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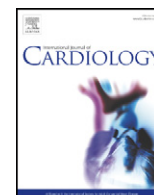

Free Light Chains in patients with acute coronary syndromes: Relationships to inflammation and renal function ☆

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ABSTRACT

Aims: We assessed changes of serum combined free immunoglobulin light chains (cFLC) levels, which are associated with increased all-cause mortality, in ST-elevation myocardial infarction (STEMI) in relation to inflammation and renal function indices.
Methods: cFLC were measured in 48 patients with STEMI on days 1, 3, 7 and 30 with assessment of their relationships with monocyte subsets, high sensitivity C-reactive protein (hsCRP), and cystatin C. Day 1 levels in STEMI patients were compared to 40 patients with stable coronary artery disease, and 37 healthy controls.
Results: There were no significant differences in cFLC levels between the study groups. In STEMI patients, cFLC values peaked on day 7 post-MI and remained elevated on day 30 ($p < 0.001$ vs. day 1 for both). hsCRP concentrations peaked on day 3 of STEMI followed by their gradual reduction to the levels seen in the controls ($p < 0.001$). In STEMI cFLC correlated with cystatin C ($r = 0.55$, $p < 0.001$), and negatively correlated with counts of CD14++CD16− monocytes ($r = -0.55$, $p < 0.001$). On multivariate Cox regression analysis, cFLC concentrations were associated with increased need for future percutaneous coronary intervention (PCI) ($p = 0.019$).
Conclusion: cFLC levels increase during STEMI with peak values on day 7 after presentation and predict the need for future PCI.

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1. Introduction

The biological significance of the adaptive immune system is complex and spreads far beyond just infection control [1–4]. The paramount role of the innate immune system in cardiovascular pathology is very well established with involvement of monocytes/macrophages in atherogenesis and post-injury tissue remodelling being classical examples [5–7]. However, limited data are available on the role of the adaptive immune system in cardiac pathophysiology. Lymphocytes have been found to be involved in atherosclerotic plaque formation, but their low (rather than high) counts are typically associated with poor outcome, for example in heart failure [5,8–10]. Lymphocyte derived biomarkers, such as immunoglobulin free light chains (FLC) which are produced in excess during antibody production and released into the circulation, may help investigation of the adaptive immune response [11].

Monoclonal generation of FLC κ and λ is a well-known parameter of plasma cell disorders, such as myeloma [12]. Until recently, limited information was available on polyclonal combined FLC (cFLC, summation of FLC κ and λ) elevations, when there is no obvious predominance of either chain. Polyclonal rise of cFLC predominantly reflects activation and proliferation of B-lymphocytes, although it could be also secondary to their impaired removal by dysfunctional kidneys or reticulo-endothelial system [13,14]. Elevation of polyclonal cFLC has been reported in inflammatory and autoimmune disorders, diabetes mellitus and chronic kidney disease [15–18]. Also, high cFLC concentrations are associated with activity of autoimmune disorders characterised by B-cell activation, with clearly distinct kinetics for cFLC and a C-reactive protein (CRP), a marker predominantly related to inflammatory responses of innate immunity [17,19,20]. cFLC may thus be of clinical value as a biomarker of the adaptive immunity state. Of note, both the innate and adaptive parts of the immune system work in close interaction [21]. Monocytes and their functional subsets represent a major cellular part of the innate immune system, but limited data are available on their relationship with cFLC [22].

High cFLC concentrations are highly predictive of mortality in the general population even after adjustment for age, gender and renal function [23,24]. Raised cFLC were associated with cardiovascular mortality in patients with chronic kidney disease after accounting for CRP levels [20]. Given the pathophysiological relationships discussed above, this biomarker might be related to prognosis in patients with myocardial infarction (MI), there are no data on changes in cFLC in patients with MI at present.

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In the present pilot study, we aimed to assess dynamic changes of cFLC levels in STEMI patients over 30 days and their relation to markers of innate immunity (monocyte subsets), inflammation (high sensitivity C-reactive protein [hsCRP]), and an index of renal function, cystatin C, and obtain data on their prognostic significance. cFLC levels in patients with STEMI were compared to levels in patients with stable coronary artery disease ('disease controls') and healthy subjects.

2. Methods

2.1. Cross-sectional analysis

cFLC levels were compared between 48 patients with ST-elevation MI (STEMI) and age- and sex-matched control groups: (i) 40 patients with stable coronary artery disease (CAD) and (ii) 37 healthy volunteers. The STEMI was diagnosed according to the European Society of Cardiology definition [25] and treated with primary percutaneous coronary intervention. Median troponin T values were 2.6 [1.30-5.68] μg/l (normal <0.01 μg/l). CAD was confirmed during elective coronary angiography, with no hospital admissions for ≥3 months. Exclusion criteria comprised infectious disease, inflammatory disorders and their treatment [including steroids and non-steroidal anti-inflammatory drugs], cancer, haemodynamically significant valvular heart disease, atrial fibrillation, renal failure and hormone replacement therapy. Additionally, no STEMI patients had a history of previous MI or left ventricular dysfunction.

