Original Article

Early Changes in Circulating Interleukins and Residual Inflammatory Risk After Acute Myocardial Infarction

Maria E. R. Coste,[1] Carolina N. França,[2] Maria Cristina Izar,[1] Daniela Teixeira,[1] Mayari E. Ishimura,[1] Ieda Longo-Maugeri,[1] Amanda S. Bacchin,[1] Henrique Tria Bianco,[1] Flavio T. Moreira,[1] Ibraim Masciarelli Pinto,[3] Gilberto Szarf,[1] Adriano Mendes Caixeta,[1] Otavio Berwanger,[4] Iran Gonçalves Jr.,[1] Francisco A. H. Fonseca[1]

Universidade Federal de São Paulo,[1] São Paulo, SP – Brazil
Universidade de Santo Amaro,[2] São Paulo, SP – Brazil
Instituto Dante Pazzanese de Cardiologia,[3] São Paulo, SP – Brazil
Hospital Israelita Albert Einstein,[4] São Paulo, SP – Brazil

Abstract

Background: **Patients with acute myocardial infarction may have a large infarcted area and ventricular dysfunction despite early thrombolysis and revascularization.**

Objective: **To investigate the behavior of circulating cytokines in patients with ST-segment elevation myocardial infarction (STEMI) and their relationship with ventricular function.**

Methods: **In the BATTLE-AMI (B and T Types of Lymphocytes Evaluation in Acute Myocardial Infarction) trial, patients with STEMI were treated with a pharmacoinvasive strategy. The plasma levels of cytokines (IL-1β, IL-4, IL-6, IL-10, and IL-18) were tested using enzyme-linked immunosorbent assay (ELISA) at baseline and after 30 days. Infarcted mass and left ventricular ejection fraction (LVEF) were examined by 3-T cardiac magnetic resonance imaging. All p-values < 0.05 were considered statistically significant.**

Results: **Compared to baseline, lower levels were detected for IL-1β ($p = 0.028$) and IL-18 ($p < 0.0001$) 30 days after STEMI, whereas higher levels were observed for IL-4 ($p = 0.001$) and IL-10 ($p < 0.0001$) at that time point. Conversely, no changes were detected for IL-6 levels ($p = 0.63$). The levels of high-sensitivity C-reactive protein and IL-6 correlated at baseline (rho = 0.45, $p < 0.0001$) and 30 days after STEMI (rho = 0.29, $p = 0.009$). At baseline, correlation between IL-6 levels and LVEF was also observed (rho = -0.50, $p = 0.004$).**

Conclusions: **During the first month post-MI, we observed a marked improvement in the balance of pro- and anti-inflammatory cytokines, except for IL-6. These findings suggest residual inflammatory risk. (Arq Bras Cardiol. 2020; 115(6):1104-1111)**

Keywords: **ST Elevation Myocardial Infarction; Interleukin-6, Interleukin-10, Interleukin-18; C-reactive Protein; Magnetic Resonance Spectroscopy.**

Introduction

Following acute myocardial infarction (MI), patients are at risk of higher rates of hospitalization and death due to heart failure associated with higher levels of high-sensitivity C-reactive protein (hsCRP), but these cardiovascular events can be decreased by anti-inflammatory therapy.[1] Interleukin-6 (IL-6) has been described as having a relevant role in ventricular remodeling in pressure overload models[2] and orchestrating the immune response after acute MI.[3]

In addition to IL-6, other interleukins such as IL-18[4] and IL-1β[5,6] seem to contribute to adverse ventricular remodeling after MI. Interestingly, IL-4 appears to contribute to fibrosis and ventricular dysfunction in arterial hypertension when induced by angiotensin II administration.[7] Conversely, IL-10 markedly attenuates the inflammatory microenvironment after MI, thus improving ventricular function.[8]

Given the growing interest in the role of inflammation in ventricular remodeling after acute MI, we examined cytokine-mediated inflammatory response during the early phase of acute MI and its relationship with ventricular remodeling using cardiac magnetic resonance imaging (cMRI).

