e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(7); 546-552

Original Research Article

A Prospective Analytical Assessment of Cardiac Failure and its Prognostication with 3C: Reactive Protein as a Marker of Severity

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Received: 10-05-2022 / Revised: 15-06-2022 / Accepted: 10-07-2022
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Conflict of interest: Nil

Abstract

Aim: To evaluate the cardiac failure and its prognostication with 3C: Reactive protein as a marker of severity.

Material & Methods: The cross-sectional analytical study was conducted in the Department of Medicine, Government Medical College, Bettiah, Bihar, India. Chagas disease was confirmed by 3 serological tests: direct agglutination, immunofluorescence, and enzyme-linked immunoassay (ELISA) and patients with 2 or more positive assays were accepted as positive.

Results: The multiple regression analysis found no correlation between age and status of Chagas disease progression. Multiple regression analysis relating Chagas phase to serum IL-6 concentrations (analyzing the variables of age, sex, diabetes mellitus, hypertension, heart failure, and dyslipidemia), confirmed the hypothesis that IL-6 values show a significant correlation to disease phase. Although the simple correlation analyses showed a positive correlation between IL-6 or CRP and LVMI, a negative correlation between IL-6 or CRP and the ejection fraction, as well as between IL-6 and BMI, the multiple regression analysis did not confirm these results.

Conclusion: Elevated IL-6 concentrations were related to the phase of Chagas disease, indicating that once these patients have progressed beyond the acute phase, they experience a chronic inflammatory process, which becomes more severe with progression to Phase III status.

Keywords: IL-6, Chagas Disease, Marker.

Introduction

In the last decade there has been growing evidence that inflammation plays a pivotal role in the etiology and progression of atherosclerosis [1–4]. Increased levels of different markers of inflammation have been associated with either an increased risk of developing coronary artery disease

(CAD) or with poor prognosis in patients with known CAD [5].

Amongst the inflammatory mediators, C-reactive protein (CRP) has emerged as an independent risk indicator. Observational studies have consistently reported that elevated CRP levels have clear prognostic value for major cardiovascular events and even mortality [6–8]. Although there is heterogeneity in the predictive value of CRP, the general consensus acknowledges a relation between CRP and cardiovascular disease. The impact of CRP on cardiovascular outcome has been emphasized by data showing that risk reduction for a first myocardial infarction seemed to be directly related to high sensitivity CRP (hsCRP) levels [9].

Elevated levels of CRP have been observed in patients with heart failure [10], and activation of the immune response may play a role in heart failure through modifications in the renin–angiotensin–aldosterone and sympathetic systems [11-12].

This study is mainly designed to evaluate the level of CRP in patients with chronic CHF and to examine the relation between the degree of CRP elevation and clinical outcome.

Material & Methods:

The cross-sectional analytical study was conducted in the Department of Medicine, Government Medical College, Bettiah, Bihar, India, for one year. The no probabilistic sample was composed of 60 non consecutive patients of both sexes. Chagas disease was confirmed by 3 serological tests: direct agglutination, immunofluorescence, and enzyme- linked immunoassay (ELISA) and patients with 2 or more positive assays were accepted as positive.

Inclusion criteria:

- The patients were classified according to the 3 phases proposed by Carrasco et al (1994): [12] Phase I (n=20), asymptomatic patients with no electrocardiographic or echocardiographic evidence of cardiac involvement; Phase II (n=20), asymptomatic patients with electrocardiographic or echocardiographic evidence of cardiac involvement; and Phase III (n=20), patients with heart failure.

Exclusion criteria:

- Patients with acute or chronic ischemic heart disease defined as a confirmed history of anterior or recent myocardial infarction, history of angina pectoris and/or positive stress test or stress echocardiogram for ischemia, or cardiac catheterization indicative of coronary artery disease.
- Patients with acute or chronic liver disease.
- Patients with acute or chronic inflammatory processes (e.g., rheumatoid arthritis, collagen disease, vasculitis, or cancer) and acute or chronic infections (e.g., endocarditis, pneumonia, and/or tuberculosis);
- Patients who are immunosuppressed or receiving corticoid therapy
- Patients with non-Chagas acute or recurrent pericarditis.
- Patients with primary valve disease due to disorders that are congenital or secondary to infectious processes (e.g., rheumatic fever and/or endocarditis).

Control group

The study also included a control group of 20 individuals over age 18 with no history or serological evidence of Chagas disease or other heart condition.

