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Perioperative in-stent thrombosis after lung resection performed within 3 months of coronary stenting☆

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Abstract

Background: Incidence of perioperative in-stent thrombosis associated with myocardial infarction in patients undergoing major lung resection within 3 months of coronary stenting. **Methods:** Retrospective multi-institutional trial including all patients undergoing major lung resection (lobectomy or pneumonectomy) within 3 months of coronary stenting with non-drug-eluting stents between 1999 and 2004. **Results:** There were 32 patients (29 men and 3 women), with age ranging from 46 to 82 years. One, two or four coronary stents were deployed in 72%, 22% and 6% of the patients, respectively. The time intervals between stenting and lung surgery were <30 days, 30—60 days and 61—90 days in 22%, 53% and 25% of the patients, respectively. All patients had dual antiplatelet therapy after stenting. Perioperative medication consisted of heparin alone or heparin plus aspirin in 34% and 66% of the patients, respectively. Perioperative in-stent thrombosis with myocardial infarction occurred in three patients (9%) with fatal outcome in one (3%). Twenty patients underwent lung resection after 4 weeks of dual antiplatelet therapy as recommended by the ACC/AHA Guideline Update; however, two out of three perioperative in-stent thrombosis occurred in this group of patients. **Conclusions:** Major lung resection performed within 3 months of coronary stenting may be complicated by perioperative in-stent thrombosis despite 4 weeks of dual antiplatelet therapy after stenting as recommended by the ACC/AHA Guideline Update.

Keywords: Ischemic heart disease; Coronary stenting; Lobectomy; Pneumonectomy; Stent thrombosis

1. Introduction

Patients with coronary artery disease (CAD) requiring major lung resection present a vexing dilemma with respect to appropriate treatment. Anatomical lung resection such as lobectomy or pneumonectomy may lead to an increased risk of perioperative myocardial infarction in patients with severe untreated CAD. Myocardial revascularisation prior to lung surgery may inappropriately delay the resection with the risk of disease progression. This holds especially true for resectable non-small cell lung cancer (NSCLC), which is the most frequent indication for elective major lung resections. The ACC/AHA Guideline Update for perioperative cardiovascular evaluation for non-cardiac surgery recommended coronary artery bypass grafting before an elective procedure of high or intermediate risk in patients with prognostic high-risk coronary anatomy [1]. Likewise, the Guideline Update recommended that the indications for percutaneous coronary interventions (PCI) in the perioperative setting should be similar to those in the ACC/AHA guidelines for use of PCI in general. However, surgery should be delayed for at least 1 week after balloon angioplasty, and if a coronary stent is used, a delay of ideally 4—6 weeks should occur before surgery to allow 4 weeks of dual antiplatelet therapy [1].

We had one perioperative death related to in-stent thrombosis after uncomplicated lobectomy for NSCLC following coronary artery stenting, despite 4 weeks of aspirin and clopidogrel medication after stenting and the administration of heparin plus aspirin in the perioperative setting [2]. This retrospective multi-institutional trial was performed to assess the incidence of perioperative in-stent

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thrombosis associated with myocardial infarction in patients undergoing major lung resection within 3 months of coronary stenting. Of particular interest was the incidence of perioperative in-stent thrombosis in patients with 4 weeks of dual antiplatelet therapy after stenting as recommended by the ACC/AHA Guideline Update.

2. Patients and methods

2.1. Patient enrolment

All patients undergoing lobectomy or pneumonectomy within 3 months of coronary artery stenting in one of the above-mentioned institutions between 1999 and 2004 were identified and the data were retrospectively analysed with respect to perioperative morbidity and mortality and the development of in-stent thrombosis associated with myocardial infarction.

2.2. Data collection

Patient demographics and cardiovascular risk factors and diseases were identified such as persistent smoking at the time of surgery, diabetes, coexisting carotid or peripheral artery disease, arterial hypertension as well as cardiac disorders including CAD, heart failure, arrhythmias, pacemaker implantation, previous PCI or CABG and the administration of beta-blockers.

Coronary stenting performed within 3 months of lung resection was analysed with respect to the nature and number of stents deployed, the indication for stenting (symptomatic coronary artery disease vs asymptomatic severe CAD detected during exercise testing), the time interval between stenting and lung surgery (<30 days vs 30–60 days vs 61–90 days) and antiplatelet therapy.

The extent of resection (lobectomy or pneumonectomy) and the nature of underlying lung disease were noted as well as the perioperative anticoagulation regimen (heparin vs heparin plus antiplatelet agents).

