight (25%) PE cases at Johns Hopkins Hospital were first diagnosed at autopsy,[11] underscoring the difficulty in clinically predicting patients who will develop massive PE. The diagnosis of PE was made only after "highly suggestive" clinical manifestations became apparent, as noted in the study by Josa *et al.*[5] No detailed clinical signs or symptoms, however, were described preceding the occurrence of PE in their study. A massive PE does not present with subtle clinical findings. As outlined by Bell and Simon,[14] it is associated with sudden chest pain (85%), dyspnea (85%), tachypnea (95%), apprehension (65%), rales in the lung (57%), cough (53%), and increase in the intensity of the pulmonic component of the second heart sound (58%). In <50% of patients with massive PE, sweat, syncope, tachycardia, diaphoresis, gallops, DVT, edema, murmur, and cyanosis could also be present. Hemoptysis is described in 30% of all and 70% of lethal pulmonary infarcts secondary to PE. In submassive PE, the same clinical manifestations also occur, but at lower frequency except for chest pain (89%), dyspnea (82%), and tachypnea (87%).

The reason for the confusion in diagnosing a PE after cardiac bypass is probably multifactorial. Clinically detected DVT in the cardiac surgical patient is extremely low, averaging <2% (Table II) of all patients with the confirmed diagnosis. The inability to detect DVT clinically masks an important precursor for PE. In addition, all signs and symptoms described with PE can be normally seen after bypass surgery. Chest pain, pleuritic or not, is a frequent complaint in a surgical patient with a recent sternal incision and a pericardiotomy. Analgesics are also administered routinely for pain control and

could blunt chest discomfort from a PE. Dyspnea, wheezing, tachypnea, and rhonchi are also seen after cardiac bypass. Fluid overload, cardiac dysfunction and CHF, atelectasis, ileus, pleural effusions, prior history of chronic obstructive pulmonary disease and deconditioning are also present in a patient with bypass and could lead to dyspnea and tachypnea. Cardiac murmurs, gallops, and elevated jugular venous distention are not uncommon in patients with cardiac dysfunction and, therefore, are not specific for PE after cardiac surgery. Venous insufficiency, lower extremity edema, pain, and swelling at the site of saphaneous bypass graft harvesting do not correlate with the presence of DVT. Tachycardia is not infrequent after bypass surgery because of postoperative increase in catecholamines, fluid overload, cardiac decompensation, discomfort, and deconditioning. Apprehension, anxiety, and restlessness are also often described after cardiac bypass. Furthermore, hypoxemia is also frequently encountered in a cardiac patient and can be related to atelectasis, pleural effusion, infection, severe ileus, or CHF. On the other hand, the lack of hypoxemia does not rule out a significant pulmonary embolus, including a large one. The triad of an abrupt and unexplained occurrence of chest pain, dyspnea, and tachypnea should raise the suspicion of a PE with or without hypoxemia.[14, 15] Roentgenograms of the chest are often abnormal after cardiac bypass, with findings of pleural effusions,[16, 17] atelectasis, pulmonary venous congestion, chronic obstructive pulmonary disease, infiltrates, or an elevated diaphragm. Pleural effusions were seen in 96% of patients with PE complicated with pulmonary infarction.[14] On the other hand, pleural effusions occur in up to 89% of patients within 7 days after bypas surgery.[17] The effusion characteristic is also not helpful. Large bloody pleural effusions after bypass were mostly secondary to bleeding in the chest cavity.[16] Finally, electrocardiographic findings in PE are often abnormal but are nonspecific; however, if a right ventricular strain pattern is noted, it should raise the suspicion of a PE.[14]

In conclusion, PE and fatal PE occur very uncommonly after bypass surgery in an ambulating patient treated with GCS and antiplatelets (Table II). Massive PE is frequently the first clinically occurring event and is often fatal. The clinical diagnosis of a submassive PE is very difficult and can be missed since most of the symptoms and signs of a PE are common findings in the postoperative cardiac patient. Routine screening for DVT or PE after bypass surgery cannot be recommended and probably is not cost effective. Unexplained and abrupt occurrence of chest pain, dyspnea, and tachypnea with or without hypoxemia should, however, raise the suspicion of a PE.

