C-Reactive Protein Velocity and the Risk of New Onset Atrial Fibrillation among ST Elevation Myocardial Infarction Patients

David Zahler MD, Ilan Merdler MD, Keren-Lee Rozenfeld MD, Gil Shenberg MD, Assi Milwidsky MD, Shlomo Berliner MD, Shmuel Banai MD, Yaron Arbel MD, and Yacov Shacham MD

Department of Cardiology, Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Elevated C-reactive protein (CRP) was shown to be associated with an increased risk for new-onset atrial fibrillation (AF) in ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI); however, the optimal time frame to measure CRP for risk stratification is not known.

Objectives: To evaluate the relation between the change in CRP over time (CRP velocity [CRPv]) and new-onset AF among STEMI patients treated with primary PCI.

Methods: We included 801 STEMI patients who underwent PCI between 2007 and 2017 and had their CRP measured with a wide range assay (wr-CRP) at least twice during the 24 hours after admission. CRPv was defined as the change in wr-CRP concentration (mg/l) divided by the change in time (in hours) between the two measurements. Patient medical records were reviewed for occurrence of new-onset AF.

Results: New onset AF occurred in 45 patients (6%). Patients with new onset AF had significantly higher median CRPv (1.27 vs. 0.43 mg/l/h, $P = 0.002$). New-onset AF during hospitalization occurred in 3.4%, 4.5 %, and 9.1% of patients in the first, second and third CRPv tertiles, respectively (P for trend = 0.006). In a multivariable logistic regression, adjusting for clinical variables the odds ratios for new onset AF was 1.93 (95% confidence interval 1.0–3.59, $P = 0.04$) for patients in the third CRPv tertile.

Conclusion: CRPv might be an independent and rapidly measurable biomarker for new-onset AF following primary PCI in STEMI patients.

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KEY WORDS: acute myocardial infarction, atrial fibrillation (AF), biomarkers, C-reactive protein (CRP), primary percutaneous coronary intervention (PCI)

The ischemic injury and myocardial necrosis following ST elevation myocardial infarction (STEMI) incite an acute inflammatory response [1-3]. The inflammatory response in STEMI is not confined to the infarct zone because cytokine expression is also upregulated in the non-infarcted myocardium [3]. Among the various pro-inflammatory cytokines, C-reactive protein (CRP) has emerged as a powerful and independent predictor of heart failure and long-term mortality [4-6]. Elevated CRP levels were shown to be associated with an increased risk for new onset atrial fibrillation (AF) among STEMI patients [7,8]. Conflicting evidence exists; however, regarding the optimal time for CRP measurement, as evidence suggested a dynamic association between CRP levels on different time points following symptoms onset following STEMI and adverse clinical outcomes [9-11]. Early detection of CRP level changes over time might thus be a more sensitive and stable biomarker than the absolute value at a specific time point for patient inflammatory state. The aim of the current study was to examine the possible association between CRP level change over time defined as CRP velocity (CRPv), and the occurrence of new onset AF among STEMI patients treated with primary PCI.

PATIENTS AND METHODS

STUDY POPULATION

We performed a retrospective, single center observational study at the Tel Aviv Sourasky Medical Center, a tertiary referral hospital with a 24/7 primary PCI service. Included were patients admitted between December 2007 and August 2017 to the cardiac intensive care unit (CICU) with the diagnosis of acute STEMI who had at least two successive serum wide range-CRP (wr-CRP) levels measurements within 24 hours of hospital admission (n=904). We excluded 28 patients who were treated either conservatively or with thrombolysis, and 37 patients with history of paroxysmal or permanent AF. An additional 38 patients were excluded because of known collagen tissue disease, advanced liver disease, malignancy, or any infectious disease. A clear diagnosis of infection was assumed for patients with a clinically suspected infection and a positive blood culture, positive urine culture, or a consolidation on chest radiography with or without a positive sputum culture. The final study population included 801 patients whose baseline demographic, cardiovas-

cular history, clinical risk factors, treatment characteristics, and laboratory results were retrieved from their medical files. Informed consent was obtained from all individual participants included in the study. The study protocol was approved by the local institutional ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. (Institutional Board Review num: TLV-16-0224).

PROTOCOL

The diagnosis of STEMI was established by a typical history of chest pain, diagnostic electrocardiographic changes, and serial elevation of serum cardiac biomarkers [12]. Primary PCI was performed in patients with symptoms ≤ 12 hours in duration as well as in patients with symptoms lasting 12 to 24 hours in duration if the symptoms continued to persist at the time of admission. Following primary PCI left ventricular ejection fraction was measured in all patients by bed side echocardiography, within the first 48 hours of admission.

