

Activation of Protein C and Hemodynamic Recovery After Coronary Artery Bypass Surgery.

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Objectives: Activated protein C (APC) is a physiologic anticoagulant that is activated by thrombin and upregulated during coronary artery bypass grafting (CABG). We studied the balance between thrombin generation and APC during CABG and hypothesized that protein C activation during reperfusion associates with postoperative myocardial damage or hemodynamic recovery.

Materials and methods: 100 patients undergoing primary, elective on-pump CABG were prospectively studied. APC, protein C, prothrombin fragment F1+2 (marker of thrombin generation), and D-dimer (marker of fibrinolysis) were measured preoperatively and at seven time points during cardiopulmonary by-pass (CPB), reperfusion, and postoperatively until the fifth postoperative day. Hemodynamic parameters were measured preoperatively and at four time points thereafter until the first postoperative day. Cardiac biomarkers, Ck-Mbm and TnT, were measured postoperatively.

Results: Thrombin generation (F1+2) increased steadily during ischemia, and reperfusion induced a significant further escalation in the rate of thrombin generation. During ischemia there was only a slight increase in the level of APC, but significant up-regulation of APC was observed after heparin neutralization, when APC level increased over three-fold and peaked (from 160%(SD 84%) to 539%(SD 238%)). APC correlated with F1+2 and D-dimer during CPB and reperfusion. The strength of this correlation increased during CPB and myocardial ischemia and peaked during early reperfusion ($r=0.55$, $p<0.001$). During surgery and early reperfusion the ratio of APC to F1+2 decreased by 70 % from the preoperative level indicating a marked delay in protein C activation in relation to thrombin generation. During this period high protein C activation associated with improved postoperative cardiac index (mean 3.1(SD 0.58) vs. 2.5(SD 0.57) L/min/m², $p<0.05$) and lower postoperative systemic vascular resistance (mean 2220(SD 651) vs. 2410(SD 671) dyne·sec/cm⁵/m², $p<0.05$). Conversely, high preoperative APC level and high APC level measured after heparin neutralization associated with inferior hemodynamic recovery postoperatively. APC or protein C levels did not associate with elevated postoperative cardiac biomarker levels.

Conclusions: Reperfusion after CABG caused significant thrombin generation that was followed by activation of the protein C pathway. An early APC response associated with favorable hemodynamic recovery after CABG while high

preoperative and high peak APC level associated with inferior hemodynamic recovery. Overall, we showed the balance between APC and thrombin to be dynamically associated with postoperative hemodynamic recovery.