XVIII International Congress for Tropical Medicine and Malaria

and

XLVIII Congress of the Brazilian Society of Tropical Medicine

XXVIII Brazilian Annual Meeting of Applied Research on Chagas Disease, XVI Brazilian Annual Meeting of Applied Research on Leishmaniasis and III Latin American Congress on Travel Medicine

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Certificate

This is to certify that Saraiva RM, Vilela MF, Waghabi MC, Silva GMS, Xavier SS, Hasslocher-Moreno AM, Araujo-Jorge TC has attended the **XVIII International Congress for Tropical Medicine and Malaria** and **XLVIII Congress of the Brazilian Society of Tropical Medicine**, held in Rio de Janeiro from September 23 to 27, 2012, as Oral Presentation at the Workshop: Protozoan: Pathogenesis and treatment of Chagas disease: Predictive Value of Transforming Growth Factor--β1 in Chagas Disease

Rio de Janeiro, September 27, 2012.

Professor Pierre Ambroise-Thomas

Professor José Rodrigues Coura

Professor Cláudio Tadeu Daniel-Ribeiro

Professor Carlos Henrique Nery Costa

phase of Chagas disease, in three different forms indeterminate, cardiac or digestive and 20 healthy controls, both groups from Botucatu Medical School University Hospital. Single-cell Electrophoresis (Comet assay) and Gress reaction were used to measure DNA damage and NO production, respectively. We also evaluated the total hydrophilic antioxidant capacity (THAC) and tocopherol levels in the plasma of Chagas patients and controls. **Results:** Chagas patients with the cardiac or digestive forms presented higher DNA damage and NO production when compared with patients with the indeterminate form and control individuals ($p<0.05$). However, the THAC and tocopherol levels were significantly lower in patients with the cardiac or digestive forms, when compared with patients with the indeterminate form and control individuals ($p<0.05$). **Conclusion:** In conclusion, our results indicate that patients with the cardiac or digestive forms of Chagas disease present more DNA damage then patients with the indeterminate form and control individuals, which is probably related with the high levels of NO. These findings support the notion that NO produced by the host as a defense strategy may not be only responsible for the parasite destruction, but in high levels may also induce oxidative damage in non-infected cells. **Keywords:** Chagas Disease, DNA damage, antioxidants, NO. **E-mail:** francilene_capel@hotmail.com

Chag9. **Predictive Value of Transforming Growth Factor--β1 in Chagas Disease**

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Introduction: Up to 30% of patients with Chagas disease progress to the cardiac phase of the disease, which has high mortality. The mechanisms underlying this progression are still poorly understood. Transforming growth factor-β1 (TGF-β1) may be implicated in the development of Chagas heart disease and our group has already reported high TGF-β1 values in the serum of patients with Chagas heart disease. **Materials and Methods:** We retrospectively analyzed the all-cause mortality of patients whose TGF-β1 serum values were determined in a previous publication of our group. Results: Sixty-eight patients (49±10 years old) were followed for a mean of 10.0±3.6 years. Eleven patients died during this period. There were a total of 22 patients at the indeterminate phase (32.3%), 20 (29.4%) patients at stage A (isolated changes in electrocardiogram), 13 (19.1%) at stage B1 (asymptomatic with mild changes at the echocardiogram), 8 (11.8%) at stage B2 (asymptomatic with moderate to severe left ventricular [LV] systolic dysfunction) and 5 (7.4%) at stage C (7.4% symptomatic heart failure). LV end-systolic diameter was an independent predictor of all-cause mortality (hazard ratio [HR] 2.8; 95% confidence interval [CI] 1.5 to 5.0; p=0.0007), while TGF-β1 was not. The optimal cutoff for LV end-systolic diameter to identify patients who died was 4.1 cm (area under the curve [AUC] 0.77, p=0.002, sensitivity 73%, and specificity 80%). However, in patients with normal to mild LV systolic dysfunction, TGF-β1 was higher among patient who died than in survivors (49.5 ± 15.5 ng/ml vs. 17.6 ± 3.1 ng/ml, p=0.003). TGF-β1 (HR 1.02; CI 1.0 to 1.04; p=0.01) and LV ejection fraction (HR 0.91; CI 0.83 to 0.99; p=0.02) were independent predictors of all-cause mortality. The optimal cutoff for TGF-β1 to identify patients who died among those with normal or mild LV systolic dysfunction was 12.9 ng/ml (AUC 0.82, p=0.003, sensitivity 100%, and specificity 57%) and for LV ejection fraction was 53% (AUC 0.74, p=0.009, sensitivity 50%, and specificity 90%). **Main Conclusions:** TGF-β1 was an independent predictor of all-cause mortality only in the group of patients with normal to mild LV systolic dysfunction. Therefore, TGF-β1 seems to be an important determinant of Chagas disease patients' outcome at earliest stages of the disease, while at the advanced stages, after moderate to severe LV dysfunction is established, LV systolic function and diameters become the main prognosis determinants. **E-mail:** roberto.saraiva@ipec.fiocruz.br

Chag10. **Immunogenetic analysis of Human Leukocyte Antigen (HLA) region for Chronic Chagas disease in Bolivia**

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Predictive Value of Transforming Growth Factor-β1 in Chagas Disease

Saraiva RM[1], Vilela MF[1], Waghabi MC[2], Silva GMS[1], Xavier SS[1], Hasslocher-Moreno AM[1], Araujo-Jorge TC[2]

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Introduction: Up to 30% of patients with Chagas disease progress to the cardiac phase of the disease, which has high mortality. The mechanisms underling this progression are still poorly understood. Transforming growth factor-β1 (TGF-β1) may be implicated in the development of Chagas heart disease and our group has already reported high TGF-β1 values in the serum of patients with Chagas heart disease.