All patients were monitored continuously in the CICU, and evaluated for new-onset AF observed or triggered by the rate dependent alarm system during their hospital stay. Diagnosis of AF was established in the presence of the following criteria in salvos of ≥ 10 beats: absence of P-waves, coarse or fine fibrillatory waves, and completely irregular R-R intervals occurring according to the available 12-lead electrocardiography recordings and reports of monitoring.

LABORATORY

The complete blood count parameters were measured using a Coulter STKS electronic counter. Blood samples for wr-CRP were drawn in all patients at admission to the emergency department or at the catheterization laboratory, prior to primary PCI (CRP 1st). A second sample of wr-CRP (CRP 2nd) was drawn following primary PCI, within 12-24 hours from CICU admission (mean 16 ± 4 hours). Quantitative wr-CRP analysis was performed by the Bayer wide-range assay as described [13]. CRPv was calculated as the delta between CRP 2nd and CRP 1st (mg/L), divided by the time (in hours) that elapsed between the two examinations.

STATISTICAL ANALYSIS

Categorical variables were expressed as frequency and percentages. Distribution of continuous variables was assessed using histogram and Q-Q plot. Normally distributed continuous variables were described using mean ± standard deviation, and non-normally distributed continuous variables were expressed using median and interquartile range (IQR). Chi-square test was used to evaluate association between categorical variables. Continuous variables were compared using the independent sample *t*-test or the Mann-Whitney U test when adequate. The influence of CRPv on the risk for new onset AF was evaluated using multivariate logistic regression adjusted for all baseline parameters found significant in the univariate analysis. A two-tailed *P* value of < 0.05 was considered significant for all analyses. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 801 patients were included (mean age of 62 ± 14, 80% males), 45 (6%) developed new-onset AF. Baseline characteristics for patients with and without AF are shown in Table 1. Patients with new onset AF were more likely to be older, female, have history of hypertension and baseline chronic kidney disease. Patients with new onset AF demonstrated lower baseline Hemoglobin and trend towards lower baseline white blood cell count. Median CRP 1st, CRP 2nd and CRPv were significantly higher among patients with AF (4.6 vs. 3.9, $P = 0.05$, 40.6 vs. 17.7, $P = 0.002$, and 1.27 vs. 0.43 $P = 0.002$, respectively) [Table 2].

Table 1. Baseline characteristics of 801 ST elevation myocardial infarction patients

Variable	No new onset atrial fibrillation (n=756)	New onset atrial fibrillation (n=45)	*P* value
Age (years), mean ± SD	61 ± 13	73 ± 13	< 0.001
Age > 60 years, n (%)	381 (50)	37 (82)	< 0.001
Gender (men), n (%)	610 (81)	28 (58)	0.003
Baseline chronic kidney disease, n (%)	152 (20)	19 (42)	< 0.001
Diabetes mellitus, n (%)	189 (25)	16 (36)	0.12
Hyperlipidemia, n (%)	393 (52)	25 (56)	0.64
Family history of CAD, n (%)	211 (28)	7 (16)	0.07
Hypertension, n (%)	342 (45)	28 (62)	0.03
Past myocardial infarction, n (%)	129 (17)	11 (24)	0.21
CAD severity, n (%)			0.29
1 vessel disease	309 (41)	15 (34)	
2 vessel disease	232 (31)	12 (27)	
3 vessel disease	207 (28)	17 (39)	
Ejection fraction, mean ± SD	47 ± 8	45 ± 8	0.22
Ejection fraction ≤ 45%, n (%)	412 (55)	27 (61)	0.40

CAD = coronary artery disease, SD =standard deviation

Figure 1. Relationship of C-reactive protein velocity tertiles to new onset atrial fibrillation
OR = odds ratio, 95%CI = 95% confidence interval

