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Original Research Article

A Prospective Study of Congestive Heart Failure and its Prognosis Using the 3C: Reactive Protein as A Measure of Disease Severity

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Abstract

Aim: The aim of this study to evaluate the cardiac failure and its prognostication with 3C: Reactive protein as a marker of severity. **Methods:** The cross-sectional analytical study was conducted in the Department of General Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India, , after taking the approval of the protocol review committee and institutional ethics committee. The non probabilistic sample was composed of 90 non consecutive patients of both sexes. Chagas disease was confirmed by 3 serological tests: direct agglutination, immunofluorescence, and enzyme- linked immunoassay (ELISA), according to previously established protocols, and patients with 2 or more positive assays were accepted as positive. **Results:** The average age of the participants was 51.4±2.7 years for the population of healthy volunteers and 63.2±1.7 years for seropositive patients. The average age of patients according to phase of Chagas disease was as follows: Phase I, 57.9±3.0; Phase II, 63.7±2.7, and Phase III, 69.3±2.2 years, respectively, with a significant difference observed in Phase II and III patients versus the control group and Phase I patients. In the means calculated for the echocardiographic parameters, 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). An assessment of left ventricular end-diastolic volume and left ventricular end-systolic volume showed a significant increase (P<.05) as the disease progressed. Mean absolute CRP values in the study group showed a significant progressive increase (P<.005) in Phase I (0.3±0.06 mg/dL), Phase II (0.7±0.3 mg/dL), and Phase III (4.2±1.4 mg/dL), respectively, with a substantial, significant difference in serum values between patients with Phase III Chagas disease and those with Phases I or II. The control group expressed similar mean values (0.21±0.05) to those of Phase I patients. **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 mild disease group (NYHA class The patients with mild disease (NYHA class 1 & 2), the correlation coefficient of E was 0.14, A was -0.087, S was 0.349, E/E was 0.21, E/A was -0.025, Deceleration was 0.236, isovloumetric relaxation time (ms) was 0.312, septal wall thickness was -0.185, left ventricular mass index (g/m2) was -0.063, left atrial volume index was -0.076, left ventricular end diastolic volume was 0.113, left ventricular end systolic volume was - 0.282 and ejection fraction was 0.032. In patients with severe disease, the correlation coefficient of E was 0.093, A was -0.081, S was -0.531, E/E was 0.316, E/A was -0.014, Deceleration was -0.043, isovloumetric relaxation time (ms) was -0.192, septal wall thickness was -0.044, left ventricular mass index (g/m2) was -0.063, left atrial volume index was 0.183, left ventricular end diastolic volume was -0.205, left ventricular end systolic volume was -0.137 and ejection fraction was -0.502. The mean (± SD) C reactive protein levels in patients with mild disease (NYHA 1 & 2) was 4.86 mg/L and mg/L in the patients with severe disease (NYHA class 3 & 4). Congestive Cardiac Failure (CCF) is a worldwide phenomenon that affects millions of people yearly and carries a high mortality. It is complex syndrome, which is characterized by shortness of breath, fatigue, congestion and cachexia and symptoms related to inadequate tissue perfusion, fluid retention and neurohormonal activation. Despite significant improvement in medical therapy of cardiovascular diseases, CHF remains a serious clinical problem. It represents a major public health burden with high morbidity and mortality. Virtually any cardiac disease may land up in cardiac failure, though the initial event leading to the development of this syndrome in many cases remains unknown[1].

Despite repeated attempts to develop a mechanistic definition that encompasses the heterogeneity and complexity of heart failure (HF), no single conceptual paradigm has withstood the test of time. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnoea and fatigue and signs of HF, namely edema and rales. Currently 5.7 million people in the US have HF, but the projections are worrisome since it is expected that by 2030 more than 8 million people will have this condition, accounting for 46% increase in prevalence[2].

HF is a burgeoning problem worldwide, with more than 20 million people affected. The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6- 10% of people over age 65 years[3].

