Activation of complement factor B contributes to postoperative myocardial necrosis after cardiac surgery

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OBJECTIVE: Cardiopulmonary bypass (CPB) and aortic cross clamping (AXCL) during cardiac surgery lead to global heart ischemia, contributing to postoperative myocardial necrosis. Basic science studies have shown that ischemia/reperfusion of heart tissue elicits an acute inflammatory response, involving several complement factors. Anticomplement C5 has been tested in clinical trials with positive results. However, activation of earlier complement factors would be unaffected. Animal model studies suggested that complement factor B (fB), an initial factor in the alternative pathway, may be involved in postoperative myocardial necrosis. Whether fB plays a similar role in humans has not been determined. To investigate the role of fB in postoperative myocardial necrosis, we evaluated fB activation in cardiac surgery patients.

METHODS: A total of 105 adult patients undergoing elective cardiac surgery with CPB were recruited after IRB approval. Blood was sampled from the coronary and peripheral circulations of cardiac patients at 7 defined perioperative periods identifying major stages in the surgery. fB activation was evaluated by ELISA assay and Western blotting, and was correlated with the myocardial necrosis marker, cardiac troponin I (cTnI). Statistically significant correlations between the levels of Bb, the active fragment of fB, and the levels of cTnI at designated time points were determined using Spearman's correlation. Multivariate regression analysis was used to test whether perioperative Bb levels can independently predict postoperative cTnI increases. $P < 0.05$ was considered to be statistically significant.

Table 2. Univariate analysis for correlation of Bb levels in coronary and peripheral blood at the various sampling time points during surgery with peripheral blood cTnI levels at the immediate post-surgery time point in the 50 patients who underwent open heart surgery.[§]

	Time	Blood collection (site).5 ml each.		Variables	Mean $\pm$ SD of listed variable (n = 50)	Spearman coefficient for correlation of variable with cTnI at the immediate post-operative time-point.	P-value for indicated correlation.
		Peripheral vein	Coronary sinus				
1	Pre-surgery / before skin incision	Yes	No	Coronary sinus Bb levels ($\mu\text{g/ml}$):			
				After CPB / before AXCL	2.4 ± 2.0	0.458	$<0.01^*$
2	After skin incision / Prior to sternotomy	Yes	No				
				5 min. after AXCL cessation	4.4 ± 2.9	0.465	$<0.01^*$
3	5min after CPB start /before the start of AXCL	Yes	Yes	Peripheral Bb levels ($\mu\text{g/ml}$):			
				1. Pre-surgery / before skin incision	1.7 ± 1.1	0.331	0.014*
4	Within 5min after AXCL cessation	Yes	Yes				
				2. After skin incision / Prior to sternotomy	2.1 ± 1.6	0.452	0.001*
5	5min after CPB cessation	Yes	No				
				3. 5min after CPB start / before the start of AXCL	2.4 ± 1.8	0.466	$<0.01^*$
6	Post-surgery day 1	Yes	No				
				4. Within 5min after AXCL cessation	5.0 ± 3.8	0.426	0.001*
7	Post-surgery day 2	Yes	No				
				5. 5min after CPB cessation	6.6 ± 7.2	0.487	$<0.01^*$
				6. Post-surgery day 1	1.7 ± 1.2	0.587	$<0.01^*$
				7. Post-surgery day 2	1.5 ± 0.9	0.462	$<0.01^*$

RESULTS: Levels of Bb increased significantly in the coronary circulation following ischemia compared with prior to application of AXCL (before AXCL = $2.4 \pm 2.0 \mu\text{g/ml}$; after AXCL cessation = $4.4 \pm 2.9 \mu\text{g/ml}$, $P < 0.01$), and increased in peripheral blood at major steps in cardiac surgery ($P < 0.05$ at all time points). Univariate analysis showed that perioperative Bb levels in the coronary and peripheral circulations correlated significantly with the postoperative cTnI levels ($P < 0.01$ at all time points). Multivariate analysis revealed that these correlations were dependent on the time lengths of CPB and AXCL.

CONCLUSIONS: Our study is the first report to demonstrate that AXCL caused significant changes in Bb in the coronary and peripheral circulation. This study indicates that fB activation contributes directly to postoperative myocardial necrosis.