Materials and Methods

Study population

This report is part of the BATTLE-AMI (B And T Types of Lymphocytes Evaluation in Acute Myocardial Infarction)

Mailing Address: Francisco A. H. Fonseca •
Setor de Lípides, Aterosclerose e BIologia Vascular - Disciplina de Cardiologia - Rua Loefgren, 1350. Postal Code 04040-001, Vila Clementino, São Paulo, SP - Brazil
E-mail: fahfonseca@terra.com.br
Manuscript received August 22, 2019, revised manuscript December 01, 2019, accepted December 27, 2019

DOI: https://doi.org/10.36660/abc.20190567

trial (ClinicalTrials.gov, NCT02428374). BATTLE-AMI is a randomized trial in which the effects of combined statin and antiplatelet therapies on infarcted mass and left ventricular ejection fraction (LVEF) in patients with ST-segment elevation myocardial infarction (STEMI) treated with a pharmacoinvasive strategy are compared.[9] The ongoing study includes patients with first STEMI who underwent thrombolysis with tenecteplase in the first 6 hours of onset of symptoms and were transferred to a tertiary care hospital in southeastern Brazil (Hospital São Paulo) in the first 24 hours for coronary angiography and invasive procedures. Patients with previous history of coronary events, coronary revascularization, contraindication to cMRI, or showing hemodynamic instability were excluded from the study.

The project was approved by the local Ethics Committee (Universidade Federal de São Paulo, Hospital São Paulo, IRB:0297/2014, CAAE: 38692514.1.1001.5505), and all patients provided written informed consent before inclusion.

Laboratory measurements

Blood samples were collected in the morning of the first day and between 27-33 days after STEMI. All samples were assayed in the Laboratory of Lipids, Atherosclerosis, and Vascular Biology (Universidade Federal de São Paulo). Cytokine levels in plasma were tested using the enzyme-linked immunosorbent assay (ELISA). IL-4, IL-6, and IL-10 were assayed using the BD Pharmingen kits (BD Biosciences, San Diego, California, USA), and IL-1β and IL-18 were assayed using the R&D Systems kits (Minneapolis, Minnesota, USA). The results were expressed in terms of absorbance using the EnSpire Multimode Plate Reader (PerkinElmer) and/or the iMark Microplate Absorbance Reader (Bio-Rad Laboratories, Hercules, California, USA), according to the manufacturers' instructions. HsCRP was measured by immunonephelometry.

Cardiac magnetic resonance imaging

All cMRI examinations were performed at Hospital São Paulo or Instituto Dante Pazzanese de Cardiologia. The first examination was done within the first 10 days (baseline), usually after hospital discharge. The second examination was performed after 27-33 days of acute MI.

The amount of infarcted mass, LVEF, and microcirculation were determined by 3-T cMRI. For left ventricular function, cMRI images were acquired using a 3-T scanner, as previously reported.[9] Briefly, quantitative assessment was performed in an offline workstation with the software Argus LV function (Siemens Healthineers). For quantification of myocardial necrosis, planimetry was performed manually by contouring late gadolinium enhancement areas, and infarcted tissue volume was calculated as the sum of those areas multiplied by the thickness of each slice.

Cine cMRI was performed using a steady-state free-precession technique (fast imaging employing steady-state acquisition). Ischemia was detected using first-pass perfusion imaging only in the short-axis orientation, with at least three slices (the maximum number of slices are limited by heart rate). Infarct detection and quantification images were acquired using the myocardial delayed enhancement technique after injection of a commercially available gadolinium-based contrast agent. Contrast-enhanced images were acquired in the same views as those used for cine cMRI, using a segmented inversion-recovery sequence. Each cMRI image was reviewed by two independent blinded readers using a dedicated software. Left ventricular function was estimated using cine cMRI images to measure LVEF volumes and mass according to standard methods. Delayed enhancement images were used for infarct characterization. In each patient, myocardial tissue was classified as hyperenhanced (scar tissue) or normally enhanced myocardium after the observer, who used manual interaction, defined a region of interest (ROI) within a remote non-infarcted territory.

Statistical analysis

Data are presented as mean ± standard deviation or median (interquartile range, IQR) according to data normality. Continuous variables were analyzed for normality using the Kolmogorov-Smirnov test. Baseline and 30-day samples were compared using the nonparametric Wilcoxon signed-rank test. Comparisons between groups were made using the Kruskal-Wallis test. Interleukin titers and cMRI parameters were correlated using the Spearman's rank correlation analysis calculator. Sample size was estimated based on previous studies involving early changes in cytokine titers.[10,11] The software SPSS, version 18.0 (IBM, Armonk, New York, USA), was used for statistical analysis. All p-values < 0.05 were considered statistically significant.

Results

Study population

In total, 139 consecutive individuals with STEMI were included in the study. The main characteristics of the study population at baseline are described in Table 1.

Measurement of circulating cytokines

Figure 1 shows that, compared to baseline, levels of IL-1β and IL-18 decreased 30 days after STEMI. Conversely, increased levels of IL-4 and IL-10 were observed 30 days after STEMI. No significant changes were observed for IL-6 levels over time.