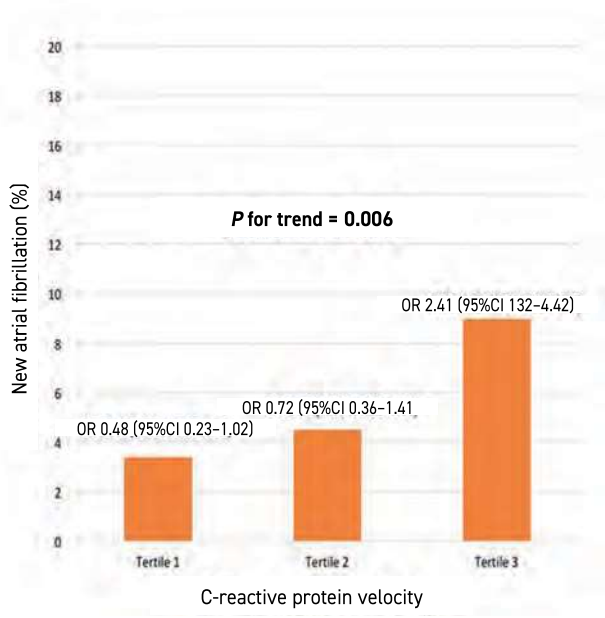

Table 2. Laboratory results of 801 ST elevation myocardial infarction patients

Variable	No new onset atrial fibrillation (n=756)	New onset atrial fibrillation (n=45)	*P* value
Hb (g/dl), mean ± SD	14.4 ± 1.6	13.6± 1.9	0.005
WBC (1000/µL), mean ± SD	11.9 ± 3.9	10.8 ± 3.4	0.08
CRP 1st (mg/L), median (IQR)	3.9 (1.4–9.7)	4.6 (2.4–14.3)	0.05
CRP 2nd (mg/L), median (IQR)	17.7 (7.6–43.7)	40.6 (14.6–76.4)	0.002
CRP velocity (mg/L/H), median (IQR)	0.43 (0.11–1.32)	1.27 (0.29–2.14)	0.002

CRP = C-reactive protein, Hb = hemoglobin, IQR = interquartile range, SD = standard deviation, WBC = white blood cells

Table 3. Unadjusted and adjusted binary logistic regression model for new onset atrial fibrillation during hospital stay

	Univariate analysis		Multivariate analysis	
Variable	**Odds ratio (95% confidence interval)**	***P* value**	**Odds ratio (95% confidence interval)**	***P* value**
Age > 60 years	4.55 (2.09–9.91)	< 0.001	2.95 (1.24–7.02)	0.015
Gender (women)	2.54 (1.35–4.76)	0.004	1.75 (0.84–3.64)	0.14
Hypertension	1.99 (1.07–3.71)	0.029	1.21 (0.62–2.35)	0.58
Chronic kidney disease	2.76 (1.49–5.13)	0.001	1.45 (0.72–2.92)	0.30
Hemoglobin (g/dl)	0.79 (0.68–0.93)	0.006	0.98 (0.81–1.20)	0.88
CRPv*				
1 Tertile	0.48 (0.23–1.02)	0.06	0.64 (0.29–1.37)	0.25
2 Tertile	0.72 (0.36–1.41)	0.33	0.69 (0.35–1.37)	0.29
3 Tertile	2.41 (1.32–4.42)	0.004	1.93 (1.04–3.59)	0.04

CRPv = C-reactive protein velocity
*In the multivariate model each CRPv tertile was evaluated as being compared to the two other tertiles.

There was a progressive increase in the frequency of in-hospital AF with increasing tertiles of CRPv (3.4%, 4.5%, and 9.1% in the first, second, and third CRP tertiles, respectively, *P* for trend = 0.006) [Figure 1]. Univariable logistic regression showed a significant association between several risk factors and AF during hospital stay, including age >60 years, female gender, hypertension, chronic kidney disease, admission hemoglobin, and the third tertiles of CRPv tertile ($P < 0.05$ for all). Multivariable logistic regression analysis identified only the third CRPv tertile (odds ratio 1.93; 95% confidence interval 1.03–3.49, $P = 0.04$) and age > 60 years as independent predictors of new onset AF during hospital stay [Table 3].

DISCUSSION

The main finding of the current study is that among patients presenting with STEMI, CRPv might be an independent biomarker associated with an increased risk for new-onset AF.

The acute-phase response shown by CRP during the acute phase of STEMI begins within few hours after symptom onset, peaking at about 48 hours [1-3]. In these patients, concentrations of CRP at hospital admission have been shown to be associated with adverse short- and long-term outcomes [14-17].

There is convincing evidence that among patients with STEMI the elevation of the CRP level may not be merely an epiphenomenon, but also contributes directly to the inflammatory state. Recent evidence suggested that following STEMI elevated CRP levels were associated with LV thrombus formation [5], LV rapture [6], as well as deterioration of renal function [5].

