Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v27i1.561_ENG

ORIGINAL PAPER

Assessment of Inflammatory Biomarkers in Pulmonary Arteries of Chagasic and Non-Chagasic Heart Transplant Recipients

Marcus Vinícius de Paula da Silva[1,*], Ildernandes Vieira Alves[2], Antonielle Rodrigues Pereira Alves[2], Virginia Soares Lemos[2], Gabriel Assis Lopes do Carmo[1], Fábio Morato de Castilho[1], Cláudio Léo Gelape[1]

1. Universidade Federal de Minas Gerais – Faculdade de Medicina – Departamento de Cirurgia Cardiovascular – Belo Horizonte (MG) – Brazil.

2. Universidade Federal de Minas Gerais – Instituto de Ciências Biológicas – Departamento de Fisiologia e Biofísica – Belo Horizonte (MG) – Brazil.

*Corresponding author: marcus@cardiol.br

Section editor: Ilka de Fátima Santana F. Boin

Received: Jan 26, 2024 | Accepted: June 11, 2024

ABSTRACT

In Brazil, Chagas cardiomyopathy is the third most common cause of indication for heart transplantation (HTx). Pulmonary arterial hypertension (PAH) is a severe condition frequently present in patients with terminal heart failure that worsens the prognosis of patients undergoing HTx. The etiological mechanism of PAH is multifactorial, with increased ventricular filling pressure being one of the main ones. Recently, however, several studies have sought to demonstrate the role of the local inflammatory process in contributing to the stiffening of the pulmonary arteries and the emergence or worsening of PAH in the heart failure (HF) setting. **Objectives:** To evaluate the inflammatory process in the pulmonary arteries of chagasic HTx (HTx-C) and non-chagasic (HTx-NC) patients, with and without PAH, through the tissue concentration of inflammatory cytokines obtained at the time of HTx. **Methods:** The levels of interleukins (IL)-6, IL-1β, TNF-α, and CD68 and CD66b neutrophils were measured in fragments of the pulmonary arteries of HTx-C and HTx-NC patients with and without PAH. **Results:** No statistically significant difference ($p \geq 0.05$) between the inflammatory biomarkers measured in HTx-C and HTx-NC pulmonary arteries, with or without PAH. **Conclusion:** We observed that HTx-C and HTx-NC patients present the same levels of inflammatory markers expressed in the pulmonary artery tissue, whether or not they have PAH. This fact suggests that PAH in HTx-C and HTx-NC patients is a process that is related to HF itself and not to the patients' inflammatory profile.

Descriptors: Heart Transplant; Pulmonary Arterial Hypertension; Inflammatory Biomarkers.

Avaliação de Biomarcadores Inflamatórios em Artérias Pulmonares de Transplantados Cardíacos Chagásicos e Não Chagásicos

RESUMO

No Brasil, a miocardiopatia chagásica constitui a terceira causa mais comum de indicação para transplante cardíaco (TxC). A hipertensão arterial pulmonar (HAP) é uma condição grave frequentemente presente em pacientes com insuficiência cardíaca (IC) terminal que piora o prognóstico daqueles submetidos a TxC. O mecanismo etiológico da HAP é multifatorial, sendo o aumento da pressão de enchimento ventricular um dos principais. Recentemente, entretanto, vários trabalhos procuraram demonstrar o papel do processo inflamatório local, contribuindo para o enrijecimento das artérias pulmonares e o surgimento ou piora da HAP no cenário da IC. **Objetivos:** Avaliar o processo inflamatório nas artérias pulmonares de transplantados cardíacos chagásicos (TxC-C) e não chagásicos (TxC-NC), com e sem HAP, por meio da concentração tecidual das citocinas inflamatórias obtidas no momento do TxC. **Métodos:** Os níveis das interleucinas (IL)-6, IL-1β, e do fator de necrose tumoral alfa [*tumor necrosis factor alpha*) (TNF-α)] e de neutrófilos CD68 e CD66b foram aferidos em fragmentos das artérias pulmonares de pacientes TxC-C e TxC-NC com e sem HAP. **Resultados:** Não houve diferença estatisticamente significativa ($p \geq 0,05$) entre os níveis dos biomarcadores inflamatórios aferidos nas artérias pulmonares dos TxC-C e TxC-NC com ou sem HAP. **Conclusão:** Observamos que os pacientes TxC-C e TxC-NC com ou sem HAP apresentam níveis semelhantes de marcadores inflamatórios expressos no tecido das artérias pulmonares. Tal fato sugere que a HAP dos pacientes TxC-C e TxC-NC é um processo que se relaciona com a própria IC e pode não ter relação com o perfil inflamatório dos pacientes.