Statistical Analysis:

After determining the respective descriptive statistics for characterizing the final sample, the multiple linear regression models used to relate the IL-6 and CRP values to the phase of Chagas disease were considered. The Kolmogorov-Smirnov test showed that the distribution of the levels

of the mediators cited was not Gaussian and therefore, logarithmic transformation of the levels of these mediators prior to inclusion in the respective models was performed. The following variables were included in the regression analysis: Chagas disease phase, sex, age, heart failure, hypertension, diabetes mellitus, and dyslipidemia. The progressive phases of Chagas heart disease were also included in the regression models as dummy variables, with 0 and 1 used to represent the absence or presence of a particular phase. The control group included individuals without Chagas disease. Backward elimination was used to exclude variables with no significant effect. Results are expressed as mean ± standard error or 95% confidence interval (95% CI). Statistical significance was set at *P*=.05. Statistix 1.0 and Prism 3.0 were used for the statistical analysis.

Results:

The average age of the participants was 50.3±2.4 years for the population of healthy volunteers and 60.3±2.4 years for seropositive patients. The average age of patients according to phase of Chagas disease was as follows: Phase I, 55.8±3.1; Phase II, 61.4±2.8, and Phase III, 67.8±2.3 years, respectively, with a significant difference observed in Phase II and III patients versus the control group and Phase I patients (Table 1).

Table 1: Age, sex, and serum interleukin-6 and C - reactive protein values in healthy individuals and in phases i, ii, and iii patients with chagas disease

Groups	Age (years)	Men	Women	IL-6 (% pg/mL)	CRP (mg/dL)
Control	50.3±2.4	10	10	0.9±0.1	0.7±0.05
Phase I	55.8±3.1	9	11	3.6±0.8	0.6±0.07
Phase II	61.4±2.8	12	8	4.2±1.4	0.4±0.2
Phase III	67.8±2.3	10	10	12.4±3.9	4.1±1.3

The multiple regression analysis found no correlation between age and status of Chagas disease progression. In the means calculated for the echocardiographic parameters (Table 2) in particular, left ventricular end- diastolic diameter, left ventricular end-systolic diameter, left atrial diastolic diameter, right ventricular diastolic diameter which indicate chamber dilation, significant quantitative increases were confirmed with respect to the degree of the disease (*P*<.05).

Table 2: Echocardiographic parameters in patients with chagas disease according to stage phase of chagas disease

Echocardiographic Parameter	Phase of Chagas Disease		
	Phase I	Phase II	Phase III
LVEDD, mm	47.3±0.7	53.6±0.7	62.4±1.30†
LVESD, mm	30.4±0.8	32.5±1.4	43.5±1.3t
Shortening, %	32.3±1.5	27.4±1.7	28.7±2.4
LVEDV, mL	99.5±3.4	139.8±5.6	162.7±13.6t
LVESV, mL	42.6±4.4	50.3±4.1	102.5±10.3t
EF, %	61.7±1.8	55.7±2.4	38.3±3.5†
LA, mm	31.6±0.8	30.2±1.2	45.6±1.6†
RV, mm	14.7±0.8	11.4±1.3	17.2±1.6†
LVM, g	255.8±18.9	338.9±27.3	420.7±29.2t
LVMI, g/m^2 SC	113.4±4.2	130.2±11.8	240.3±14.6†

*LA indicates diastolic diameter of the left atrium; LVEDD, left ventricular end- diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; LVMI, left

ventricular mass index; LVM, left ventricular mass; RV, right ventricular diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume. †*P*<.05 with respect to Phases I and II.

An assessment of left ventricular end-diastolic volume and left ventricular end-systolic volume showed a significant increase (*P*<.05) as the disease progressed. The ejection fraction was inversely proportionate to the phase of disease progression; the parameters measuring dilation and cardiac remodeling (e.g., left ventricular mass and left ventricular mass index, LVMI), showed similar alterations, with direct changes according to the phase of the disease, which were only significant in the most advanced phase.

Multiple regression analysis relating Chagas phase to serum IL-6 concentrations (analyzing the variables of age, sex, diabetes mellitus, hypertension, heart failure, and dyslipidemia), confirmed the hypothesis that IL-6 values show a significant correlation to disease phase (Table 3).

Table 3: Relationship between the phase of chagas disease and interleukin-6 values. multiple linear regression analysis*

Variable	**Coefficient**	95% Cl	P value
Intercept	-0.438	-0.957 to 0.112	0.281
Age, years	0.001	-0.006 to 0.0108	0.681
Male	-0.174	-0.348 to 0.115	0.440
Diabetes mellitus	-0.149	-0.566 to 0.289	0.672
Hypertension	–0.139	–0.329 to 0.120	.493
Congestive heart failure	0.127	–0.409 to 0.657	.821
Dyslipidemia	0.280	–0.006 to 0.571	.05
Phase I	0.682	0.340 to 1.036	.001
Phase II	0.766	0.421 to 1.128	<.001
Phase III	1.122	0.567 to 1.679	.001

*Logarithmic transformation was used to normalize the data; only significant variables remaining after backwards elimination are shown

Phase I showed a coefficient of 0.7 (95% CI, –0.68 to 0.56) and *P*<.0001, Phase II showed a coefficient of 0.9 (95% CI, –0.68 to 0.9) and *P*<.0001, Phase III showed a coefficient of 1.3 (95% CI, 0.61 to 2.80) and *P*<.0001. C-reactive protein correlated only to Chagas Phase III (Table 4), obtaining intercept values of –1.6 (95% CI, –1.4 to –1.0) and *P*<.0001, for Phase III of 1 (95% CI, 0.5-1.6) and *P*=.0001.