Risk Factors for DVT and PE after Cardiac Bypass Surgery

A few studies have addressed the issue of thromboembolic risk factors after cardiac bypass. Data suggest that delayed recovery or immobilization, as well as postoperative CHF are major risk factors for PE by both univariate and multivariate analysis.[11] Recent cardiac catheterization and age were not significant risk factors by univariate analysis[5, 11] but became important with multiple logistic regression analysis.[8, 11] Individual reports using univariate analysis without adjusting for other risk factors suggested that obesity,[5] prior history of DVT and PE,[5, 11] recent myocardial infarction,[16] hyperlipidemia,[5] preoperative atrial fibrillation,[6] blood type A,[6] and HIT[5] were also significant risks for DVT or PE. When slow recovery and CHF were controlled for in multivariate analysis, prior history of DVT, myocardial infarction, and obesity were not significant risks.[11] On the other hand, gender, presence of varicose veins, cigarette use, past malignancy, race, peripheral vascular disease, preoperative and postoperative intra-aortic balloon pump, diabetes, and repeat surgery for hemorrhage do not appear to increase the risk of thromboembolic disease significantly after cardiac surgery.[3, 11]

Immobility, Delayed Recovery, and CHF

Delayed postoperative recovery defined as unable "to complete level III of the rehabilitation program by postoperative Day 6" was associated with a high incidence of PE after cardiac surgery.[3, 5] In the study by Josa *et al.*,[5] 54.5% of the 33 patients with PE and 83.3% of the 6 patients with fatal PE had delayed recovery. Delayed recovery was significantly present in more patients with than without PE ($p < 0.01$). This was further confirmed by the study of Gillinov *et al.*[3] who demonstrated, using multiple regression analysis, that postoperative bed rest of more than 3 days and preoperative bed rest in a patient undergoing cardiac bypass were associated with a higher incidence of PE ($p = 0.015$ and 0.011, respectively). This risk factor was conceptualized as early as 1860 by Virchow who described the triad of stasis, vein wall damage, and hypercoagulability as significant pathophysiologic factors that predispose to PE.[18] Venous stasis is thought to be the single most important factor that precedes the occurrence of most PE. Prolonged immobility leads to reduction in the velocity of venous flow reaching its nadir after 7 days of continuous bed rest.[14]

Pulmonary embolus occurred on average at Day 12 in all cardiac surgical patients (Table II). Although it is possible that vein wall damage can account for the high rate of DVT in orthopedic patients, this probably does not apply to patients undergoing cardiac bypass who have an equal rate of DVT in both ipsilateral and contralateral legs to the site of saphenous vein graft harvesting.[3, 8] Also, hypercoagulability under general anesthesia is probably not a major issue in a cardiac patient receiving 40,000 to 50,000 U of heparin intraoperatively. Myocardial infarction[6] and prior history of DVT[5, 11] were found to be risk factors for PE by univariate analysis. However, they were not independent risk factors for PE in multivariate analysis when slow recovery and CHF were considered.[11] Goldhaber *et al.*[8] described age as an independent risk factor for DVT following cardiac bypass, using multivariate analysis after controlling for gender, prophylaxis assignment (GCS or GCS and SCD), compliance with prophylaxis, presence of cancer, or length of hospital stay. Unfortunately, they did not adjust for delayed recovery, immobility, or the presence of CHF in their patients. When these were controlled for in the study of Josa *et al.*,[5] age did not seem to remain an independent risk factor.

We conclude that delayed recovery and immobility with or without CHF are significant risk factors for DVT or PE after bypass surgery. Venous trauma and hypercoagulability due to surgery and anesthesia are probably less important in a patient undergoing cardiac bypass. Myocardial infarction, prior history of DVT, and age do not seem to be independent risk factors when slow recovery and/or CHF are controlled for in a multiple logistic regression analysis.