Descritores: Transplante Cardíaco; Hipertensão Arterial Pulmonar; Biomarcadores Inflamatórios.

INTRODUCTION

Heart transplantation (HTx) is an excellent therapeutic option for patients with advanced heart failure (HF) refractory to clinical treatment, according to national and international guidelines[1]. HF is a progressive disease that affects millions of people. Approximately 10% of patients with HF have the advanced form of the disease or stage D, which is associated with high mortality and inferior quality of life[1,2]. There is consensus that HTx, with appropriate selection criteria, increases survival quality of life and exercise capacity and provides a faster return to work compared to conventional treatment[1,2].

Brazil has become increasingly prominent in transplants, especially in Latin America[3]. In the 2019 International Society for Heart & Lung Transplantation (ISHLT) registry of HTx recipient data, the most frequent diagnoses of the cause of HF were non-ischemic cardiomyopathy (50.8% of cases), ischemic cardiomyopathy (32.4%), restrictive cardiomyopathy (3.5%), hypertrophic cardiomyopathy (3.4%), congenital heart disease (3.1%), retransplantation (2.8%), valvular cardiomyopathy (2.5%) and others (1 .5%)[4].

Currently, the state of Minas Gerais is the second with the highest number of HTx performed in the country[5], with Chagas disease (CHD) responsible for 50% of cases[6]. CHD is responsible for the chronic and persistent inflammatory process of the myocardium that leads to the destruction of cardiomyocytes, associated with arrhythmias and embolic events, the leading causes of death[7].

Pulmonary arterial hypertension (PAH) is often associated with HF due to increased left ventricular filling pressures[8]. This condition worsens the HTx result and may be a contraindication if very high and fixed[8].

PAH is defined as a condition with a mean pulmonary artery pressure greater than 20 mmHg[9]. Recently, it was demonstrated that local inflammation at the tissue level may be a critical aspect in the etiology of PAH and that T cells, B cells, mast cells, macrophages, neutrophils and dendritic cells participate in this process[10]. There appears to be an initial insult to the endothelium that leads to the propagation of an inflammatory process with the production of cytokines, culminating in vascular remodeling[10].

Therefore, understanding the etiology and mechanism of PAH in candidate patients for HTx and the contribution of the local inflammatory process to this condition can open up a new and promising field of research. The aim is to improve the clinical status of patients for HTx and, furthermore, increase the number of candidates for the procedure.

The cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor-alpha (TNF-α) are produced by monocytes/macrophages, endothelial cells and many other types of cells and have pro-inflammatory action[11,12]. These cytokines may be particularly relevant to the pathogenesis of PAH[13]. Cluster of differentiation 66b (CD66b) and 68 (CD68), respectively, markers of neutrophils and macrophages, are reported in patients with PAH[14,15].

This study contributes to elucidating pathophysiological mechanisms involved in PAH associated with HTx.

OBJECTIVES

To evaluate the contribution of the local inflammatory process to the etiology of PAH in chagasic and non-chagasic patients who are candidates and undergo HTx.

METHODS

Were included 29 patients undergoing HTx at the Hospital das Clínicas of the Federal University of Minas Gerais (HC-UFMG) and the Hospital Santa Casa de Belo Horizonte from January 2021 to February 2023. The study's sample size was carried out with a sample of convenience. It was impossible to collect pulmonary artery fragments from all patients undergoing HTx in these reference centers during the study period. The main factors that interfered with the experiments not being carried out were not specifically collecting the pulmonary artery, insufficient quantity of pulmonary arterial tissue for the experiments and resection of adipose tissue devoid of the vessel itself.

This study was approved by the UFMG Research Ethics Committee, CAAE: 39274420.0.0000.5149. All patients signed the free and informed consent form (ICF). It is a comparative cross-sectional study of parallel groups.

The clinical data of the study sample were collected through analysis of medical records accessed in the databases of the participating hospitals.

Inclusion criteria

Recipients who agreed to sign the informed consent form, patients of both sexes, aged 18 or over and with terminal cardiomyopathy undergoing HTx were included.

Exclusion criteria

Exclusion criteria covered patients with cancer, dementia, clinically diagnosable inflammatory process, type I diabetes mellitus, history of surgery or trauma in the last 4 weeks, pregnant women, autoimmune disease, known to have the human immunodeficiency virus, hepatitis C, hepatitis B and those who did not agree to sign the ICF.

PAH was measured by pulmonary manometry during right heart catheterization and by echocardiography performed preoperatively. The echocardiogram defined elevated pulmonary artery systolic pressure (PASP) as higher than 35 mmHg[16].

