Infliximab reduces cardiac output in rheumatoid arthritis patients without heart failure

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Summary

Objective: Human anti-tumor necrosis factor (TNF-α) monoclonal antibody (infliximab) is used to treat autoimmune diseases such as rheumatoid arthritis (RA). Although the risk of worsening heart failure has been described in patients under chronic treatment, the acute cardiovascular effects of this drug are unknown in RA patients without heart failure. **Methods:** 14 RA patients with normal echocardiography and no history of heart failure were evaluated during the 2-hour infliximab (3-5 mg/kg) infusion period, using a noninvasive hemodynamic beat-to-beat system (Portapres). Stroke volume (SV); systolic, diastolic and mean blood pressures (SBP, DBP and MBP, respectively); cardiac output (CO); heart rate (HR); and total peripheral vascular resistance (PVR) were recorded. All patients also received saline infusion instead of infliximab as a control. Significant differences in hemodynamic parameters were determined using Tuckey's test. All values were expressed as mean ± standard deviation (SD). **Results:** Fourteen RA patients (6M/8F) with mean age of 47.2 ± 8.8 years were evaluated. A significant decrease was found in cardiac output and stroke volume (7.04 ± 2.3 to 6.12 ± 2.1 l/min and 91 ± 29.0 to 83 ± 28.8 mL/beat, respectively) after infliximab infusion. Although not statistically significant, a progressive increase was detected in SBP, DBP and total PVR during infusion. Saline infusion did not cause significant hemodynamic changes in the same group of RA patients. No adverse effects were observed during the infusion period. **Conclusion:** Acute infliximab administration decreased cardiac output due to low stroke volume in RA patients without heart disease. The results also demonstrated that, in spite of its negative inotropic effect, infliximab enhanced BP, probably by increasing PVR.

Keywords: Infliximab; TNF-α inhibitors; autoimmune diseases; rheumatoid arthritis; heart failure.

Resumo

Infliximabe reduz débito cardíaco em pacientes com artrite reumatoide sem insuficiência cardíaca

Objetivo: O inibidor de fator de necrose tumoral (TNF-α) infliximabe é usado no tratamento de doenças autoimunes como a artrite reumatoide (AR). Embora o risco de piora de insuficiência cardíaca em pacientes submetidos a tratamento crônico tenha sido descrito, os efeitos cardiovasculares agudos da infusão desta droga em pacientes com AR sem insuficiência cardíaca são desconhecidos. **Métodos:** Pacientes com AR e ecocardiogramas normais e sem antecedentes de insuficiência cardíaca foram avaliados durante o período de infusão de infliximabe (3-5mg/kg), de 2 horas, utilizando um sistema de monitoramento hemodinâmico não invasivo batimento-a-batimento (Portapres). As variáveis avaliadas foram: volume sistólico (VS), pressão arterial sistólica, diastólica e média (PAS, PAD e PAM, respectivamente), débito cardíaco (DC), frequência cardíaca (FC) e resistência vascular periférica total (RVPT). Todos os voluntários também receberam infusão de soro fisiológico (SF) como estudo controle. Estatísticas foram avaliadas usando o teste de Tuckey. Os valores estão expressos em média ± desvio-padrão. **Resultados:** Catorze pacientes (6M/8F), com idade média de 47,2 ± 8,8 anos, foram avaliados. Reduções significativas no débito cardíaco e volume sistólico foram encontradas após a infusão do infliximabe (7,04 ± 2,3 a 6,12 ± 2,1 L/min e 91 ± 29,0 a 83 ± 28,8 mL/batimento, respectivamente). Embora não estatisticamente significante, detectaram-se aumentos progressivos na PAS, PAD e RVPT durante a infusão. A infusão controle de SF não causou mudanças hemodinâmicas significativas nos pacientes estudados. Não foram observados efeitos adversos no período de infusão. **Conclusão:** A administração de infliximabe reduz agudamente o débito cardíaco devido a redução no volume sistólico em pacientes com AR sem insuficiência cardíaca. Nossos resultados mostram que, apesar do efeito inotrópico negativo, o infliximabe elevou a pressão arterial, provavelmente devido ao aumento na RVPT.

Unitermos: Infliximabe; inibidores de TNF-α; doenças autoimunes; artrite reumatoide; insuficiência cardíaca.

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Leandro Boer-Martins is an employee of Novartis Biociências S.A. (Brazil). The other authors declare to have no conflict of interest.

Introduction

Affecting men and women, rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, whose prevalence increases with age. It primarily affects distal joints, causing destruction and deformation due to bone and cartilage erosion. In addition to joints, it affects other sites, such as the lungs and heart.