Obesity and Hyperlipidemia

Univariate analysis by Josa *et al.*[5] indicated that obesity and hyperlipidemia are risk factors for PE after cardiac bypass. In contrast, data by Gillinov *et al.*[11] using univariate and multivariate analysis failed to indicate that obesity is a significant risk factor for PE ($p = 0.41$). Similarly, in patients undergoing gastric bypass because of obesity, with a minimum weight of 100 pounds over normal, the incidence of fatal PE was < 1%.[19] No patient had prophylactic therapy for DVT in this study. The authors concluded that extreme obesity might not necessarily be a major independent risk factor for postoperative DVT.

Although hyperlipidemia was reported to increase the risk of PE after bypass,[5,20] multivariate analysis controlling for important risk factors such as immobilization, delayed recovery, and CHF was not performed in these studies. The importance of hyperlipidemia as an independent risk factor for DVT or PE after cardiac surgery should await further studies.

Preoperative Hospital Stay and Time between Cardiac Catheterization and Bypass Surgery

Recent cardiac catheterization and longer preoperative hospital stay were associated with increased risk of PE after cardiac surgery as demonstrated by multivariate analysis.[11] The average preoperative hospital stay in patients with PE was 5.3 days compared with 3.1 days in patients with no PE ($p = 0.003$). Many DVTs may have occurred in hospital prior to the surgery (20–40%) as was demonstrated by Heatley *et al.*[21] and Sigel *et al.*[22] in a group of general surgery patients. Preoperative inactivity was thought to be a significant risk for preoperative DVT.[11] Recent cardiac catheterization was also found by multivariate analysis to be a risk factor for DVT.[11] The frequency of right heart catheterization performed via the common femoral vein, the use of indwelling venous catheters, heparinization during the test, and activity of these patients preoperatively were not reported. Further data are needed to confirm whether recent cardiac catheterization is a preoperative risk factor for PE after cardiac bypass. Minimizing preoperative hospital stay, however, may prove to be part of an important strategy for PE prevention postoperatively.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (type II) is a significant complication of heparin therapy, often associated with arterial and venous thrombosis.[23] It occurs when platelet factor 4 (PF4) binds heparin and forms PF4/heparin complexes (H-PF4). IgG antibodies then attach to the H-PF4 complexes, which subsequently bind to platelets[24] and heparin sulfate on cell walls.[25] This leads to platelet activation and endothelial damage, both predisposing to clot formation. The hallmark of HIT is its occurrence after Day 5 in heparin-treated patients.[26,27] Patients exposed to heparin prior to surgery might have an accelerated course of HIT.

Cardiopulmonary bypass (CPB) has been described to activate platelets and induce the release of PF4. The interaction of heparin and PF4 could potentially lead to further platelet activation and thrombus formation. Bauer *et al.*[28] demonstrated that 50% of patients who received a short treatment with unfractionated heparin had antibodies to H-PF4 on postoperative Day 5. Similarly, Pouplard *et al.*[12] recently showed that patients who received continuous unfractionated heparin after valve surgery, or subcutaneous dalteparin 5000 IU daily after bypass surgery, had a significantly high rate of antibodies to H-PF4 on postoperative Day 8 (29.3 and 21.6%, respectively). In their study, "early" benign thrombocytopenia occurred during and immediately after cardiac surgery but resolved between Days 4–6 postoperatively.[12] "Late" thrombocytopenia in patients with HIT followed a similar course to benign early postoperative thrombocytopenia until approximately Days 7–10 after surgery when suddenly platelet count fell sharply (Fig. 1). The sudden "late" drop in platelet count should alert physicians about the possibility of HIT and heparin should be discontinued. In the study of Pouplard *et al.*,[6] (3.8%) patients in the unfractionated heparin group but none in the dalteparin group developed HIT. Patients with HIT had a significantly lower platelet count on Days 8–10 after surgery ($p < 0.03$).