The causes of HF and demographic of the patients suffering are not uniformly distributed, and great geographic variance exists. Observational studies show that, hypertension, rheumatic heart disease (RHD) and idiopathic cardiomyopathies are the main causes of heart failure in a significantly younger group of patients when compared to those of developed countries[4,5].

There is no definitive diagnostic test for heart failure, it remains a clinical diagnosis that is largely based on a careful history and physical

examination and supported by ancillary test such as chest radiograph, electrocardiogram and echocardiography[6]. There are 2 mechanisms of reduced cardiac output and heart failure: systolic dysfunction and diastolic dysfunction. The most common causes of systolic dysfunction are ischemic heart disease, idiopathic dilated cardiomyopathy, hypertension and valvular heart disease. Diastolic dysfunction may occur in up to 40 – 50% of the patients with heart failure, it is more prevalent in women, and it increases in frequency with each decade of life. Diastolic dysfunction can occur in many of the same conditions that lead to systolic dysfunction. The most common causes are hypertension, ischemic heart disease, hypertrophic cardiomyopathy and restrictive cardiomyopathy. Many patients who have symptoms suggestive of heart failure including shortness of breath, peripheral edema, paroxysomal nocturnal dyspnoea but also have preserved left ventricular function may not have diastolic dysfunction: instead, their symptoms are caused by other aetiologies, such as lung disease, obesity or occult coronary ischemia[7]. The research available shows that the CHF should be seen as neurohormonal mode, in which the syndrome of CHF progress because of activation of neurohormones and proinflammatory cytokines following an initial cardiac insult or injury or a mutation of genetic programme, over expression of these biologically active molecules exerts toxic effects on the heart and circulation[8,9].

Activation of the immune system has been implicated in the pathogenesis of CHF. Experimental studies have shown that the known biologic effects of proinflammatory cytokines could explain many aspects of syndrome of heart failure, such as LV dysfunction, pulmonary oedema & process of left ventricular remodelling. The inflammatory marker that presently seems most suitable to assess inflammation is CRP[10]. Cytokines such as tumour necrosis factor alpha (TNF – α) and interleukin – 6 are significantly elevated, producing negative inotropic effects on the heart and the levels of these cytokines may be negatively associated with prognosis[11].

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 and methods

The cross-sectional analytical study was conducted in the Department of General Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India, after taking the approval of the protocol review committee and institutional ethics committee. The no probabilistic sample was composed of 90 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=30), asymptomatic patients with no electrocardiographic or echocardiographic evidence of cardiac involvement; Phase II (n=30), asymptomatic patients with electrocardiographic or echocardiographic evidence of cardiac involvement; and Phase III (n=30), 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).

The study also included a control group of 30 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 51.4±2.7 years for the population of healthy volunteers and 63.2±1.7 years for seropositive patients. The average age of patients according to phase of Chagas disease was as follows: Phase I, 57.9±3.0; Phase II, 63.7±2.7, and Phase III, 69.3±2.2 years, respectively, with a significant difference observed in Phase II and III patients versus the control group and Phase I patients (Table 1). The multiple regression analysis (see below) found no correlation between age and status of Chagas disease progression.

Distribution according to sex was similar in both study groups, with a significant decrease in the proportion of women as the disease progressed and a higher proportion of men in Chagas Phases II and III (Table 1). However, the multiple regression analysis (see below) did not disclose any correlation between sex and the phase of Chagas disease.

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). 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.

Mean absolute CRP values in the study group showed a significant progressive increase

(*P*<.005) in Phase I (0.3±0.06 mg/dL), Phase II (0.7±0.3 mg/dL), and Phase III (4.2±1.4 mg/dL), respectively, with a substantial, significant difference in serum values between patients with Phase III Chagas disease and those with Phases I or II. The control group expressed similar mean values (0.21±0.05) to those of Phase I patients (Table 1).

