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BIPHASIC RELEASE OF SECRETORY PHOSPHOLIPASE A₂ DURING AND AFTER CARDIOPULMONARY BYPASS

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Recently Nakamura and colleagues¹ reported on the enhancement of secretory phospholipase A₂ (sPLA₂) activity during cardiac operations. sPLA₂ activity increased after systemic heparinization, before the patient was connected to the extracorporeal circuit, and was partially reduced after protamine administration. PLA₂ hydrolyses the *sn*-2-ester bond of phospholipids and catalyzes the rate-limiting step in the formation of eicosanoids from membranes. Consistent herewith, Nakamura and colleagues¹ showed that sPLA₂ activity correlated with the generation of circulating 6-keto-prostaglandin F_{1α} during cardiac surgery and concluded that systemic heparinization stimulates eicosanoid production, which contributes to the vasodilating and anticoagulant action of heparin during cardiopulmonary bypass (CPB). However, cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α also stimulate the production of sPLA₂ by cells including neutrophils, platelets, endothelial cells, and liver cells. The regulatory sequences of the sPLA₂ gene contain a putative interleukin-6 responsive element, homologous to that found in several acute-phase genes.² Hence sPLA₂ may be an acute-phase protein. The acute-

phase response is a sequential series of events that are induced by proinflammatory cytokines. An acute-phase response is clinically marked by leukocytosis, fever, metabolic changes, and increased (but also decreased) synthesis of various liver proteins. The physiologic importance of this response is unknown. The first acute-phase proteins to rise during the acute-phase response are sPLA₂ and C-reactive protein (CRP). We studied the release of sPLA₂ not only during CPB but also during the acute-phase reaction induced by this procedure.

Methods. We studied the release of sPLA₂ and CRP in 10 patients, seven men and three women aged 58 years (range 54 to 67 years) and weighing 82 kg (range 79 to 91 kg) scheduled to undergo elective coronary artery bypass grafting. The study was approved by the Medical Ethics Committee of the Academic Medical Centre of Amsterdam and written informed consent was obtained from each patient. Anesthesia and surgical procedure were standardized and identical for all patients. In brief, on the morning of the operation, patients received their usual dose of antianginal drugs and lorazepam (2 to 4 mg) as premedication. Anesthesia was induced intravenously with etomidate (0.2 mg/kg), fentanyl (50 μg/kg), pancuronium bromide (0.1 mg/kg), and midazolam (0.1 mg/kg) and maintained by supplemental doses. After endotracheal intubation, patients were ventilated to normocapnia with oxygen and air mixture. Cefamandole (2 gm) was given intravenously for infection prophylaxis. A radial artery catheter and a flow-directed pulmonary artery catheter (Swan-Ganz, Baxter/American Edwards Laboratories, Santa Ana, Calif.) were inserted for hemodynamic measurements and collection of blood samples. Volume was supplemented and further deviations from pressures or vascular resistances were treated with appropriate vasoactive medication. The extracorporeal circuit consisted of a hollow-fiber oxygenator with integrated heat exchanger (Univox, Baxter Healthcare Corp., Irvine, Calif.) and roller pump. CPB duration was 93 minutes (80 to 111 minutes). Heparinization was identical for both

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Fig. 1. Release of sPLA₂ and CRP during and after cardiac surgery. During heparinization, a minor release of sPLA₂ of threefold baseline levels is found, which is partly antagonized by the administration of protamine sulfate. During the acute phase response, a second and major release of sPLA₂ occurs, reaching levels of thirty times baseline levels. Data presented are medians with interquartile range. **p* < 0.01 compared with baseline, Wilcoxon rank-sum test.

groups (250 U/kg body weight, Leo Pharmaceutical Products, Weesp, The Netherlands). Blood samples were collected from the radial artery catheter or the arterial site of the extracorporeal circuit and by venous puncture after removal of the radial artery catheter. Platelet-poor plasma was prepared by centrifugation immediately after collection and stored at -70° C. Circulating concentrations of PLA₂ and CRP were determined with enzyme-linked immunosorbent assays as previously described.³

Results. Consistent with the data of Nakamura and coworkers,¹ we found significant increases, that is, up to threefold the baseline levels, of sPLA₂ during CPB (Fig. 1). However, levels increased tremendously, that is, up to thirty times baseline levels, on the first and second postoperative days. To demonstrate that sPLA₂ release during CPB is induced by systemic heparin, we incubated 0.2 ml of whole blood of a healthy volunteer in phosphate-buffered saline solution containing increasing heparin (Leo Pharmaceutical Products) concentrations for 15 minutes at room temperature on a shaker (200 rpm). Heparin at a concentration of 3 U/ml, comparable with that during systemic heparinization, caused a 2.5-fold increase (± 0.55 , standard deviation) of sPLA₂ from blood cells and reached a maximal 4.1-fold increase (± 0.81) at 25 U/ml (Fig. 2). These in vitro data also suggest that the elevations of sPLA₂ during CPB are mainly explained by heparinization of the patient.