Pulmonary artery fragments were collected from recipients during cardiectomy and placed in vials with the lactated ringer.

The pulmonary artery was isolated, and the surrounding perivascular tissue was removed. Then, these segments were embedded in Tissue-Tek® OCT™ freezing medium (Sakura®, USA), and cross sections (10 µm) of the arteries were obtained using a cryostat. Slides were fixed in 4% paraformaldehyde solution for 15 minutes before immunofluorescence. CD68 and CD66b neutrophil counts were performed using the immunofluorescence technique. Fiji software (version 1.51j8) was used to quantify positive cells for labeling of interest and nucleus. The result was expressed as the number of positive cells per μm^2 of tissue.

The inflammatory cytokines IL-1β, TNF-α and IL-6 were quantified in pulmonary artery fragments. The immunosorbent assay technique [enzyme-linked immunosorbent assay (ELISA)] was used to quantify the concentration of TNF-α, IL-6 and IL-1β, as indicated in the instructions of the commercial kits (R&D Systems). Results were presented as picograms (pg) of protein per milliliter of tissue (pg/mL).

In this study, the descriptive measures median (Q_2), quartiles (Q_1 and Q_3), mean, and standard deviation (SD) were presented to describe, respectively, the variables of the quantitative type of non-normal and normal distribution and absolute frequencies (n) and relative (%) as statistics to describe the results of categorical variables. Comparison of the distribution between the variable's measurements (median, Q1 and Q3) was carried out using the Mann-Whitney tests. A value of $p < 0.05$ was considered significant.

RESULTS

Samples were collected from 29 patients undergoing HTx, 19 of whom were chagasic patients. Table 1 demonstrates the characteristics of the studied population. The patients' age was 54.9 ± 9.1 years, 13 of whom were female. Their body mass index (BMI) was 23.1 ± 4.7.

Nineteen patients (65.5%) had chagasic cardiomyopathy; four had non-ischemic cardiomyopathy; three had ischemic cardiomyopathy (10.4%); one (3.4%) had congenital heart disease, and two had other etiologies (6.9%).

Table 1. Clinical characteristics of recipient patients (heart transplant recipients).

Parameters	Recipient (n = 29)
Age (years)[a]	54.9 ± 9.1
Sex (female/male)	13/16
BMI[a]	23.1 ± 4.7

Source: Elaborated by the authors. a = data expressed as mean ± SD.

Clinical characteristics, expression of the inflammatory cytokines IL-1 β, TNF-α and IL-6 and counts of CD68 macrophages and CD66b neutrophils were evaluated in the pulmonary artery tissue of chagasic (HTx-C) and non-chagasic (HTx) heart transplant patients. -NC) (Table 2).

Table 2. Descriptive and comparative analyses between HTx-C and HTx-NC recipients regarding clinical, echocardiographic, and manometric variables, number of cells per square micrometer and cytokine concentration (pg/mL).

Variables	Chagasics (n = 19)	Non-Chagasic (n = 10)	*p*	r
Age (years)	58.0 (51.0-61.0)	55.0 (41.5-59.5)	0.370	0.17
BMI	21.4 (18.7-24.2)	23.9 (20.9-30.4)	0.099	0.31
PSAPeco (mmHg)	41.0 (33.0-47.0)	40.0 (26.8-47.3)	0.890	0.03
PT média (mmHg)	25.3 (19.3-35.0)	31.0 (20.9-49.3)	0.383	0.16
PVR (W)	3.24 (1.96-5.36)	3.70 (2.57-7.75)	0.582	0.10
IND PVR (W)	5.12 (3.95-9.84)	6.39 (4.72-12.53)	0.359	0.17
SVR(W)	22.96 (19.67-26.17)	22.51 (19.32-28.83)	0.854	0.03
IND SVR (W)	38.02 (34.70-42.46)	38.78 (31.61-48.02)	0.854	0.03
TPG (mmHg)	10.0 (6.0-16.0)	13.5 (6.8-21.3)	0.301	0.20
VPS (SNP) (W)	2.74 (2.47-3.46)	1.77 (0.94-3.05)	0.178	0.33
CD66b	0.000130 (0.000047-0.000172)	0.000161(0.000061-0.000234)	0.484	0.15
CD68	0.00001202 (0.00000811-0.00002136)	0.00001854 (0.00000196-0.00002204)	0.751	0.07
IL-6	393.6 (344.3-630.3)	378.7 (335.0-470.8)	0.624	0.10
IL-1β	152.2 (124.9-334.1)	168.5 (94.9-508.4)	1.000	0.00
TNF-α	1.100.0 (657.5-1.777.5)	770.0 (277.5-1.210.0)	0.280	0.24