Relationship between cytokines and cardiac magnetic resonance imaging

At baseline, no significant correlations were observed between IL-1β, IL-4, IL-10, and IL-18 levels and cMRI parameters, such as the amount of infarcted mass or LVEF; however, there was a negative correlation between IL-6 levels and LVEF (Spearman's rho = -0.50, p = 0.004). A trend for correlation between IL-6 levels and the percentage of infarcted left ventricular mass was also noted (rho = 0.41, p = 0.05) (Table 2).

There was a positive correlation between baseline levels of IL-4 and the amount of infarcted mass as measured by

cMRI (rho = 0.24; p = 0.03) at 30 days (Table 3). No other correlations between cytokine levels and cMRI parameters were found when they were assessed 30 days after STEMI.

Relationship between cytokines and high-sensitivity C-reactive protein

The levels of hsCRP correlated with those of IL-6 at baseline (rho = 0.45; p < 0.0001) and 30 days after STEMI (rho = 0.29, p = 0.009). No other cytokine showed correlation with hsCRP levels either at baseline or after 30 days of STEMI (data not shown).

Relationship between IL-6 and culprit coronary artery

Right coronary artery was the most common culprit coronary artery related to STEMI (46%), followed by left anterior descending artery (42%) and left circumflex artery (12%). IL-6 levels examined in the first day after STEMI did not differ between the culprit arteries (p = 0.063, Kruskal-Wallis test), as well as after 30 days of STEMI (p = 0.131, Kruskal-Wallis test).

Cardiac magnetic resonance imaging

Table 4 shows the results of cMRI according to the culprit coronary artery. No significant differences were seen for infarcted mass (%), left ventricular mass, or LVEF at baseline or 30 days after STEMI.

Table 1 – Baseline characteristics of the study population

Parameters	N = 139
Age, years*	56 (50-63)
Male gender, n (%)	92 (66)
Smoking, n (%)	28 (20)
Diabetes, n (%)	32 (24)
HbA1c, %**	6.4 ± 1.4
Hypertension, n (%)	82 (60)
SBP, mm Hg**	128 ± 21
DBP, mm Hg**	80 ± 14
Weight, kg**	75 ± 13
BMI, kg/m2**	27.2 ± 4.78
Cholesterol, mg/dL**	208 ± 45
LDL-C, mg/dL**	138 ± 41
HDL-C, mg/dL**	41 ± 12
Triglycerides, mg/dL*	124 (86-213)
hsCRP, mg/L*	15 (7-63)
Myocardial infarction location	
Anterior, n (%)	60 (43)
Inferior, n (%)	73 (53)
Lateral, n (%)	6 (4)

*median (interquartile range); **mean ± standard deviation; BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure.*

Discussion

Our study shows the behavior of cytokine concentrations in the early phase of STEMI in patients who were treated with a pharmacoinvasive strategy and received standard medical care. Our main findings were a marked decrease in the titers of proinflammatory cytokines (IL-1β and IL-18), but not IL-6, and an increase in the titers of protective cytokines (IL-10 and IL-4). Interestingly, LVEF obtained by cMRI showed a correlation with IL-6 concentrations at baseline, but not 30 days post-STEMI. In addition, the infarcted mass quantified by cMRI at 30 days showed a correlation with IL-4 levels at baseline. Together, these data suggest an important role of the interleukin profile on the first day after acute MI, which seems to have some relationship with the infarcted mass and ventricular remodeling. Moreover, the substantial decline in some inflammatory cytokines combined with the remarkable increase in IL-10 appears to attenuate, at least in part, the harmful effects of IL-6 on ventricular remodeling.[12]

Early coronary recanalization and use of both antithrombotic and highly effective lipid-lowering drugs are well-established strategies in the treatment of patients with MI. However, improved knowledge of the residual inflammatory risk during the early follow-up of MI may contribute to creating new therapeutic opportunities.[13]

In our study, IL-6 concentrations were inversely associated with left ventricular function. Mendelian randomization studies have suggested a causal role of IL-6 in coronary heart disease[14,15] and in the development of abdominal aortic aneurysm.[16] Two recent large prospective studies involving individuals after acute coronary events showed an independent association between higher concentrations of IL-6 and main cardiovascular outcomes, including cardiovascular death, even after multiple adjustments to classical biomarkers of cardiovascular disease.[17,18] The interaction of IL-6 with its receptor seems to modulate the inflammatory microenvironment in cardiovascular diseases related to both plaque destabilization and long-term prognosis.