Table 4: Relationship between the phase of chagas disease and CRP values. Multiple linear regression analysis*

Variable	**Coefficient**	95% Cl	P value
Intercept	–1.134	–2.129 to –0.178	.001
Age, years	–0.005	–0.004 to –0.01	.639
Male	0.087	–0.38 to 0.58	.562
Diabetes mellitus	–0.038	–0.89 to 0.79	.880
Hypertension	–0.002	–0.46 to 0.48	.841
Dyslipidemia	–0.075	–0.68 to 0.52	.701
Phase I	–0.119	–0.72 to 0.56	.766
Phase II	–0.019	–0.68 to 0.9	.742

Phase III	0.635	0.61 to 2.80	.001

A multiple regression analysis was performed between values for the functional variables obtained from echocardiographic studies and serum IL-6 and CRP values, taking into consideration the intervening variables. The results showed that LVMI was associated with male sex, Phase III disease, and IL-6 values (Table 5).

Table 5: Multiple regression analysis between left ventricular mass index and interleukin-6 values*

Variable	**Coefficient**	95% Cl	P value
Intercept	95.73	75.4-114.72	<.001
IL-6 (log)	46.71	15.62-69.01	.001
Male	38.63	15.68-57.73	.001
Phase III of Chagas disease	94.81	65.46-122.81	<.001

Only significant variables remaining after backwards elimination are shown. Adjusted r^2=0.68; n=60

Although the simple correlation analyses showed a positive correlation between IL-6 or CRP and LVMI, a negative correlation between IL-6 or CRP and the ejection fraction, as well as between IL-6 and BMI, the multiple regression analysis did not confirm these results.

Discussion:

High-sensitivity C-reactive protein has several features appealing for clinical and epidemiologic use. These include a long circulating half-life, long-term stability in frozen samples, insensitivity to recent food intake or circadian effects, and the availability of precise and inexpensive assays. [13] With acute infection, levels increase by orders of magnitude, well beyond normal variation, making it possible to identify outliers. Conversely, hsCRP levels tend to remain stable overtime in the absence of acute infection, with within-person variability over time similar to systolic blood pressure and low-density lipoprotein (LDL) cholesterol. [14-15] These characteristics, along with its strong prognostic power for identifying incident cardiovascular events independently of common risk markers in diverse populations, have ledto a role in clinical risk stratification and decision-making. [16]

There is evidence that chronic activation of the immune system exists during heart failure. Some patients present evidence of monocyte-macrophage and lymphocyte activation. It appears clear that patients with either ischaemic or non-ischaemic heart failure show activation of proinflammatory cytokines (tumour necrosis factor-a, IL-1, IL-6). What factor triggers this immune response is unknown, but at present, possible agents include the renin–angiotensin–aldosterone system and the sympathetic nervous system [10, 11, 17, and 18].

Therapeutic inhibition of an excessive CRP response could thus be a promising new approach to cardio protection in STEMI patients. In this context Pepys *et al*. developed a specific small-molecule inhibitor of CRP [19]. In rats undergoing AMI this inhibitor could abrogate the increase in infarct size and cardiac dysfunction. In another interesting approach Sheriff *et al*. developed a specific CRP adsorber and showed that CRP depletion by apheresis led to a reduction of infarct size in a porcine animal model of AMI [20]. Although it is difficult to transfer these data to the clinical setting of patients suffering STEMI, it supports the assumption that therapeutic inhibition of CRP could be a promising approach to cardio protection after STEMI. However, further investigations need to be performed to test

the impact of therapeutic CRP depletion in a human clinical setting.

An assessment of plasma CRP concentrations in patients with Chagas disease according to phase and in the controls showed a clear, significant increase among Phase III patients. This difference suggests that inflammatory changes are present and active during the more advanced stage of the disease. The presence of inflammatory foci and myocyte necrosis due to lymphocyte migration has been described in Chagas disease, even in the presence of a low degree of parasitism [21]. The inflammatory foci may be the result of microcirculation changes, which cause ischemic alterations followed by fibrosis and myocardial remodeling [22]. T cruzi infection in experimental animal models leads to elevated serum and tissue IL6 [23], which is induced during the increasing stage of parasitemia in the acute period of Chagas disease [24]. It has been postulated that the main inducer of IL-6 in T cruzi infection is the enzyme transialidase of the parasite itself [25,26].