Source: Elaborated by the authors. Database: 29 patients overall (yes, 19 cases and no, 10 cases). Data expressed as median (Q1-Q3). Data measured by echocardiogram: PSAPeco (PSAP). Data measured by right heart catheterization: PT mean [mean pressure in the pulmonary trunk (pulmonary artery)]; PVR; IND PVR (PVR index); SVR (systemic vascular resistance); IND SVR (SVR index); TPG (transpulmonary pressure gradient); PVR (SNP) (pulmonary resistance after sodium nitroprusside). *p* = probability of significance from the Mann-Whitney test (z–test statistic); r = effect size for the non-parametric test; W =Wood.

The data in Table 2 demonstrate that there was no significant difference ($p \geq 0.05$) between HTx-C and HTx-NC concerning physiological variables (age and BMI), echocardiographic, manometric and those referring to inflammatory markers.

Table 3 shows data on comparative inflammatory parameters between HTx concerning PAH measurement < 20 mmHg or ≥ 20 mmHg.

There was no statistically significant difference between interleukins when comparing the group with PAH and patients without PAH.

Table 3. Descriptive and comparative analyses between HTx with mean PT ≥ 20 or mean PT < 20 regarding the number of cells per square micrometer and concentration of cytokines and HTx-C regarding the number of cells per square micrometer.

Variables	PT mean < 20 – HTx (n = 5)	PT mean ≥ 20 – HTx (n = 18)	*p*	r
CD66b	0.000140 (0.000061-0.0000267)	0.000139 (0.000061-0.000174)	0.804	0.05
CD68	0.00002136 (0.00000502– 0.00002295)	0.00001270 (0.00000785– 0.00001940)	0.611	0.11
IL-6	333.7 (241.2-393.2)	385.7 (347.4-630.3)	0.063	0.38
IL-1β	138.0 (36.5-438.6)	160.9 (118.4-368.8)	0.371	0.19
TNF-α	800.0 (0.0-0.0)	970.0 (490.0-1.530.0)	-	-

Variables	PT mean < 20 – HTx-C	PT mean ≥ 20 – HTx-C		
CD66b	0.000111(0.000051-0.000265)	0.000130 (0.000047-0.000172)	0.896	0.03
CD68	0.00001480 (0.00000341-0.00002323)	0.00001202 (0.00000811-0.00001858)	1	0

Source: Elaborated by the authors. Database: 29 patients overall. Data expressed as median (Q1-Q3). Data measured by right heart catheterization: PT mean. The difference between the total number of patients surveyed and those presented in Table (n) refers to the number of cases without information. *p* = probability of significance from the Mann-Whitney test (z–test statistic); r = effect size for non-parametric test.

DISCUSSION

Preliminarily, quantitative analysis of the inflammatory cytokines IL-1 β, TNF-α and IL-6 and the count of CD68 macrophages and CD66b neutrophils in HTx pulmonary artery tissue were carried out. It is believed that the dosage of such inflammatory biomarkers in the pulmonary artery tissue better reflects the inflammatory process in the vessel than the analysis carried out in the plasma of surgical patients, which are known to be very elevated[17].

PAH is a condition associated with terminal HF that represents an additional challenge in the care of HTx patients[2]. Different mechanisms can explain the pathophysiology of PAH in the setting of HF, but little research exists into the real effect of the local inflammatory process on the development of this serious problem.

Pulmonary vascular lesions occurring in patients with PAH and in animal models of pulmonary hypertension are characterized by varying degrees of perivascular inflammatory infiltrates, comprising T and B lymphocytes, macrophages, dendritic cells, and mast cells[18]. In addition to increased perivascular immune cells and intravascular infiltration, circulating levels of specific cytokines are abnormally elevated in PAH, including the cytokines IL-1β, IL-6, and TNF-α[18]. Increased pulmonary pressure is one of the most important predictors of death after HTx[19], determining the importance of analyzing pulmonary arterial pressure and its pulmonary reactivity in the pre-transplant period[19].

It is known that IL-6 is a pro-inflammatory cytokine that has a significant association with mortality in patients with PAH[20]. Similar findings have been reported in patients with congestive HF[21], suggesting that IL-6 plays a role in the pathophysiology of HF and PAH[21]. IL-1β is well recognized as clinically relevant in patients with hypertension[22]. Due to its essential role in inflammation, how IL-1β influences changes related to vascular pathology in hypertension has gained much interest and is currently being explored[23]. For example, recent reports suggest that IL-1β not only participates in the pro-inflammatory response in vessels but also influences the phenotype and functions of vascular smooth muscle cells and vascular remodeling in various types of hypertension through inflammation[24].