Mean IL-6 values for the controls and Chagas patients showed that lower values in the control group (0.9±0.1 pg/mL); conversely, patients with Chagas disease showed significant serum IL-6 increases (*P*<.05) according to the phase, with values of 3.5±0.7, 4.0±1.2, and 12.2±3.8 pg/mL for Phases I, II, and III, respectively (Table 1).

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). Backward elimination of non significant variables yielded an intercept with a coefficient of –0.3 (95% CI, –0.7 to –0.3) and *P*=.0002, Phase I showed a coefficient of 0.6 (95% CI, –0.5 to –0.9) and *P*<.0001, Phase II showed a coefficient of 0.9 (95% CI, –0.6 to –0.9) and *P*<.0001, Phase III showed a coefficient of 1.3 (95% CI, –0.8 to –1.3) and *P*<.0001. C-reactive protein correlated only to Chagas Phase III (Table 4), obtaining intercept values of –1.3 (95% CI, –1.6 to –1.1) and *P*<.0001, for Phase III of 1 (95% CI, 0.6-1.2) and *P*=.0001. Finally, 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). 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.

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	51.4±2.7	15	15	0.9±0.1	0.4±0.05
Phase I	57.9±3.0	8	22	3.5±0.7	0.3±0.06
Phase II	63.7±2.7	16	14	4.0±1.2	0.7±0.3
Phase III	69.3±2.2	19	11	12.2±3.8	4.2±1.4

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	48.0±0.8	52.2±0.8	61.1±1.33†
LVESD, mm	31.7±0.8	35.7±1.3	44.6±1.2t
Shortening, %	30.8±1.6	29.1±1.6	29.1±2.1
LVEDV, mL	99.3±3.9	141.5±5.5	194.0±13.1t
LVESV, mL	44.2±4.6	50.5±4.0	104.4±10.6t
EF, %	63.3±1.6	57.1±2.2	38.0±3.2†
LA, mm	32.9±0.7	32.5±1.0	44.7±1.3†
RV, mm	14.0±0.9	14.9±1.1	18.6±1.5†
LVM, g	264.9±18.5	328.3±29.7	426.5±29.6t
LVMI, g/m^2 SC	110.8±4.6	131.0±11.2	245.3±14.1†

*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.

Table 3: Relationship between the Phase of Chagas Disease and Interleukin-6 Values. Multiple Linear Regression Analysis*

Variable	**Coefficient**	95% Cl	P value
Intercept	-0.419	-0.914 to 0.106	0.13
Age, years	0.002	-0.007 to 0.0105	0.63
Male	-0.138	-0.356 to 0.110	0.31
Diabetes mellitus	-0.146	-0.539 to 0.278	0.53
Hypertension	–0.128	–0.338 to 0.113	.35
Congestive heart failure	0.121	–0.410 to 0.642	.63
Dyslipidemia	0.274	–0.007 to 0.570	.051
Phase I	0.680	0.338 to 1.024	.0001
Phase II	0.751	0.411 to 1.101	<.0001
Phase III	1.124	0.552 to 1.665	.0003

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

Table 4: Relationship between the Phase of Chagas Disease and CRP Values. Multiple Linear Regression Analysis*

Variable	**Coefficient**	95% Cl	P value
Intercept	–1.131	–2.117 to –0.174	.021
Age, years	–0.003	–0.003 to –0.01	.63
Male	0.083	–0.36 to 0.54	.59
Diabetes mellitus	–0.035	–0.82 to 0.74	.88
Hypertension	–0.002	–0.45 to 0.43	.87
Dyslipidemia	–0.065	–0.61 to 0.48	.74
Phase I	–0.101	–0.71 to 0.53	.71
Phase II	–0.015	–0.66 to 0.62	.72
Phase III	0.621	0.59 to 2.77	.003

Table 5: Multiple Regression Analysis Between Left Ventricular Mass Index and Interleukin-6 Values*