2.2. Longitudinal analysis

In patients with STEMI plasma markers were measured at four time-points: day 1 (during the first 24 h after primary percutaneous coronary intervention (PCI)), day 3, day 7 and day 30. Eighteen patients did not complete follow-up due to withdrawal of consent or death. Thirty patients with cFLC levels available for all time points were included in the longitudinal analysis.

Blood samples were collected from all participants and plasma stored at −70 °C for batched analysis. Fresh blood was used for haematological analysis and quantification of monocyte subsets as described previously [26,27].

All study patients received standard treatment according to current guidelines [25]. The study was performed in accordance with the Helsinki declaration and was approved by the Coventry Research Ethics Committee. All participants provided written informed consent.

2.3. Outcome analysis

The prognostic significance of cFLC levels in STEMI was assessed with the primary outcome defined as a composite of 'death, admission for ACS, newly diagnosed HF or HF related hospital admission or new PCI' and the secondary end-point of 'need for new PCI' during follow up.

2.4. Flow cytometry

Monocytes and their subsets, as cellular markers of innate immunity and inflammation, were analysed by flow cytometry (BD FACSCalibur™ flow cytometer, Becton Dickinson [BD], Oxford, UK) as previously described [26,27]. Absolute count of monocyte subsets was established using mouse anti-human monoclonal fluorochrome conjugated antibodies anti-CD16-Alexa Fluor 488 (clone DJ130c; AbD Serotec,Oxford, UK), anti-CD14-PE (cloneM/P9; BD), and anti-CCR2- APC (clone 48607, R&D Systems, Abingdon, UK) in 50 μL of fresh EDTA anticoagulated whole blood in TruCount™ tubes (BD). Monocyte subsets were defined as CD14++CD16CCR2+ (classical), CD14++CD16 + CCR2+ (intermediate) and CD14 + CD16++ CCR2 (non-classical) in accordance with contemporary nomenclature.

2.5. Plasma markers

cFLC concentrations were determined using the Combylite™ assay on the SPAPLUS® turbidimeter (The Binding Site Group Ltd, Birmingham, UK, 95% percentile reference range 9.3-43.3 mg/L (determined in serum samples), following the manufacturers recommendations [23]. Combylite quantifies the combined FLC κ and FLC λ concentration in a single assay [28]. Cystatin C (The Binding Site Group Ltd, reference range 0.56-0.99 mg/L) and hsCRP (Roche/Hitachi Tina-quant® cardiac C-reactive protein high sensitive, Switzerland, reference range 0-3 mg/L) concentrations were measured on the BNII™ nephelometer (Siemens, Germany) following the manufacturers recommendations.

2.6. Power calculation

As there are no data for FLC, we calculated that minimum number of participants required to achieve 80% power to detect changes of 0.5 standard deviation in non-classical monocytes subsets was $n = 35$ for the cross-sectional study and $n = 25$ for the longitudinal study.

2.7. Statistical analysis

Normal data are presented as mean [standard deviation - SD] non-normal data are shown as median [interquartile range, IQR]. Cross-sectional comparisons between the three study populations were made using a chi-square test (for categorical variables), one way analysis of variance (ANOVA) with Tukey post-hoc test (for normal data) or Kruskal Wallis test with Dunn's post-hoc test (for non-normal data). Longitudinal analysis was performed using repeated measures ANOVA with Bonferroni adjustment (normal data) or Friedman test with Dunn's post-hoc test (non-normal data). Only STEMI patients who had blood samples for all time-points were included in the longitudinal analysis. For STEMI patients, correlation coefficients were calculated by Spearman tests (non-normal data). Linear regression analysis was used to establish predictive value of cFLC for LVEF measured 6-weeks post-STEMI. Predictive value of the cFLC for the study outcome parameters in STEMI was assessed using a Cox regression analysis and the Kaplan-Meier log-rank test. In the multivariable Cox regression analysis adjustments were made for parameters showing significant predictive value (or a strong trends towards significant predictive value) in multivariate analysis. Additionally the multivariable Cox regression analysis included cystatin C (a marker of renal function) and troponin concentrations (a marker of myocardial damage). Data analysis was carried out using SPSS 18.0 (SPSS Inc, Chicago, IL, USA) and a two-sided p-value of <0.05 was considered statistically significant.

3. Results

The 3 patient groups were well matched for age, gender, current blood pressure level and body mass index, creatinine and estimated glomerular filtration rate (eGFR) (Table 1). Patients with acute STEMI had increased counts of monocytes and neutrophils compared to other groups ($p < 0.001$). Healthy controls included a smaller proportion of smokers than other groups ($p < 0.001$).

Increased hsCRP and Cystatin C levels were evident in patients with acute STEMI compared to the control groups (Table 1). No significant difference was observed in cFLC values at day 1 between STEMI patients and the two control groups.

In acute STEMI, cFLC correlated with cystatin C (Spearman $r = 0.55$, $p = 0.00009$), and negatively correlated with counts of 'classical' CD14++CD16− monocyte counts (Spearman $r = -0.55$, $p = 0.00005$). There was no correlation between cFLC and other monocyte subsets, troponin T, or CRP. Absolute values of the monocyte subsets in this study population have been reported previously [27].

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