Conclusion:

Elevated IL-6 concentrations were related to the phase of Chagas disease, indicating that once these patients have progressed beyond the acute phase, they experience a chronic inflammatory process, which becomes more severe with progression to Phase III status.

References:

1. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999; 340: 115-26.
2. Koyama K, Yoneyama K, Mitarai T, et al. Association between inflammatory biomarkers and thin-cap fibroatheroma detected by optical coherence tomography in patients with coronary heart disease. Arch Med Sci 2015; 11: 505-12.
3. Mrowiecki W, Sagan A, Guzik B, et al. Inflammatory aortic abdominal aneurysm – immunophenotypic characterization of inflammatory infiltrate. Arch Med Sci 2014; 10: 1258-62.
4. Tiyerili V, Becher UM, Camara B, et al. Impact of peroxisome proliferator-activated receptor gamma on angiotensin II type 1 receptor-mediated insulin sensitivity, vascular inflammation and atherogenesis in hypercholesterolemic mice. Arch Med Sci 2015; 11: 877-85.
5. Dibra A, Mehilli J, Schwaiger M et al. Predictive value of basal C-reactive protein levels for myocardial salvage in patients with acute myocardial infarction is dependent on the type of reperfusion treatment. Eur Heart J 2003; 24: 1128-33.
6. Bisoendial RJ, Kastelein JJ, Stroes ES. C-reactive protein and atherogenesis: from fatty streak to clinical event. Atherosclerosis 2007; 195: e10-8.
7. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107: 499-511.
8. Xie D, Hu D, Zhang Q, Sun Y, Li J, Zhang Y. Increased high-sensitivity C-reactive protein, erythrocyte sedimentation rate and lactic acid in stroke patients with internal carotid artery occlusion. Arch Med Sci 2016; 12: 546-51.
9. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-9.
10. Werdan K. The activated immune system in congestive heart failure. From dropsy to the cytokine paradigm. J Intern Med 1998; 243:87 –92.

11. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation 1995; 92:1479 –86.
12. MacGowan GA, Mann DL, Kormos RL, Feldman AM, Murali S. Circulating interleukin-6 in severe heart failure. Am Cardiol 1997; 79:1128 –31.
13. Ridker PM, Rifai N. C-Reactive Protein and Cardiovascular Disease. 1st ed. St-Laurent, Canada: Medi Edition Inc; 2006.
14. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375:132–140.
15. Ridker PM. A test in context: high-sensitivity C-reactive protein. J Am Coll Cardiol 2016; 67:712–723.
16. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW; American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63:2889–2934.
17. Samsonov M, Lopatin J, Tiltz GP. The activated immune system the renin–angiotensin–aldosterone system in congestive heart failure. J Intern Med 1998; 243:93 –8.
18. MacGowan GA, Mann DL, Kormos RL, Feldman AM, Murali S. Circulating interleukin-6 in severe heart failure. Am J Cardiol 1997; 79:1128 –31.
19. Pepys MB, Hirschfield GM, Tennent GA, et al. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature 2006; 440: 1217-21.
20. Sheriff A, Schindler R, Vogt B, et al. Selective apheresis of C-reactive protein: a new therapeutic option in myocardial infarction? J ClinApher 2015; 30: 15-21.
21. Cunha-Neto E, Kalil J. Autoimmunity in Chagas' heart disease. Sao Paulo Med J. 1995; 113:757-66.
22. 17. Rossi MA. Microvascular changes as a cause of chronic cardiom- yopathy in Chagas' disease. Am Heart J. 1990; 120:233-6
23. Gao W, Pereira MA. Interleukin-6 is required for parasite specific response and host resistance to Trypanosoma cruzi. Int J Parasi- tol. 2002; 32:167-70. Truyens C, Angelo-Barrios A, Torrico F, Van Damme J, Here- mans H, Carlier Y. Interleukin-6 (IL-6) production in mice infec- ted with Trypanosoma cruzi: effect of its paradoxical increase by anti-IL-6 monoclonal antibody treatment on infection and acute- phase and humoral immune responses. Infect Immun. 1994;62: 692-6.
24. Saavedra E, Herrera M, Gao W, Uemura H, Pereira MA. The Trypanosoma cruzi trans-sialidase, through its COOH-terminal tandem repeat, upregulates interleukin 6 secretion in normal hu- man intestinal microvascular endothelial cells and peripheral blood mononuclear cells. J Exp Med. 1999; 190:1825-36
25. Hays P. Evidence Basis for Pharmacogenetic Testing in Psychiatry. Journal of Medical Research and Health Sciences, 2022:5(3), 1838–1859.