This inflammatory microenvironment involving endothelial and inflammatory biomarkers may be modulated by the antiplatelet therapy chosen.[19,20] However, in the large DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2) study,[21] comparing ticagrelor with clopidogrel after recent acute coronary syndrome, no differences were found in inflammatory biomarkers at baseline, at discharge, and after 4 weeks. The marked decrease in the levels of other inflammatory markers, such as IL-1β and IL-18, and the increase in the levels of protective IL-10 may have contributed to a more favorable inflammatory response, despite persistently high levels of IL-6. Furthermore, these patients received an effective lipid-lowering treatment of proven anti-inflammatory action, with either rosuvastatin[22] or simvastatin/ezetimibe combination.[23] Interestingly, only the level of IL-6 showed no change after the medical treatment, suggesting that the control of this cytokine requires additional therapy, such as the use of a monoclonal antibody or a drug that can reduce IL-6-triggered inflammatory activity.[24,25]

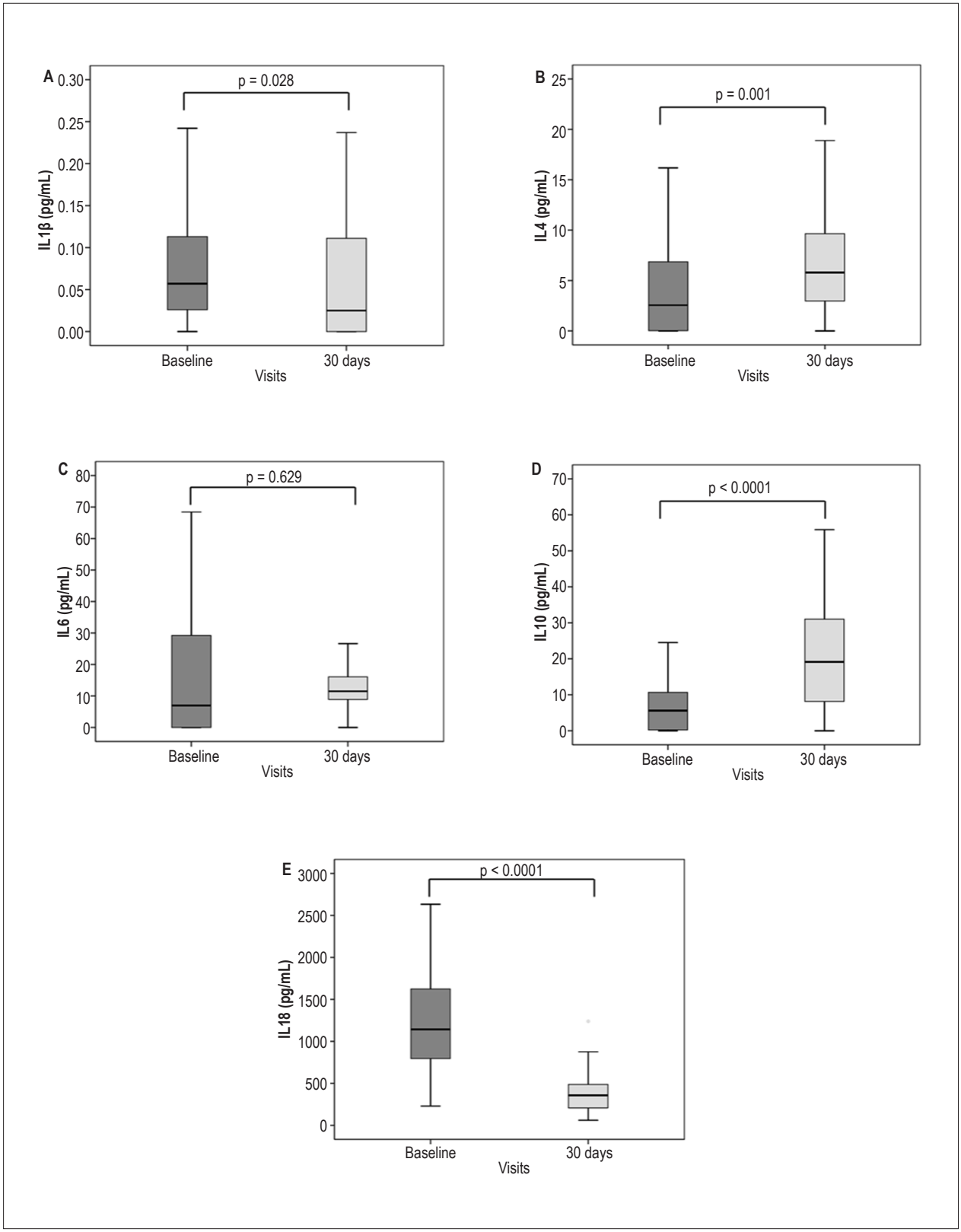

Figure 1 – *Box-plots of interleukin (IL) concentrations at baseline and 30 days after STEMI. (A) IL-1ß; (B) IL-4; (C) IL-6; (D) IL-10; (E) IL-18. Significant changes were observed in all cytokines, except for IL-6. Titers were compared using the Wilcoxon test.*