Over the last decade, the use of some antirheumatic drugs (DMARDs) has changed the disease course; particularly, methotrexate (MTX) and corticosteroids have dramatically enhanced the success of RA management[1,2]. In addition, the use of tumor necrosis factor-alpha (TNF-α) inhibitors was a major breakthrough in RA treatment.

Cardiovascular diseases are associated with increased inflammatory activity in RA, and this fact may be related to increased risk of heart failure[3]. TNF-α is an inflammatory cytokine present in RA and is also related to cardiac injury through a variety of biological mechanisms, thus contributing to the progression of heart failure[3]. Although TNF-α inhibitors represent a major advance in the treatment of rheumatic disease, their impact on cardiovascular risk in RA is unknown. These observations led to several large randomized controlled trials designed to assess the efficacy of TNF-α inhibitor therapy in the treatment of heart failure. Unfortunately, these efforts were unsuccessful, since such trials were stopped prematurely due to lack of efficacy and worsening of heart failure in the groups treated with anti-TNF-α[3-5].

Thus, although some useful insights were offered, there are still several unanswered questions regarding the safety of anti-TNF-α use[6]. For example, it is still unknown whether TNF-α inhibitor infusion causes acute cardiovascular effects in RA patients without cardiac diseases.

Methods

Patient population

RA patients followed in the Rheumatology Outpatient Clinic at the Teaching Hospital of the Universidade de Campinas with RA refractory to the usual treatment, according to the Brazilian Consensus for the Diagnosis and Treatment of Rheumatoid Arthritis[7] as well as the American College of Rheumatology/European League Against Rheumatism classification criteria[8], participated in a protocol using the TNF-α inhibitor infliximab (Remicade®, Merck & Co – United States). Fourteen patients following treatment with methotrexate 12.5mg to 20mg/week and at least one conventional DMARD were included in the present study. Eight of them were also using corticosteroids. At the time of the study, each patient had received at least four cycles of infliximab infusion.

All individuals completed a medical history questionnaire, and were submitted to physical examinations, electrocardiography, echocardiography, and biochemical tests. Patients with signs and symptoms of heart failure and abnormal echocardiogram[9] were excluded. In addition, patients with impaired renal function, ischemic heart disease, liver disease, stroke, peripheral vascular disease, dyslipidemia, diabetes, or any other major diseases, as well as smokers, were also excluded. All subjects signed an informed consent, and the study was approved by the university's ethics committee.

Study design

This study comprised 14 patients with RA. Data collection was performed before, during, and after a 3-5 mg/kg infliximab dose was intravenously administered to each patient over a two-hour period. During this time, the calm, comfortably seated patients were monitored by a noninvasive system for hemodynamic evaluation, 15 minutes before and 15 minutes after infusion, and by office blood pressure (BP) measurements. After infusion, patients underwent a two-hour observation period, and were then discharged.

Two weeks after this first protocol, all 14 patients received a saline intravenous infusion (500 mL) for two hours, and hemodynamic measurements were obtained as a control.

Office blood pressure

Clinical values of BP were obtained three times from each patient, using a digital monitor (HEM-907 XL OMRON)[10]. While measuring BP, the participant remained seated with the arm comfortably placed at heart level[11]. BP was considered the mean of the two readings. Pulse pressure (PP) was calculated as: systolic BP (SBP) - diastolic BP (DBP).

Hemodynamic assessment (Portapres system)

The Portapres system (Finapres Medical Systems B.V. – Amsterdam, the Netherlands) was used for hemodynamic monitoring[4,12-14]. Two cuffs were positioned on the middle phalanx of the third and fourth fingers, with the device alternating fingers every 30 min; the hand to which the measurement unit was applied was held in a constant position. The device measured hemodynamic parameters in real-time (beat-to-beat), including: heart rate (HR), the number of heartbeats per minute; SBP; and DBP. Portapres also registered the arterial pressure wave, comparing it with a database of more than 2,000 waves and then estimating: stroke volume (SV), the volume of blood ejected from the left ventricle with each beat; cardiac output (CO), the volume of blood pumped by the heart in an one minute interval (CO = SV x HR); mean blood pressure (MBP); and total peripheral vascular resistance (PVR), the sum of the resistance of peripheral vasculature in the systemic circulation. Thus, it provided a complete hemodynamic assessment of the cardiovascular system using a noninvasive method.

Disease activity

Disease activity was measured using two parameters: a functional disability questionnaire known as Health Assessment Questionnaire (HAQ)[15,16] and the disease activity score (DAS 28), as well as certain routine inflammatory markers such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The anti-cyclic citrullinated peptide usually used for RA diagnosis was not performed in this study[8].