Perioperative complications and mortality after lung resection were analysed up to 30 days after surgery with special consideration of local and distant haemorrhage and in-stent thrombosis associated with myocardial infarction. All patients were admitted to the intensive care unit after lung resection and perioperative cardiac events were recorded on the base of clinical symptoms and postoperative ECG changes. Patients with clinical, electrocardiographic or enzymologic suspicion of in-stent thrombosis associated with myocardial infarction underwent coronary angiography. A diagnosis of in-stent thrombosis required confirmation by coronary angiography.

3. Results

3.1. Patient demographics

Thirty-two patients were identified as having a lobectomy or a pneumonectomy within 3 months of coronary artery stenting between 1999 and 2004. There were 29 men and 3 women with a mean age of 64.3 years, ranging from 46 to 82 years.

3.2. Cardiovascular risk factors and diseases

Persistent smoking was found in 11 patients (34%), diabetes mellitus in 5 (16%), peripheral vascular disease in 10 (31%) and arterial hypertension in 18 (56%). Symptomatic CAD with angor or myocardial infarction was found in 17 patients (53%), requiring previous PCI in 9 (28%) or CABG in 2 (6%). A history of heart failure was found in 2 patients (6%) and atrial fibrillation in 2 (6%). Eleven patients (34%) had beta-blocker administration.

3.3. Coronary stenting prior to lung resection

Fifteen patients (47%) underwent coronary stenting for asymptomatic CAD detected during exercise testing. Non-drug-eluting stents were applied in all patients. One stent was implanted in 23 patients (72%), two stents in 7 patients (22%) and four stents in 2 patients (6%). The time interval between stenting and lung resection was less than 30 days in 7 patients (22%), 30–60 days in 17 patients (53%) and 61–90 days in 8 patients (25%). All patients received dual antiplatelet therapy with aspirin and clopidogrel after stenting. Clopidogrel was stopped in all the patients 7–10 days before surgery. Aspirin was stopped before surgery in 11 patients (34%) and continued during the perioperative period in 21 (66%). Twenty patients underwent lung resection after 4 weeks of dual antiplatelet therapy as recommended by the ACC /AHA Guideline Update.

3.4. Lung resection

The indication for resection was non-small cell lung cancer in 30 patients (94%) and haemoptysis due to infection in 2 (6%). Lobectomy was performed in 27 patients (84%), left pneumonectomy in 4 (13%) and right pneumonectomy in 1 (3%). Perioperative anticoagulation beginning 1 day before the operation consisted in the administration of heparin in 11 patients (34%) and of heparin plus aspirin in 21 patients (66%). Thirty patients (94%) received low molecular weight heparin (Fraxiparine® 0.4 s.c. 1 × daily) and two (6%) had continuous intravenous heparin administration (20,000 IU/day).

3.5. Perioperative mortality and morbidity after lung resection

Three patients (9%) died within 30 days after resection. Two of them (6%) succumbed from adult respiratory distress syndrome occurring after bilobectomy in one and after lobectomy following radiochemotherapy in one. One patient (3%) died from myocardial infarction due to in-stent thrombosis.

Non-fatal, non-cardiac complications were observed in 6 patients (19%), including empyema in 2, hemothorax in 2, retroperitoneal hematoma in 1 and chylothorax in 1. Non-fatal cardiac complications were found in 6 patients (19%), including arrhythmias in 4 (13%) and coronary in-stent thrombosis in 2 (6%). Overall, 3 patients (10%) revealed postoperative bleeding complications (hemothorax in 2 and

retroperitoneal hematoma in 1) that did not require reoperations but blood transfusions in 2 patients.

Overall, 3 of the 32 patients (9%) developed perioperative in-stent thrombosis documented by coronarography and associated with myocardial infarction. Two of these patients underwent single stent deployment for asymptomatic CAD followed by pneumonectomy and lobectomy after an interval between stenting and lung resection of 31 and 90 days, respectively. In-stent thrombosis and myocardial infarction were followed by an uneventful course without cardiac reinterventions in both patients. One patient underwent uneventful lobectomy 44 days after deployment of four stents for symptomatic CAD. He developed in-stent thrombosis and myocardial infarction in the recovery room and underwent PCI without fibrinolysis. He then developed reinfarction after initial successful recanalisation, and died 4 days after lobectomy.

Twenty patients underwent lung resection according to the recommendations of the ACC/AHA Guideline Update with 4 weeks of dual antiplatelet therapy after stenting; however, two out of three perioperative in-stent thrombosis occurred in this group of patients.