Table 2 – Correlations between baseline interleukin concentrations (pg/mL) and cardiac magnetic resonance imaging parameters in the acute phase of myocardial infarction

Variables	Spearman's rho	P-value
IL-1β and infarcted mass*	0.16	0.43
IL-1β and infarcted mass**	-0.05	0.84
IL-1β and LVEF	0.12	0.55
IL-4 and infarcted mass*	-0.26	0.19
IL-4 and infarcted mass**	-0.20	0.37
IL-4 and LVEF	0.15	0.44
IL-6 and infarcted mass*	0.16	0.39
IL-6 and infarcted mass**	0.41	0.05
IL-6 and LVEF	-0.50	0.004
IL-10 and infarcted mass*	0.30	0.10
IL-10 and infarcted mass**	0.24	0.28
IL-10 and LVEF	-0.31	0.09
IL-18 and infarcted mass*	-0.11	0.57
IL-18 and infarcted mass**	-0.24	0.28
IL-18 and LVEF	0.01	0.96

**grams; **percentage of left ventricular mass; IL: interleukin; LVEF: left ventricular ejection fraction.*

Table 3 – Correlations between baseline interleukin concentrations (pg/mL) and cardiac magnetic resonance imaging parameters after 30 days of myocardial infarction

Variables	Spearman's rho	P-value
IL-1β and infarcted mass*	-0.02	0.85
IL-1β and infarcted mass**	-0.07	0.59
IL-1β and LVEF	0.19	0.10
IL-4 and infarcted mass*	0.24	0.03
IL-4 and infarcted mass**	0.14	0.20
IL-4 and LVEF	-0.14	0.19
IL-6 and infarcted mass*	0.13	0.23
IL-6 and infarcted mass**	0.13	0.22
IL-6 and LVEF	-0.17	0.10
IL-10 and infarcted mass*	0.13	0.23
IL-10 and infarcted mass**	0.07	0.55
IL-10 and LVEF	0.09	0.40
IL-18 and infarcted mass*	0.14	0.31
IL-18 and infarcted mass**	-0.12	0.38
IL-18 and LVEF	0.07	0.52

**grams; **percentage of left ventricular mass; IL: interleukin; LVEF: left ventricular ejection fraction.*

Table 4 – Cardiac magnetic resonance imaging results by culprit coronary artery at baseline and 30 days after acute myocardial infarction

Culprit coronary artery	Baseline	30 days
Left anterior descending artery		
Infarct size, % LV	10.0 (5.5-19.0)	12.7 (8.0-21.0)
LV mass, grams	117.3 (101.0-171.8)	90.5 (69.0-127.9)
LVEF, %	46.0 (43.3-59.0)	51.6 (40.5-59.3)
Right coronary artery		
Infarct size, % LV	12.0 (10.0-18.5)	10.0 (6.0-17.9)
LV mass, grams	96.0 (86.5-123.0)	99.0 (80.0-113.0)
LVEF, %	48.0 (42.0-50.5)	55.5 (50.0-60.0)
Left circumflex artery		
Infarct size, % LV	11.5 (5.0-18.0)	7.0 (4.0-8.7)
LV mass, grams	103.0 (76.0-130.0)	103.0 (75.0-106)
LVEF, %	51.0 (50.0-52.0)	54.0 (51.0-58.0)

Data presented as median (interquartile range). LV: left ventricular; LVEF: left ventricular ejection fraction. Baseline cardiac magnetic resonance imaging was obtained within 10 days of myocardial infarction. At baseline, no differences were observed for infarct size between culprit coronary arteries (p = 0.59) as well as for LV mass (p = 0.08) or LVEF (p = 0.62) (Kruskal-Wallis test for all analyses). No differences were observed between culprit coronary arteries at 30-days for infarct size (p = 0.13), LV mass (p = 0.86), or LVEF (p = 0.10) (Kruskal-Wallis test was used for comparisons).