Comment. The elevation on the postoperative days likely reflected that sPLA₂ is an acute-phase protein, as stated previously.²⁻⁴ Its production and release continued for several days while preceding the release of the prototype of acute-phase proteins in man, CRP. The role of sPLA₂ in the acute-phase response in general and after cardiac surgery more specifically is not clear. It has been hypothesized that sPLA₂ and CRP, in a combined effort, promote phagocytosis of injured cells and tissue debris by

Fig. 2. Effect of heparin on the release of secretory phospholipase A₂ levels in whole blood. Whole blood was incubated with various concentrations of heparin (U/ml) for 15 minutes at room temperature. Data presented are medians with range (*n* = 3). **p* < 0.01 compared with baseline, Wilcoxon rank-sum test.

neutrophils. The molecular base for this hypothesis is that sPLA₂ preferentially hydrolyzes phospholipids of cells that have undergone a flip-flop (i.e., an exchange of phospholipids of the inner and outer leaflet of the plasma membrane, for example, as a consequence of ischemia) to generate binding sites for CRP. Bound CRP in turn may induce complement activation via the classical pathway and so promote phagocytosis of metabolically compromised cells that are generated during inflammation or ischemia.⁴ During cardiac surgery, the tissues of heart and lungs especially are deprived of oxygen during aortic crossclamping and may therefore be the primary target for sPLA₂ activity, subsequent CRP deposition, and finally complement- and neutrophil-mediated damage.⁵ Alternatively, sPLA₂ release during the first postoperative day may further contribute to the generation of proinflammatory prostaglandins and leukotrienes by the mechanism described by Nakamura and associates.¹ Most typical, one in three patients have rhythm disturbances, mainly atrial fibrillation with fast ventricular rate, but all patients have leukocytosis and fever on the first, second, or third postoperative day.⁵ Our data suggest that sPLA₂ may be involved in the pathogenesis of these complications.

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SYNCHRONOUS PATENT FORAMEN OVALE AND BRONCHOPLEURAL FISTULA AFTER RIGHT PNEUMONECTOMY: NONOPERATIVE MANAGEMENT WITH SURVIVAL

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The occurrence of an acute right-to-left shunt after pneumonectomy has been reported in only 20 cases. Bronchopleural fistula (BPF) and postpneumonectomy empyema are common in 2% to 5% of patients, with mortality ranging between 20% and 70%. Synchronous patent foramen ovale (PFO) and BPF has not been reported in the literature. The successful nonoperative control of these two major postpneumonectomy complications is described.

A 70-year-old man underwent a right pneumonectomy for stage II adenocarcinoma. Preoperative lung function studies and preoperative blood gas are presented in Table I.

The immediate postpneumonectomy course was complicated by profound hypoxemia noted on the evening of the operation when the patient was recumbent. The mediastinum was sharply shifted into the postpneumonectomy space (Fig. 1). The postpneumonectomy drainage tube was unclamped and air injected to centralize the mediastinum. This dramatically relieved the hypoxemia, improving oxygen saturation from 77% to 98% with the patient breathing 100% oxygen delivered by means of a face mask. The patient had periods of hypoxia in both the recumbent position (platypnea) and the upright position (orthodeoxia), necessitating daily centralization of the mediastinum.

An echocardiogram revealed an acute intraatrial shunt. Almost synchronously with the diagnosis of the shunt, the patient had a paradoxical embolism to the left suboccipital region that resulted in a right hemianopia.

Symptoms of cough, hemoptysis, and fever developed on postoperative day 14, and a clinical diagnosis of BPF was made. The space on the right side was drained with a chest tube. The BPF was closed temporarily by endoscopic

placement of a felt pledget into the defect, and it was oversealed with fibrin glue. This resulted in closure of the BPF with no further air leakage.

Several days later, the interatrial defect was effectively closed by transvenous placement of a 33 mm double clamshell device (Nitinol; Boston, Mass.). Symptoms lessened immediately, and oxygen saturation returned to 95%. Supplemental oxygen was discontinued and the closed drainage system of the empyema was converted to open drainage by a thoracostoma. Subsequent follow-up examinations at 1, 3, 6, and 8 months show that the BPF has closed spontaneously.

Discussion. The common causes of dyspnea after pneumonectomy are chronic obstructive pulmonary disease, loss of alveolar volume, pain, restriction of the vascular bed, and diaphragmatic dysfunction.¹ Acute PFO is uncommon and numerous mechanisms for its appearance have been postulated. The weight of the heart after a right pneumonectomy causes a shift that pulls the interatrial septum downward, causing the foramen ovale to open or widen.² PFO is found in approximately 20% of postmortem studies in the general public. The heart in this new position provides a direct course for blood from the inferior vena cava through the PFO (streaming effect). Distortion is accentuated in an upright position, creating an increasing shift of the right atrium and widening the orifice of the PFO.³ A pressure gradient is created across the PFO, producing a large shunt and the symptoms of orthodeoxia and platypnea. Another theory is based on the anatomic distortion and decreased compliance of the

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Table I. Preoperative pulmonary function test

	Actual	Predicted	%
FVC (L)	4.42	4.37	101
FEV ₁ (L)	3.22	2.94	110
FEF _{25%-75%} (L/sec)	2.14	2.65	81
FEV ₁ /FVC (%)	73	67	108
MVV (L/min)	132	117	112
Arterial blood gas values	7.42/32/88/20/96%		

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF, forced expiratory flow; MVV, maximal voluntary ventilation.