Variable	**Coefficient**	95% Cl	P value
Intercept	95.51	75.2-112.78	<.001
IL-6 (log)	43.41	15.57-68.35	.0024
Male	37.41	15.75-58.07	.0012
Phase III of Chagas disease	93.62	65.40-118.84	<.001

Only significant variables remaining after backwards elimination are shown. Adjusted r^2=0.61; n=90

Discussion

In the control groups and in patients with Chagas disease, a similarity was observed with regard to the sex of the individuals, thus supporting the validity of the sample; nevertheless, there was a predominance of men in the more advanced phases of the disease (Table 1). However, the multiple regression analysis found NO correlation between Chagas phases and either age or sex. Male sex in Chagas cardiomyopathy is a factor of poor prognosis, with a higher overall mortality among men between age 31 and 60, a finding that has been related to a higher frequency of electrocardiographic abnormalities[13].

The controls and the patients with Phase I disease had basically the same characteristics in terms of age, whereas the patients with Phases II and III showed significant differences when compared to both the control group and Phase I group. Studies show that the onset of the clinical symptoms of Chagas disease occurs around age 40, with an estimated average of 6 to 12 years elapsing before the patient reaches Phase II and an identical period occurring in most cases until Phase III is reached[14].

Various authors support the theory that the chronic inflammatory mechanisms of Chagas cardiomyopathy are due to autoimmune processes in the host. The cells involved in the autoimmune process are modulators of CRP and interleukin production, which could trigger the cascade of focal or generalized inflammatory responses[15].

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[16]. The inflammatory foci may be the result of microcirculation changes, which cause ischemic alterations followed by fibrosis and myocardial remodeling[17].

Serum CRP concentrations increase during the acute phase of Chagas disease[18,19] however, elevated values in the chronic stage[19,20] have not been reported, something apparently not consistent with the findings observed in this research. Nevertheless, the investigations cited were conducted with individuals in an indeterminate stage of Chagas disease, which would correspond to Phases I and II of our study, in which we were unable to find statistically significant CRP increases.

T cruzi infection in experimental animal models leads to elevated serum and tissue IL-6[21], which is induced during the increasing stage of parasitemia in the acute period of Chagas disease[22]. It has been postulated that the main inducer of IL-6 in T cruzi infection is the enzyme transialidase of the parasite itself[23]. The relationship between IL-6 and the development of CCC is still unclear and contradictory; for instance, transgenic mice that do not express IL-6 present greater parasitemia and die earlier than wild strains[21]. On the other hand, animals sensitized with T cruzi transialidase and therefore, with elevated IL-6 values are also more susceptible to invasion by the parasite[23]. In the present study, multiple regression analysis showed that the IL-6 values were associated with the progressive phases of Chagas disease, indicating that the values of this cytokine might increase as the disease progresses, thus contributing to the progression of the myocardial damage.

Sato et al (1999)[24] showed that IL-6 has a negative ionotropic effect which induces a hypo contractile state in the myocardium. These investigators have also shown that plasma IL-6 concentrations are higher in the decompensated stage of heart failure syndrome compared to the recovery stage.

Petretta et al (2000)[25] correlated IL-6 concentrations to the functional class of patients with heart failure syndrome and found that IL-6 concentrations were progressively higher with a higher functional class (NYHA). This study concludes that IL-6 determination provides a more accurate indication of hemodynamic deterioration among patients with heart failure.

Lastly, the multiple regression analysis revealed that plasma IL-6 concentrations are related to the echocardiographic parameter LVMI and to male sex. Left ventricular mass index reflects the cellular remodeling that leads to chamber dilation and, secondarily, to ejection alterations. The relationship between IL-6 and higher LVMI in male patients could help explain the worse prognosis of these patients in Chagas disease.

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. C-reactive protein elevation appears to occur later and be related to progression toward Phase III and functionally to heart failure, which would reflect recurrence of the acute inflammatory process.

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