Materials and Methods: We retrospectively analyzed the all-cause mortality of patients whose TGF-β1 serum values were determined in a previous publication of our group (Araujo-Jorge TC et al *J Infect Dis* 2002; 186:1823-28).

Results: 68 patients were followed for 10.0±3.6 years. At the beginning of the study there were 22 patients at the indeterminate phase (32.3%), 20 (29.4%) patients at stage A (isolated changes in electrocardiogram), 13 (19.1%) at stage B1 (asymptomatic with mild changes at the echocardiogram), 8 (11.8%) at stage B2 (asymptomatic with moderate to severe left ventricular [LV] systolic dysfunction) and 5 (7.4%) at stage C (7.4% symptomatic heart failure). The group of patients who died presented complete right bundle branch block more frequently, had larger left atrium (LA) and LV end-diastolic (LVd) and end-systolic (LVs) diameters, and lower ejection fraction (EF) than to patients who did not die (Table I).

Table I. Clinical characteristics of study patients with and without primary or secondary end points.

	Total (n=68)	*No Mortality (n=57)*	*All-cause death (n=11)*
Age, years	49 ± 10	50 ± 10	48 ± 7
Sex, male	54%	53%	64%
TGF-β1, ng/ml	26 ± 42	25 ± 44	33 ± 34
Electrocardiogram			
Complete right bundle branch block	54%	49%	82%*
Left anterior hemi-block	46%	42%	64%
Left bundle branch block	11%	10%	18%
Echocardiogram			
LA, cm	3.6 ± 0.5	3.5 ± 0.5	3.9 ± 0.4*
LVd, cm	5.3 ± 0.7	5.2 ± 0.6	5.9 ± 0.8*
LVs, cm	3.7 ± 1.0	3.6 ± 0.9	4.5 ± 1.0*
EF, %	59 ± 14	61 ± 14	49 ± 12*
Diastolic function			
Normal	51%	57.9%	18.2%†
Delayed relaxation	32%	29.8%	45.4%
Pseudonormal	5%	3.5%	9.1%
Restrictive	12%	8.8%	27.3%

*p<0.05; † p=0.07

LV end-systolic diameter (LVs) was an independent predictor of all-cause mortality (hazard ratio [HR] 2.8; 95% confidence interval [CI] 1.5 to 5.0; p=0.0007), while TGF-β1 was not. The optimal cutoff for LVs to identify patients who died was 4.1 cm (sensitivity 73%, and specificity 80%; Figure 1).

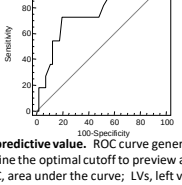

Figure 1: LVs predictive value. ROC curve generated for LVs to determine the optimal cutoff to preview all-cause mortality. AUC, area under the curve; LVs, left ventricular end-systolic diameter; ROC, receiver operating characteristic.

- *Survival analysis of patients with normal or mild LV systolic dysfunction*

In patients with normal to mild LV systolic dysfunction, TGF-β1 was higher among patient who died than in survivors (Table II). The multivariate analysis showed significant association between all-cause mortality and LV ejection fraction (HR 0.91; 95% CI 0.83 to 0.99; p=0.02) and TGF-β1 serum levels TGF-β1 (HR 1.02; 95% CI 1.0 to 1.04; p=0.01). The optimal cutoff for TGF-β1 to identify patients who presented all-cause mortality was 12.9 ng/ml (AUC=0.82 p=0.003, sensitivity 100%, and specificity 57%). According to Kaplan-Meier survival analysis, the prognosis was worse in patients with TGF-β1 >12.9 ng/ml (p=0.02; Figure 2).

Table II. Clinical characteristics of patients normal or mild LV systolic dysfunction by the occurrence of the study endpoint.

	No Mortality (49)	*All-cause death (6)*
Age, years	49 ± 10	47 ± 5
Sex, male	51%	50%
TGF-β1, ng/ml	18 ± 22	49 ± 38*
Electrocardiogram		
Complete right bundle branch block	47%	83%
Left anterior hemi-block	37%	50%
Left bundle branch block	10%	33%
Echocardiogram		
LA, cm	3.5 ± 0.4	3.8 ± 0.4
LVd, cm	5.1 ± 0.5	5.4 ± 0.6
LVs, cm	3.3 ± 0.6	3.9 ± 0.7
EF, %	65 ± 9	57 ± 10*
Diastolic function		
Normal	65%	33%
Delayed relaxation	29%	67%
Pseudonormal	2%	-
Restrictive	4%	-

*p<0.05

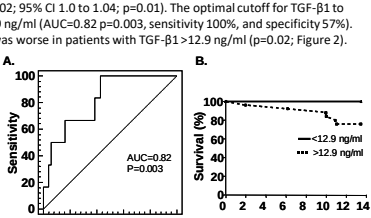

Figure 2: TGF-β1 predictive value in patients with normal or mild LV systolic dysfunction. A. ROC curve generated for TGF-β1 in to determine the optimal cutoff to preview all-cause mortality. **B.** Kaplan-Meier curve of all-cause mortality-free survival according to TGF-β1 > 12.9 ng/ml. AUC, area under the curve; ROC, receiver operating characteristic; TGF-β1, transforming growth factor-b1.

Main Conclusions:

- TGF-β1 was an independent predictor of all-cause mortality only in the group of patients with normal to mild LV systolic dysfunction but not in patients with advanced heart failure.
- Therefore, TGF-β1 seems to be an important determinant of Chagas disease patients' outcome at earliest stages of the disease, while at the advanced stages, after moderate to severe LV dysfunction is established, LV systolic function and diameters become the main prognosis determinants.

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