Statistical analysis

The Statistical Analysis System, version 8.02 (SAS Institute Inc. – Cary, NC, USA), was used for all statistical analyses. Normal distribution was assessed by the Kolmogorov-Smirnov test. Significant hemodynamic differences during the protocol were determined using Tuckey's test. A p-value < 0.05 indicated significance. All values were expressed as mean ± standard deviation (SD).

Results

The general characteristics of the patients are listed in Table 1. Baseline echocardiographic findings are shown in Table 2. The mean age of RA was 47.2 ± 8.8 years; women comprised 57% of the patients, and biochemical test results were normal. The mean left ventricle ejection fraction was 70.3 ± 4.3%.

Disease activity variables are also shown in Table 1, including rheumatoid factor levels at the time of treatment evaluation.

A significant decrease in cardiac output and stroke volume was observed after two-hour infliximab infusion (7.04 ± 2.3 to 6.12 ± 2.1 L/min and 91± 29.0 to 83 ± 28.8 mL/beat, respectively). Conversely, SBP, DBP, and PVR progressively increased during infliximab infusion. These hemodynamic findings were normalized to each individual body surface area and are expressed in Graphic 1.

No symptoms were reported during the TNF-α inhibitor administration.

No hemodynamic changes were observed during saline infusion protocol in the same RA patients. Results are shown in Table 3.

Discussion

The present study demonstrated that cardiac index and stroke volume index progressively decreased during infliximab infusion in individuals not presenting clinical and echocardiographic evidences of heart failure and following chronic treatment for rheumatoid arthritis. In healthy subjects, but not in RA patients, the normal cardiac response for saline infusion should be an increase in stroke volume and cardiac output of approximately 10%, without significant change in heart rate or blood pressure[17]. These results found could not be due to other drugs taken by

Table 1 – General characteristics of patients with rheumatoid arthritis

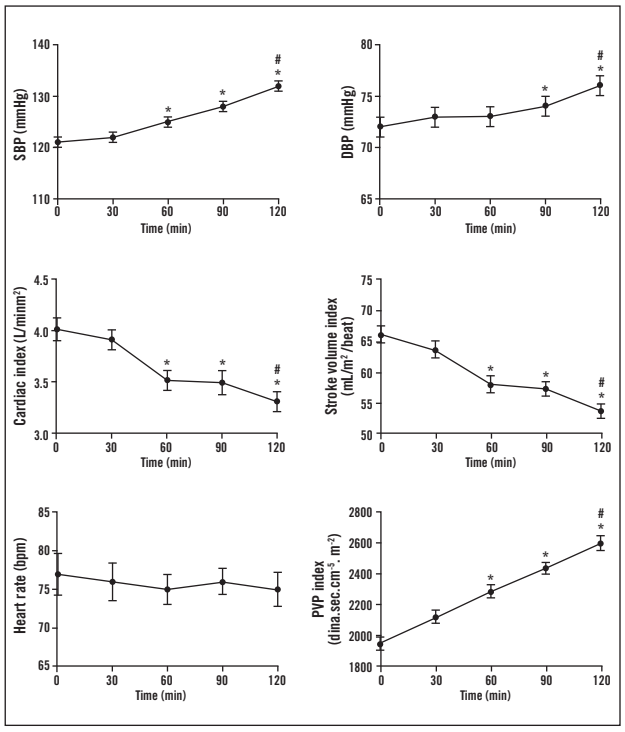
Clinical data	RA (n = 14)
Age (years)	47.2 ± 8.8
BMI (kg/m^2)	27.6 ± 1.3
Gender M/F	6/8
RA duration (years)	10.9 ± 4.4
Blood pressure	
Office SBP (mmHg)	121.0 ± 10.9
Office DBP (mmHg)	78.1 ± 10.7
Laboratory parameters	
Glycemia (mg/dL)	78.6 ± 17.0
Total cholesterol (mg/dL)	174.1 ± 20.5
LDL cholesterol (mg/dL)	89.3 ± 16.7
Triglycerides (mg/dL)	141.8 ± 58.7
Potassium (mEq/L)	4.1 ± 0.7
Creatinine (mg/dL)	1.0 ± 0.1
AST (mg/dL)	20 ± 3.4
ALT (mg/dL)	20 ± 10
DAS	
DAS 28	4.3 ± 2.0
HAQ	11.4 ± 3.6
Inflammatory markers	
CRP	2.4 ± 1.8
ESR	31.9 ± 18.6
Rheumatoid factor +/-	10/4

RA, rheumatoid arthritis; n, number of patients; BMI, body mass index; M/F, male/female; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoproteins; AST, aspartate transaminase; ALT, alanine transaminase; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate. Values are expressed as means ± SD.