IL-4 has several biological properties, including differentiation of Th1 lymphocytes into cells with less inflammatory activity (Th2).[25] In addition, chronically elevated IL-4 was reported to have a causal relationship with cardiac fibrosis and adverse cardiac remodeling.[26] Furthermore, dilated cardiomyopathy induced by angiotensin II is modulated by IL-4 levels.[27] In our study, we observed an association between baseline IL-4 levels and the amount of infarcted mass after 30 days of MI. These findings suggest an important role for this cytokine, possibly by attenuating the myocardial inflammatory process through greater cell differentiation into less inflammatory phenotypes (M2 macrophages and Th2 lymphocytes). In this setting, IL-4 may influence the entire ventricular remodeling process. It may take several weeks to occur and seems to depend on the crosstalk between inflammatory cells and cardiomyocytes, thus determining elimination of necrotic cells and promoting cell replacement and formation of the fibrotic scar.[28]

Inflammasomes are a family of the innate immune system that includes NLRP3, which has been recognized as a relevant trigger for the inflammatory cascade related to cardiovascular disease.[29] This platform can be activated by many stimuli, including hypoxia, promoting the release of the highly inflammatory cytokines IL-1β and IL-18.[30] Furthermore, metabolic syndrome and diabetes are related to IL-18 concentrations. Whereas IL-1β is related to the inflammatory cascade of cardiovascular disease, IL-18 seems to be associated with inflammatory mechanisms, favoring cancer development and showing higher concentrations in subjects with diabetes and insulin resistance.[31,32] Our study showed a decrease in both cytokines (IL-1ß and IL-18), suggesting a decrease in the stimuli for NLRP3 activation after 30 days of STEMI.

Our study also reinforces the important role of IL-6, the only unmodified cytokine 30 days after MI, showing a significant correlation with hsCRP at baseline and 30 days after STEMI, a previously reported association.[33] In our study, only patients with STEMI undergoing thrombolysis in the first 6 hours and referred to coronary angiography in the first 24 hours were included. Thus, this is a highly homogeneous population receiving standard medical care. Taking into account the association of chronically elevated levels of IL-6 with the recurrence of coronary events, heart failure, cardiovascular mortality, and all-cause mortality, an additional decrease in the residual inflammatory risk seems to be a promising target for intervention.[34,35]

Study limitations

The study population received lipid-lowering and antiplatelet therapies whose anti-inflammatory effects may have contributed to the study results. However, these treatments are part of the standard of care for these subjects. Some inflammatory cytokines capable of activating the inflammatory pathway mediated by IL-6, such as tumor necrosis factor-alpha (TNF-α) or IL-1R, were not measured and may have relevance in host tissue responses and ventricular remodeling.[36,37] In fact, MI per se could be related to an increase in IL-6 as a response to injury. However, IL-6 titers remained elevated while other cytokines changed their serum levels after 30 days of STEMI. Another important inflammatory biomarker not evaluated in the study was IL-1α, which is released from necrotic cardiomyocytes and activates the immune responses from fibroblasts.[38] IL-1α blockade decreases chemoattractant activity for many cells mediated by CCL2/MCP-1 and IL-6.[38] In addition, monocyte and lymphocyte recruitment in ischemic heart can be stimulated by several chemoattractants such as CCL2 and CCL5, thus influencing tissue healing.[39] Finally, the transforming growth factor beta (TGF-β), which is highly expressed after acute MI, was not evaluated in our study as well but has been implicated in cardiomyocyte survival and ventricular remodeling.[40]

The results presented herein refer to a relatively early period after acute MI, but this is the time when inflammatory infiltrate seems to be more relevant to cell recovery or reperfusion injury.

Conclusions

During the first month post-MI, we observed a marked improvement in the balance of pro- and anti-inflammatory cytokines, except for IL-6. These findings suggest residual inflammatory risk.

Highlights

- Current strategies in the care of patients with acute myocardial infarction seem to be insufficient to modify the inflammatory pathway mediated by interleukin-6.
- Higher concentrations of this cytokine appear to be associated with decreased left ventricular ejection fraction.
- Therapies targeting interleukin-6 seem promising for their additional decrease in residual inflammatory risk in subjects with acute myocardial infarction.
- The great challenge for reducing residual inflammatory risk lies in the development of safe and affordable therapies.

Author contributions

Conception and design of the research: Izar MC, Maugeri IL, Pinto IM, Szarf G, Caixeta AM, Berwanger O, Fonseca FAH; Acquisition of data: Coste MER, Izar MC, Teixeira D, Ishimura ME, Bacchin AS, Bianco HT, Moreira FT, Pinto IM, Szarf G, Caixeta AM, Gonçalves Jr. I, Fonseca FAH; Analysis and interpretation of the data: Coste MER, França CN, Izar MC, Teixeira D, Ishimura ME, Maugeri IL, Bacchin AS, Bianco HT, Moreira FT, Pinto IM, Szarf G, Caixeta AM, Berwanger O, Gonçalves Jr. I, Fonseca FAH; Statistical analysis: Coste MER, França CN, Fonseca FAH; Obtaining financing: Fonseca FAH; Writing of the manuscript: Coste MER, Fonseca FAH; Critical revision of the manuscript for intellectual content: Izar MC, Maugeri IL, Fonseca FAH.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by FAPESP (2012/51692-7) and CNPq 300937/2015-6 e 428793/2016-9. Antiplatelet and lipid-lowering drugs were obtained through an investigator initiated grant from AstraZeneca (ESR 14-10726), which did not influence the study conception, data collection, statistical analysis, and publications.