4. Comment

Several reports suggest that coronary bypass grafting prior to non-cardiac surgery may reduce the risk of perioperative myocardial infarction after non-cardiac surgery. This holds especially true for patients with a critical left main stem stenosis or severe proximal three vessel disease in the presence of positive exercise testing or impaired left ventricular function [3—5]. The influence of prior coronary artery bypass surgery (CABG) versus medical therapy for reducing the risk of postoperative cardiac complications after non-cardiac surgery was assessed by use of the Coronary Artery Surgery Database [4]. Among 1961 patients undergoing higher risk (abdominal, vascular, thoracic) surgery, prior CABG was associated with fewer postoperative deaths (1.7% vs 3.3%, $p = 0.03$) and myocardial infarction (0.8% vs 2.7%, $p = 0.002$) compared with medically managed coronary disease [4]. Likewise, abdominal aortic aneurysm repair performed within 60 days after CABG was associated with a low perioperative mortality (0%) and myocardial infarction rate (6%) in patients with severe coronary artery disease [5].

However, the role of PCI prior to non-cardiac surgery remains unclear in this respect. Percutaneous coronary balloon angioplasty performed before non-cardiac surgery seems to reduce the risk of perioperative cardiac complications in patients with severe CAD [6—9]. In the era of coronary stenting, these patients faired worse as a consequence of perioperative in-stent thrombosis especially if non-cardiac surgery was performed within 4 weeks of stenting [10,11].

Coronary stenting adds thrombogenic material to a prothrombotic perioperative milieu, which holds especially true in the context of oncological procedures [12]. A recent experimental study endorses the impression that surgical interventions may be accompanied by a prothrombotic state demonstrating that wound monocytes preferentially accelerate activation of factor VII and factor X in the presence of wound plasma tissue factor during surgery [13]. This represents a novel mechanism for thrombin generation during surgical interventions and may explain the perioperative thrombotic and non-surgical bleeding complications, which may be observed in this respect. In addition, increased concentrations of circulating plasma tissue factor also occur in a variety of diseases such as cardiovascular disorders and malignancies that may further increase the risk of thromboembolic events in the perioperative setting [13].

Several authors have questioned an uncritical approach in the context of coronary stenting before non-cardiac surgery [1,10,12,14]. However, most of these studies investigated patients with vascular procedures. There is actually no data available regarding the risk of in-stent thrombosis after major lung resection performed after coronary stenting. Our results indicate a 9% incidence of perioperative in-stent thrombosis associated with myocardial infarction after major lung resection performed within 3 months of coronary stenting. Moreover, two of three of perioperative in-stent thrombosis occurred in the group of patients receiving 4 weeks of dual antiplatelet therapy after stenting as suggested by the recommendations of the ACC /AHA Guideline Update.

Caution in the interpretation of the results is indicated because of the small sample size and the retrospective data collection. However, an incidence of 9% in-stent thrombosis after coronary stenting is substantially higher than that reported in routine clinical practice. In-stent thrombosis after elective coronary stenting occurs in less than 1% of cases [15]. A recent publication reported a 0.5% incidence of in-stent thrombosis after successful coronary stenting with non-drug-eluting stents and dual antiplatelet therapy [16].

As the number of patients scheduled for lung surgery after coronary stenting will increase in near future, strategies for prevention of perioperative in-stent thrombosis are required. There is some evidence that vascular repair after stenting may take a protracted period of time. Moreover, this remodelling process may be further lengthened after deployment of drug-eluting stents that inhibit the repair process in order to prevent neointimal hyperplasia and restenosis. A period of 4 weeks of dual antiplatelet medication after stenting may not be sufficient to allow reepithelialisation of the stented vessel. Since there is evidence that dual antiplatelet therapies have additional benefits for up to 12 months following coronary stenting [17] it might be appropriate to maintain aspirin and clopidogrel administration during the perioperative phase of lung surgery following coronary stenting irrespective of the time interval between stenting and lung resection. Aspirin and clopidogrel administration during surgery may increase the risk of bleeding and may interfere with epidural analgesia. However, these drawbacks have to be balanced with the risk of perioperative in-stent thrombosis and its inherent high mortality in case of withdrawal of aspirin and clopidogrel before surgery, especially in the presence of drug-eluting stents. Patients with coronary artery disease requiring revascularisation prior to high-risk non-cardiac surgery should preferably be treated by percutaneous coronary balloon angioplasty instead of stenting. However, if non-cardiac surgery is required after coronary stenting, dual antiplatelet therapy (aspirin and clopidogrel) should be used in the perioperative setting.

In conclusion, our results extend previous investigations indicating a persistent risk of perioperative in-stent thrombosis after coronary stenting in the setting of lung resection performed within 3 months of stenting. Larger prospective trials are required to determine the risk of perioperative in-stent thrombosis in patients with coronary stents undergoing major lung resections.

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