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Alternative complement pathway activation during invasive coronary procedures in acute myocardial infarction and stable angina pectoris

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ABSTRACT

The effect of invasive percutaneous coronary procedures on complement activation has not been elucidated. We enrolled stable angina patients with elective percutaneous coronary intervention (SA-PCI, n = 24), diagnostic coronary angiography (CA, n = 52) and 23 patients with ST segment elevation myocardial infarction and primary PCI (STEMI-PCI). Complement activation products (C1rC1sC1inh, C3bBbP and SC5b-9) were measured on admission, 6 and 24 h after coronary procedures. The alternative pathway product, C3bBbP significantly and reversibly increased 6 h after elective PCI (baseline: 7.81 AU/ml, 6 h: 16.09 AU/ml, 24 h: 4.27 AU/ml, $p < 0.01$, n = 23) and diagnostic angiography (baseline: 6.13 AU/ml, 6 h: 12.08 AU/ml, 24 h: 5.4 AU/ml, $p < 0.01$, n = 52). Six hour C3bBbP values correlated with post-procedural CK, creatinine level and the applied contrast material volume ($r = 0.41$, $r = 0.4$, $r = 0.3$, $p < 0.05$, respectively). In STEMI-PCI, baseline C3bBbP level was higher, compared to SA-PCI or CA patients (11.33 AU/ml vs. 7.81 AU/ml or 6.13 AU/ml, $p < 0.001$). Similarly, the terminal complex (SC5b-9) level was already elevated at baseline compared to SA-PCI group (3.49 AU/ml vs. 1.87 AU/ml, $p = 0.011$). Complement pathway products did not increase further after primary PCI.
Elective coronary procedures induced transient alternative complement pathway activation, influenced by the applied contrast volume. In STEMI, the alternative complement pathway is promptly activated during the atherothrombotic event and PCI itself had no further detectable effect.

1. Introduction

Over the last decades, percutaneous catheter intervention (in coronary or in peripheral vasculature) has become a major therapeutic strategy, particularly in patients with ischemic heart disease [1]. Several data proved that percutaneous revascularization via implantation of endovascular stents provides benefits when focusing on relief of angina pectoris or claudication [2]. Currently, percutaneous coronary intervention (PCI) represents the essential form of coronary revascularization worldwide. Several clinical trials have shown that early PCI performed in patients with ST-segment elevation myocardial infarction (STEMI) effectively restores coronary artery flow and improves cardiovascular prognosis [3–5]. Moreover, symptomatic stable angina patients with documented significant myocardial ischemia benefit from coronary revascularization as well [6].

The complement system - as component of the innate immunity and participant of the systemic inflammatory reaction - plays an essential role in primary immune response [7]. The complement system can be activated via three different mechanisms, namely by the classical, the alternative, or the lectin pathway. The classical pathway cascade is typically initiated by antibody/antigen immune complexes [8,9]. In contrast, the alternative pathway is activated in an antibody-independent manner [8,9]. The lectin pathway is triggered by the binding of mannose binding lectin or ficolins to special carbohydrate structures of bacteria or dying host cells [10]. Initiation of each pathway results in the formation of the terminal C5b-9 complex (also known as membrane attack complex, MAC), responsible mostly for cell lysis and for the activation of macrophages [8,9].

Abbreviations: ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ASAT, aspartate aminotransferase; BMS, bare metal stent; CA, coronary angiography; CABG, coronary artery bypass graft; CK, creatine kinase; CK-MB, creatine kinase, muscle and brain; DES, drug-eluting stent; ECG, electrocardiogram; HGF, hepatocyte growth factor; hsCRP, high sensitive C-reactive protein; ICAM-1, intercellular cell adhesion molecule-1; IGF-1, insulin-like growth factor-1; LDH, lactate dehydrogenase; MAC, membrane attack complex; MASP, MBL/ficolin-associated serine proteases; MBL, mannose-binding protein; MCP-1, monocyte chemoattractant protein-1; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; VCAM, vascular cell adhesion molecule-1; vWF, Von Willebrand factor.

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To our best knowledge, only limited and controversial data are available concerning the effect of invasive coronary intervention on complement components in ischaemic heart disease patients [11,12]. Speidel et al. measured plasma levels of C3a and C5a, the common activation products of the classical, lectin and alternative pathways in stable angina patients undergoing PCI. They found significant increase in C5a levels after stent implantation indicating considerable complement activation [13]. However, the factual contribution of the alternative, the lectin or the classical pathway was not elucidated. Hognestad et al. evaluated the alternative pathway mediated complement activation and inflammatory reaction (*by* ICAM-1, hsCRP, MCP-1, vWF, L-selectin) before and after PCI in 11 heart transplant recipients with coronary allograft vasculopathy and native atherosclerosis. In this study, no relevant complement activation was observed after PCI [14]. Taken together, results from coronary heart disease patients are limited, controversial and further analyses are needed.

Activation of the complement cascade in patients with myocardial infarction is evidenced by elevated levels of activated complement by-products, especially C3a, C5a and C5b-9 [15], Bb, C4d, C3d and MASP-1 [16]. In several studies, C5b-9 levels at admission for acute myocardial infarction predicted risk of death and secondary events [17,18]. Results suggest that complement system activation under acute ischemic events represents a unique entity and the pathomechanism is different as seen in stable ischemic heart disease patients. Detailed, systematic analysis of the upstream complement activation products is still lacking.