Study Association

This article is part of the thesis of master submitted by Maria E. R. Coste, from Universidade Federal de São Paulo.

References

1. Everett BM, Cornel J, Lainscak M, Anker SD, Abbate A, Thuren T, et al. Anti-inflammatory therapy with Canakinumab for the prevention of hospitalization for heart failure. Circulation. 2019;139(10):1289-99.
2. Zhao L, Cheng G, Jin R, Afzal MR, Samanta A, Xuan YT, et al. Deletion of interleukin-6 attenuates pressure overload-induced left ventricular hypertrophy and dysfunction. Circ Res. 2016;118(12):1918-29.
3. Huang M, Yang D, Xiang M, Wang J. Role of interleukin-6 in regulation of immune responses to remodeling after myocardial infarction. Heart Fail Rev. 2015;20(1):25-38.
4. Su Z, Lin R, Chen Y, Shu X, Zhang H, Nie R, et al. Knockdown of EMMPRIN improves adverse remodeling mediated by IL-18 in the post-infarcted heart. Am J Transl Res. 2015;7(10):1908-16.
5. Suetomi T, Willeford A, Brand CS, Cho Y, Ross RS, Miyamoto S, et al. Inflammation and nlrp3 inflammasome activation initiated in response to pressure overload by ca_{2+}/calmodulin-dependent protein kinase ii δ signaling in cardiomyocytes are essential for adverse cardiac remodeling. Circulation. 2018;138(22):2530-44.
6. Ørn S, Ueland T, Manhenke C, Sandanger Ø, Godang K, Yndestad A, et al. Increased interleukin-1β levels are associated with left ventricular hypertrophy and remodelling following acute ST segment elevation myocardial infarction treated by primary percutaneous coronary intervention. J Intern Med. 2012;272(3):267-76.
7. Peng H, Sarwar Z, Yang XP, Peterson EL, Xu J, Janic B, et al. Profibrotic role for interleukin-4 in cardiac remodeling and dysfunction. Hypertension. 2015;66(3):582-9.
8. Jung M, Ma Y, Iyer RP, DeLeon-Pennell KY, Yabluchiansky A, Garrett MR, et al. IL-10 improves cardiac remodeling after myocardial infarction by stimulating M2 macrophage polarization and fibroblast activation. Basic Res Cardiol. 2017;112(3):33.
9. Fonseca FAH, Izar MC, Maugeri IML, Berwanger O, Damiani LP, Pinto IM, et al. Effects of four antiplatelet/statin combined strategies on immune and inflammatory responses in patients with acute myocardial infarction undergoing pharmacoinvasive strategy: design and rationale of the B and T Types of lymphocytes evaluation in acute myocardial infarction (BATTLE-AMI) study: study protocol for a randomized controlled trial. Trials. 2017 Dec 19;18:601.
10. Gong X, Zhou R, Li Q. Effects of captopril and valsartan on ventricular remodeling and inflammatory cytokines after interventional therapy for AMI. Exp Ther Med. 2018;16(4):3579-83.
11. Morariu M, Hodas R, Benedek T, Benedek I, Opincariu D, Mester A, et al. Impact of inflammation-mediated response on pan-coronary plaque vulnerability, myocardial viability and ventricular remodeling in the post-infarction period – the VIABILITY study: protocol for a non-randomized prospective clinical study. Medicine (Baltimore). 2019;98(17):e15194.
12. Kotter S, Kazmierowska M, Andresen C, Bottermann K, Grandoch M, Gorressen S, et al. Titin-based cardiac myocyte stiffening contributes to early adaptive ventricular remodeling after myocardial infarction. Circ Res. 2016;119(9):1017-29.
13. Ridker PM. From CRP to IL-6 to IL-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016;118(1):145-56.
14. Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JEL, Shah T, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012;379(9822):1214-24.
15. IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet. 2012;379(9822):1205-13.
16. Harrison SC, Smith AJ, Jones GT, Swerdlow DI, Rampuri R, Bown MJ, et al. Interleukin-6 receptor pathways in abdominal aortic aneurysm. Eur Heart J. 2013;34(48):3707-16.
17. Fanola CL, Morrow DA, Cannon CP, Jarolim P, Lukas MA, Bode C, et al. I. Interleukin-6 and the risk of adverse outcomes in patients after an acute coronary syndrome: observations from the SOLID-TIMI 52 (Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52) trial. J Am Heart Assoc. 2017;6(10):e005637.
18. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018;39(38):3499-507.
19. Wei P, Han B, Zhang WJ, Bai J, Jiang CY, Qiu CR, et al. Effect of ticagrelor on the serum level of hs-CRP, ESM-1 and short-term prognosis of patients with acute STEMI. Exp Ther Med. 2017;13(2):604-8.
20. Gao CZ, Ma QQ, Wu J, Liu R, Wang F, Bai J, et al. Comparison of the Effects of ticagrelor and clopidogrel on inflammatory factors, vascular endothelium functions and short-term prognosis in patients with acute ST-Segment Elevation Myocardial Infarction Undergoing Emergency Percutaneous Coronary Intervention: a pilot study. Cell Physiol Biochem. 2018;48(1):385-96.
21. Husted S, Storey RF, Harrington RA, Emanuelsson H, Cannon CP. Changes in inflammatory biomarkers in patients treated with ticagrelor or clopidogrel. Clin Cardiol. 2010;33(4):206-12.
22. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJP, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373(9670):1175-82.
23. Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation. 2015;132(13):1224-33.
24. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J. 2014;35(27):1782-91.
25. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-31.