The use of heparin preoperatively during cardiac catheterization does not seem to alter the course of "early" and "late" thrombocytopenia after cardiac surgery. All patients enrolled in the study of Pouplard *et al.*[12] were exposed to heparin during angiography. Early HIT (< 6 days) did not develop in these patients since the early drop in platelet count did spontaneously recover despite the continuous use of therapeutic heparin. The lack of early HIT (Day 1–6) can be explained by the very

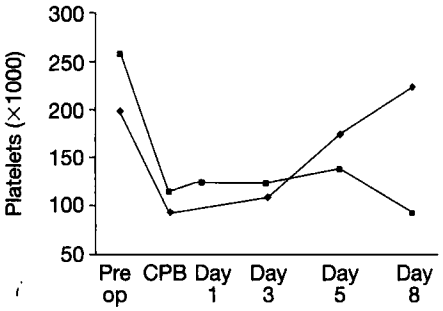

FIG. 1 Platelet counts prior to (pre op), during, and after cardiopulmonary bypass (CPB) in patients receiving continuous intravenous unfractionated heparin postoperatively with (■) and without (◆) heparin-induced thrombocytopenia. Heparin-induced thrombocytopenia developed approximately on Day 8 with relative reduction in platelet count starting Day 5. Modified from Ref. No. 12 with permission.

small doses of heparin administered during the diagnostic cardiac catheterization (1000–3000 U). In prospective studies, larger therapeutic doses of heparin were generally needed (> 20,000 U/day) for the development of HIT in the majority of patients.[29] Similar to the findings of Pouplard *et al.*,[12] Josa *et al.*[5] demonstrated that early thrombocytopenia resolved in patients in whom HIT was serologically proven within the first few days after surgery. Patients were not on subcutaneous heparin postoperatively for thromboprophylaxis, and all of them received 2000 U of heparin intravenously during the cardiac catheterization. Unfortunately, no data on late thrombocytopenia were provided in their study. Patients, however, developed their PE between Days 6 and 16 postoperatively, suggesting that late HIT had occurred.

In a study by Josa *et al.*,[5] univariate analysis demonstrated that patients with HIT had a higher chance of developing PE ($p < 0.02$). Aggressive clinical follow-up is indicated in patients who develop HIT and who should be monitored closely for thrombosis. The diagnosis of HIT can then be confirmed by different laboratory assays, including heparin-induced platelet activation (HIPA), serotonin release assay (SRA), or PF4/heparin ELISA.[29, 30] Unfortunately, these tests are very specialized and not widely available in many hospitals. Therefore, the diagnosis of HIT is mostly suspected on clinical grounds. The course of "early" benign versus "late" malignant thrombocytopenia (HIT) is not unique in the patient who had undergone cardiac surgery. In a large trial of 665 patients undergoing hip replacement, Warkentin *et al.*[27] demonstrated "early" thrombocytopenia in 189 (28.4%) patients all of whom had either a negative serology for HIT or a spontaneous recovery of platelets despite continuing heparin. Eleven (1.7%) patients developed late (Days 5–10) thrombocytopenia, and of these, nine had confirmed HIT by serologic testing. Clinically, two (22.2%) of these nine patients developed PE and eight (88.9%) developed DVT.

In summary, late thrombocytopenia occurring after Day 6 following cardiac surgery seems to be a significant factor in the development of DVT and PE. Multivariate analyses are needed to determine with certainty whether thrombocytopenia after bypass surgery will hold as an independent risk factor for DVT and PE after controlling for strong variables such as slow recovery or CHF. Patients who develop HIT need to be monitored aggressively for thromboembolism. Recombinant hirudin (lepirudin) is a recently approved drug for the treatment of HIT-associated thromboembolic complications. In a recent study by Greinacher *et al.*,[31] lepirudin was shown to be effective in restoring and sustaining a rapid platelet recovery and prolonging the partial thromboplastin time sufficiently. The combined incidence of death, amputation, and new thromboembolic complications was significantly reduced with lepirudin compared with historical control ($p = 0.014$).