The development of AF in the setting of STEMI is multifactorial; however, the precise mechanisms remain unclear. Possible contributing mechanisms include pericarditis, atrial ischemia or infarction, changes in autonomic tone, metabolic abnormalities, and increased atrial pressures [14]. Recent evidence suggests that inflammation may be related to AF occurrence. Inflammatory changes have been observed in atrial tissues obtained from patients with isolated/persistent AF [18]. Serum CRP level were found to be significantly higher in patients with paroxysmal and chronic AF than in normal controls [19]. Several mechanisms have been suggested for the relationship between inflammation and AF. CRP binds to phosphocholine resulting in membrane dysfunction with inhibition of sodium and calcium ions exchange [20]. Accumulation of calcium within atrial myocytes leading to overload, and in some cases to the initiation of apoptosis of atrial myocytes may also lead to the development of arrhythmia [21]. Elevated CRP levels were recently shown to be associated with an increased risk for new onset AF among STEMI patients [7,8]. In patients with STEMI, CRP may localize in myocardial and atrial tissue, possibly binding to the membranes of myocardial cells in inflamed tissues. This acute-phase protein promotes local complement activation, and hence tissue damage [22]. These mechanisms may contribute to the association between increased markers of inflammation and occurrence of AF in patients with STEMI.

In all previous reports CRP levels were obtained at a single time point (at admission or within 12 to 24 hours from symptom onset). Conflicting data exist regarding the optimal time for CRP measurement. Evidence points to a dynamic association between CRP levels on different time points following symptoms onset and adverse clinical outcomes [8-10]. Thus, it may be possible that early detection of CRP level changes over time might be a more sensitive and stable biomarker than the absolute value at a specific time point for a patients' inflammatory state and the risk for subsequent adverse outcomes following STEMI. In the current report, changes in CRPv were strongly associated to AF. Early detection and characterization of inflammatory process severity using CRPv might help to detect a subset of inflammation-prone patients who might benefit from some anti-inflammatory intervention and are at increased risk for a worse outcome.

The use of statins or glucocorticoids in patients with AF was associated with a significant decrease in the risk of recurrent AF after successful cardioversion [23,24]. As statins are known to have pleiotropic and anti-inflammatory effects, independent of their lipid-lowering function [24], early administration of high dose potent statins may blunt the acute inflammatory response elicited by the occurrence of STEMI as indicated in current guidelines [12].

LIMITATIONS

Not adjusting for the normal dynamics of the CRP curve during STEMI and to its temporal variation might result in over-simplification of the recorded changes in CRP levels. Also, we could not positively determine the cause for rise of CRP (e.g., infectious vs. secondary to inflammation during STEMI). It is also possible that elevated CRP levels were confounded with traditional clinical risk factors for AF such as age, hypertension, left ventricular dysfunction, and compromised renal function. However, even after adjustment for these concomitant risk factors, CRPv was still independently associated with increased risk of AF. In addition, as data regarding concomitant use of statins, renin/angiotensin blockers and beta blockers throughout hospitalization was not available for many patients, their effect on AF occurrence could not be assessed. Finally, our data lacked information regarding other inflammatory markers. These include fibrinogen, which may have a possible role in inflammation, damage, and repair in the context of post-ischemic reperfusion injury.

CONCLUSIONS

CRPv is an independent and rapidly measurable biomarker for new onset AF following primary PCI in STEMI patients. The use of CRPv concomitantly with other established clinical risk factors may further contribute to early identification of those at risk for AF following primary PCI.

Correspondence

Dr. D. Zahler
Dept. of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv, 6423906 Israel
Phone: (972-3) 697-3222
Fax: (972-3) 697-3704
email: david.zahler@gmail.com

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Are you a politician asking what your country can do for you or a zealous one asking what you can do for your country?

Kahlil Gibran (1883–1931), Lebanese-American poet and artist

Capsule

The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk

To address how the microbiome might modify the interaction between diet and cardiometabolic health, **Wang** et al. analyzed longitudinal microbiome data from 307 male participants in the Health Professionals Follow-Up Study, together with long-term dietary information and measurements of biomarkers of glucose homeostasis, lipid metabolism, and inflammation from blood samples. The authors demonstrate that a healthy Mediterranean-style dietary pattern is associated with specific functional and taxonomic components of the gut microbiome, and that its protective associations with cardiometabolic health vary depending on microbial composition. In particular, the protective association between adherence to the Mediterranean diet and cardiometabolic disease risk was significantly stronger among participants with decreased abundance of *Prevotellacopri*. These findings advance the concept of precision nutrition and have the potential to inform more effective and precise dietary approaches for the prevention of cardiometabolic disease mediated through alterations in the gut microbiome.

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Eitan Israeli