Besides the above described pathological responses throughout development of atherosclerosis and/or acute plaque rupture, biosurface induced complement activation has been recently recognized as an important, new issue [19]. Although implanted synthetic biomaterials are carefully designed to ensure maximal biocompatibility, subsequent contact activation, complement pathway/coagulation cascade activation might lead to unfavourable adverse effects.

Based on the above data, we aimed to clarify the role of complement system activation in cardiovascular patients undergoing either acute or elective PCI/coronary angiography. Plasma levels of several complement activation products (C1rC1sC1inh – classical pathway, C3bBbP – alternative pathway, and SC5b-9 – the terminal complex) were determined at different time points.

2. Materials and methods

2.1. Patient population

We recruited ninety-nine cardiovascular patients undergoing coronarography at our institution within a 23 months period. To ascertain whether the complement system is activated by percutaneous coronary intervention performed during the acute ischemic event, twenty-three patients were enrolled with the diagnosis of acute STEMI (STEMI-PCI group) based on the presence of permanent chest pain (>30 min) and ≥2 mm ST-segment elevation on consecutive leads on ECG. All STEMI patients underwent urgent coronary angiography and PCI with implantation of bare metal (BMS, n = 9) or drug-eluting stents (DES, n = 14) within 12 h after the onset of chest pain. In all cases, the culprit coronary artery was successfully recanalyzed. Seventy-six stable angina patients, referred for elective coronary angiography at our institution were also enrolled. In each patient, non-invasive tests (ECG exercise stress test or myocardial perfusion scan) indicated significant inducible myocardial ischemia prior to coronary angiography. In 24 stable angina patients (SA-PCI group), coronary angiography showed significant coronary artery stenosis and successful PCI was performed with implantation of bare metal (BMS, n = 16) or drug-eluting stents (DES, n = 8). To determine, whether the complement system is activated by the coronary procedure alone (coronary catheter manipulation, contrast material (iopromide) injection without stent implantation), the remaining 52 patients with coronary angiography alone were also examined (CA group). These patients were advised for CABG (n = 27) or for conservative medical therapy (n = 25). The exclusion criteria were history of severe renal or hepatic disease, haematological disorders, acute or chronic inflammatory disease, autoimmune disease, malignancy and coronary angiography/PCI within 8 months. The study protocol was approved by the institutional and regional ethics review committee, and written informed consent was obtained from all patients.

2.2. Blood sample preparation and laboratory assessment of complement activation products by ELISA

For the determination of complement activation products, 8 ml of venous blood was drawn from the cubital vein into EDTA-anticoagulated tubes. The plasma was separated by centrifugation at 1800*g* for 10 min. Aliquots were frozen immediately at −80 °C and were thawed before measurements. In each patient, several complement activation products - C1rC1sC1inh (representing activation of classical pathway), C3bBbP (representing activation of alternative pathway), and SC5b-9 (terminal complex) – were serially determined on admission, as well as 6 and 24 h after the coronary angiography/PCI. Plasma concentrations of C1rC1sC1inh, C3bBbP, and SC5b-9 were determined by standardized, home-made enzyme-linked immunosorbent assays (ELISA), as described previously [20,21].

2.3. Statistical analysis

Statistical analysis was performed with GraphPad Prism v4.0 (GraphPad Software Inc., San Diego, CA, www.graphpad.com) and SPSS v13.0 (SPSS Inc., Chicago, IL) software. Since most data exhibited non-normal distribution, we used non-parametric tests throughout. Differences between the subgroups were evaluated by the Mann - Whitney and Kruskal – Wallis tests. For repeated measures Wilcoxon signed-rank test and Friedman test was used, followed by the Dunn post hoc test. Categorical variables were compared with Fisher's exact test. Surface plot was depicted based on pair-wise regression analysis with linear-fit.

3. Results

3.1. Demographic data

Demographic data, as well as the results of coronary angiography and laboratory tests are listed in Table 1 and in Table 2. There were no significant differences in gender or body mass index between the patient groups. As expected, majority of these patients had multiple conventional cardiovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia and tobacco use (Table 1). Patients in the STEMI-PCI group were significantly younger compared to CA group (54.78 ± 10.7 vs. 60.32 ± 9.45 years of age, $p < 0.05$) (Table 1). Concerning prior cardiovascular events, significantly more patients had previous acute myocardial infarction or previous percutaneous coronary in the SA-PCI and CA group, compared to the STEMI-PCI population (Table 1). Majority of the SA patients received antiplatelet therapy, ACE - inhibitor, beta- blocker, statin or nitrate (Table 1). These observations indicate, that STEMI patients were younger, without previous medication and in many case, the index acute atherothrombotic event was the first manifestation of the coronary artery disease.

According to the coronary angiography results, significantly higher mean number of coronary occlusion per patients was found in the STEMI-PCI group compared to SA-PCI (1.08 ± 0.28 vs. 0.83 ± 1.09, $p < 0.05$) and to CA group (1.08 ± 0.28 vs. 0.55 ± 0.93, $p < 0.0001$). Significantly more contrast material volume was used in the STEMI-PCI and SA-PCI groups (median: 188.6 ± 91.96 ml and 222.8 ± 132.2 ml) compared to CA group (median: 75.46 ± 48.2 ml, $p < 0.0001$; respectively). Important to note that SA-PCI patients received the highest contrast material volume (median: 222.8 ± 132.2 ml). Elevated levels of CK, CK-MB, LDH, ASAT in the STEMI-PCI group confirmed myocardial damage (Table 2).