DVT and PE Prophylaxis after Cardiac Bypass

To our knowledge, there have been no specific consensus guidelines on venous thromboprophylaxis after bypass surgery. Currently, in the first 24 h after surgery, the leg from which the vein harvest was obtained is kept wrapped with ace bandages. No indwelling venous catheters are left in the lower extremity veins, and patients are generally ambulating from Day 1 after surgery to prevent immobility and venous stasis. Graded compression stockings have been used on both legs during in-hospital stay (Table II). All patients with bypass are generally on some form of antiplatelet therapy after surgery, mostly aspirin. Despite these measures, the DVT rate continues to be as high as 23% (Table I), but the clinical course of these DVTs appears mostly benign in the majority of patients, with an incidence of fatal PE of approximately 0.5%. In a randomized study, SCDs have been shown to add no protection against DVT prophylaxis in an ambulating patient after bypass surgery who was on aspirin and was treated with GCS.[8] Also, they are generally uncomfortable to a patient with recent long leg incisions. The use of SCD has not been recommended for routine thromboprophylaxis after cardiac surgery.[6]

No data on the safety and efficacy of subcutaneous heparin after bypass surgery are available. Cardiac surgeons have avoided the use of heparin after bypass surgery because of the increased incidence of bleeding.[8] Continuous unfractionated heparin also carries the risk of thrombotic complications in a cardiac patient predisposed to HIT.[12] After cardiopulmonary bypass, patients have an increased incidence of antibodies against H-PF4 complexes, which could predispose them to the formation of "white clots." Low molecular weight heparin (LMWH) has not been approved in the United States for thromboprophylaxis after bypass surgery. Also, LMWH after cardiopulmonary bypass causes an increase in IgG antibodies against H-PF4 equal in magnitude to unfractionated heparin. Although the incidence of HIT appears low with LMWH,[12, 27] further data are needed to demonstrate its efficacy and safety after cardiac surgery prior to recommending its routine use. It should be noted that mortality reduction trials from PE are very difficult to conduct after bypass surgery. It has been estimated that in a randomized trial, 20,000 patients are needed to demonstrate a reduction of fatal PE from 0.8 to 0.4% and a 90% power of achieving conventional level of significance.[32] It is not surprising, therefore, to see no randomized pharmacologic venous thromboprophylaxis mortality studies conducted yet after bypass surgery. Caval interruption should be considered in patients who cannot take anticoagulation or have recurrent PE and have a documented first PE.[6] Also, since the rate of fatal PE recurrence is high (25%) despite therapeutic anticoagulation, patients with a first PE and documented large proximal DVT, particularly involving the iliacs and the inferior vena cava, should be considered for caval interruption.[6]

Conclusion

Deep vein thrombosis after cardiac bypass results in a low incidence of approximately 0.5% fatal PE. The clinical recognition of DVT in a patient after cardiac surgery is extremely low (< 2%, Table II) given its silent nature. Currently, venous thromboprophylaxis in a patient after bypass surgery includes

early ambulation, GCS, and the routine use of aspirin. Beyond these measures, SCD does not appear to add significant protection. The routine use of subcutaneous unfractionated heparin cannot be recommended at this time because its benefits have not been weighed against its risks after CPB, namely, bleeding and possibly HIT with subsequent thrombosis. Although the risk of HIT was 3.8% after cardiac valve surgery with the continuous use of high-dose unfractionated heparin, this risk is unknown for patients receiving low-dose thromboprophylaxis heparin after bypass. Low molecular weight heparin probably results in a lower incidence of HIT in a patient after cardiac bypass surgery, but its overall safety and cost effectiveness in preventing PE above GCS, early ambulation, and aspirin need to validated. Currently, LMWH is not an approved drug for thromboprophylaxis after bypass surgery in the United States. In a patient with slow recovery and CHF, the incidence of fatal PE might increase significantly (up to 0.7%), and the additional use of SCD and/or subcutaneous LMWH for thromboprophylaxis might prove beneficial in this subgroup of patients. Data are needed to confirm this hypothesis and determine the cost effectiveness of this preventative approach.

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