26. Yagi R, Suzuki W, Seki N, Kohyama M, Inoue T, Arai T, et al. The IL-4 production capability of different strains of naive CD4(+) T cells controls the direction of the T(h) cell response. Int Immunol. 2002;14(1):1-11.

27. Peng H, Sarwar Z, Yang XP, Peterson EL, Xu J, Janic B, et al. Profibrotic Role for interleukin-4 in cardiac remodeling and dysfunction. Hypertension. 2015;66(3):582-9.

28. Gomez I, Duval V, Silvestre JS. Cardiomyocytes and macrophages discourse on the method to govern cardiac repair. Front Cardiovasc Med. 2018 Oct 2;5:134.

29. Folco EJ, Sukhova GK, Quillard T, Libby P. Moderate hypoxia potentiates interleukin-1β production in activated human macrophages. Circ Res. 2014;115(10):875-83.

30. Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol. 2013;13(6):397-411.

31. Ahechu P, Zozaya G, Martí P, Hernández-Lizoáin JL, Baixauli J, Unamuno X, et al. NLRP3 inflammasome: a possible link between obesity-associated low-grade chronic inflammation and colorectal cancer development. Front Immunol. 2018 Dec 11;9:2918.

32. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17(2):179-88.

33. Gabriel AS, Martinsson A, Wretlind B, Ahnve S. IL-6 levels in acute and post myocardial infarction: their relation to CRP levels, infarction size, left ventricular systolic function, and heart failure. Eur J Intern Med. 2004;15(8):523-8.

34. Eskandari V, Amirzargar AA, Mahmoudi MJ, Rahnemoon Z, Rahmani F, Sadati S, et al. Gene expression and levels of IL-6 and TNFα in PBMCs correlate with severity and functional class in patients with chronic heart failure. Ir J Med Sci. 2018;187(2):359-68.

35. Ridker PM. Clinician's guide to reducing inflammation to reduce atherothrombotic risk: JACC review topic of the week. J Am Coll Cardiol. 2018;72(25):3320-31.

36. Mahmoud AH, Taha NM, Zakhary M, Tadros MS. PTEN gene & TNF-alpha in acute myocardial infarction. Int J Cardiol Heart Vasc. 2019 Apr 29;23:100366.

37. Orrem HL, Shetelig C, Ueland T, Limalanathan S, Nilsson PH, Husebye T, et al. Soluble IL-1 receptor 2 is associated with left ventricular remodeling in patients with ST-elevation myocardial infarction. Int J Cardiol. 2018 Oct 1;268:187-92.

38. Lugrin J, Parapanov R, Rosenblatt-Velin N, Rignault-Clerc S, Feihl F, Waeber B, et al. Interleukin-1 alpha is a crucial danger signal triggering acute myocardial inflammation during myocardial infarction. J Immunol. 2015;194(2):499-503.

39. Dutta P, Nahrendorf M. Regulation and consequences of monocytosis. Immunol Rev. 2014;262(1):167-78.

40. Hanna A, Frangogiannis NG. The role of the TGF- ß superfamily in myocardial infarction. Front Cardiovasc Med. 2019 Sep 18;6:140.