TNF-α is considered one of the main cytokines related to inflammatory and immune processes[25], directly influencing the adhesion of circulating inflammatory cells in tissues[26]. Studies showed that TNF-α was notably higher in PAH[27]; however, our study did not corroborate this fact.

Recent research has evaluated the role of perivascular macrophages infiltrating pulmonary arterioles in PAH[18]. CD68 macrophages are prominent in advanced plexiform obliterans lesions observed in experimental and clinical studies of PAH[28,29], and depletion or inactivating macrophages prevents PAH in several experimental study models[30,31]. M1-type macrophages amplify inflammation by secreting pro-inflammatory factors, while M2-type macrophages promote inflammation and tissue repair, playing an essential role in pulmonary vascular remodeling[32].

Neutrophils are the most abundant type of white blood cells in human circulation[33]. In contrast to monocytes and macrophages, neutrophils are traditionally considered bystanders of cardiovascular disease, but studies in recent years have demonstrated important functional roles of neutrophils in inflammation and cardiovascular repair[34,35]. CD66b is a marker of neutrophil activation[36].

This research demonstrated that the median mean pressure measured in the pulmonary artery trunk by manometry was 25.3 (19.3-35.0) in chagasic patients and 31.0 (20.9-49.3) in those with non-chagasic patients. When comparing the various pressure parameters measured by right heart catheterization and echocardiography, there was no significant difference between their levels and the fact that the patients were HTx-C and HTx-NC (Table 2). Gelape et al.[8] found lower pulmonary vascular resistance (PVR) levels based on hemodynamic parameters in patients with Chagas cardiomyopathy, a fact not identified in this study.

The HTx studied here had increased levels of the cytokines IL-1 β, TNF-α and IL-6, regardless of whether the etiology was chagasic (Table 2). This suggests that these inflammatory markers participate in the HF pathophysiological process. This data indicates that the etiology of cardiomyopathy does not influence the different levels of inflammatory cytokines.

Furthermore, we did not find significant differences in the tissue levels of IL-1 β, TNF-α, IL-6, CD66b and CD68 when comparing HTx patients with and without PAH (Table 3). It was also observed that HTx-C with and without PAH presented the same number of CD66b and CD68 inflammatory cells in the tissue. These data suggest that the pathophysiological mechanism of PAH is more related to HF than the inflammatory response.

Patients with advanced HF often develop an increase in pulmonary pressure through a retrograde mechanism.[37] Left ventricular dysfunction causes an increase in end-diastolic pressure transmitted to the pulmonary vascular bed, increasing venous pressure[37]. Over time, vascular vasoconstriction and, subsequently, pathological restructuring occur with increased cell proliferation and hypertrophy associated with intimal fibrosis[8]. Up to a third of patients develop PAH[8].

It is known that chronic HF activates the immune system and inflammatory responses characterized by elevated levels of circulating pro-inflammatory cytokines[38,39]. Inflammation and immune cells participate in both acute myocyte injury and chronic HF[40]. Inflammatory factors such as TNF-α, IL-1β and IL-6 are increased in patients with HF[40]. Small animal models of myocarditis and pressure overload suggest immune activation during HF[41]. Such arguments may justify the levels of inflammatory markers being similar in HTx recipients despite the diagnosis of PAH.

CONCLUSION

We observed that HTx-C and HTx-NC, with or without PAH, presented similar levels of inflammatory markers expressed in the pulmonary arteries, which suggests that the mechanism of PAH is more associated with HF itself than with the inflammatory response secondary to associated cardiomyopathy. In this study, Chagas cardiomyopathy, even though it is a disease with a very evident and proven local inflammatory substrate, does not present higher levels of PAH and local inflammation compared to other HF etiologies.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silva MVP, Gelape CL, Lermos VS, Castilho FM; **Conception and design:** Silva MVP, Gelape CL, Castilho FM; **Data analysis and interpretation:** Silva MVP, Gelape CL, Castilho FM, Alves IV, Alves ARP, Lemos VS, Carmo GAL; **Article writing:** Silva MVP, Gelape CL, Castilho FM; **Critical revision:** Silva MVP, Gelape CL, Castilho FM; **Final approval:** Silva MVP, Gelape CL, Castilho FM.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

FUNDING

Fundação de Apoio à Pesquisa do Estado de Minas Gerais ROR
Grant N.° APQ-01480-21

Conselho Nacional de Desenvolvimento Científico e Tecnológico ROR
Grants N.°s 311643/2022-1; 406097/2021-6

ACKNOWLEDGEMENT

Not applicable.

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