Table 2 – Pre-study transthoracic echocardiography parameters in RA patients

	RA (n = 14)
Aorta (mm)	28.1 ± 2.0
LA (mm)	36.6 ± 2.7
LV septal thickness (mm)	9.5 ± 0.5
LV posterior wall thickness (mm)	9.1 ± 1.1
LV end-diastolic diameter (mm)	50.8 ± 3.0
LV end-systolic diameter (mm)	31.9 ± 2.8
Ejection fraction (%)	70.3 ± 4.3
LV mass/BSA (g/m^2)	96.0 ± 9.2

RA, rheumatoid arthritis; LA, left atrium; LV, left ventricle; BSA, body surface area. Values are expressed as means ± SD.



Graphic 1 – Hemodynamic changes during 2-hour infliximab infusion (3-5 mg/kg) in RA patients (n = 14). *p < 0.001 *versus* before infusion. #p < 0.05 *versus* 60 minutes. SBP, systolic blood pressure; DBP, diastolic blood pressure, PVR, peripheral vascular resistance.

Table 3 – Control group hemodynamic parameters

RA (n=14)	Before saline	After saline
SBP (mmHg)	163 ± 13	161 ± 15
DBP (mmHg)	86.7 ± 8.2	88.3 ± 3.1
Heart rate (bpm)	74.3 ± 17.0	74.67 ± 11.7
Stroke volume (mL)	80.5 ± 16.9	80.9 ± 24.4
Cardiac output (L/min)	6.1 ± 2.7	6.2 ± 2.9
Peripheral vascular resistance (dina.sec.cm^{-5})	1,701 ± 708.9	1,771 ± 718.4

RA, rheumatoid arthritis; n, number of patients; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are expressed as means ± standard deviation.

patients, since infliximab was the only new treatment administrated during the study. Also, there are no reports of cardiac injury caused by infliximab synergism with other drugs. Therefore, only a direct effect of infliximab on the heart could be responsible for the impairment in cardiac output in these patients. Inversely to healthy individuals[17], SPB and total PVR increased during the TNF-α inhibitor administration. To the authors' knowledge, this is the first time that hemodynamic parameters have been evaluated in RA patients during acute infusion of infliximab in order to better evaluate its impact on cardiovascular function. It is noteworthy that hemodynamic measurements were obtained by using the Portapres system, which has a near-zero bias (7% error) when compared with gold standard invasive methods such as triplicate thermodilution. It is probable that the two large randomized trials that studied anti-TNF-α infusion in heart failure patients did not detect cardiovascular effects because low doses of infliximab were administrated, and hemodynamic parameters were not monitored by an accurate method such as the Portapres system. Using this system, the present findings demonstrated that, even using moderate infliximab doses, its acute infusion may cause asymptomatic cardiac dysfunction.

It is known that the main cause of death in RA is cardiovascular disease (CVD)[18], and the overall increase in heart failure among RA patients may be related to increased inflammatory activity, perhaps leading to premature atherosclerosis. In fact, clinical markers of inflammation have been associated with cardiovascular mortality and morbidity in RA patients[5]. Contrarily to the healthy cardiac tissue, heart failure is of special interest because the failing heart produces TNF[19]. Inversely to the lack of data regarding the effects of circulating TNF-α on cardiovascular function in humans[19-22], studies in mice using heart failure models suggest improvement in ventricular dysfunction by circulating TNF blockade[23,24]. However, these results could not be reproduced in patients, and on the contrary, clinical trials showed that patients with heart failure had no benefit from the anti-TNF-α drug use, and it could even make their disease worse. These large randomized trials confirmed that patients with heart failure NYHA class III-IV had disease progression associated with infusion of high doses of anti-TNF-α (10mg/kg). Nevertheless, the safety of patients without heart failure is still uncertain[21,25].

Several pathophysiologic mechanisms contribute to cardiac injury, especially elevated oxidative stress and inflammation, which correlate with a variety of conditions such as hypertension, coronary artery disease, cardiomyopathy, atherosclerosis, and heart failure[26]. TNF-α is the most important cytokine related to these mechanisms. Increased TNF-α levels in inflammatory states lead to a high concentration of reactive oxygen species (ROS), in a vicious cycle, causing elevation of pro-oxidants. The imbalance between pro-oxidants and antioxidants causes systemic injury, including heart failure by DNA damage, protein nitration, lipid peroxidation, and activation of matrix metalloproteinases[27,28].

Conversely, despite the fact that TNF-α inhibition can both preserve cardiac function and partially reverse pathological changes in congestive heart failure[24] in animal models, this could not be reproduced in humans. Such

difficulty has probably occurred because mice heart failure models were transgenic (TNF1.6) with cardiac-specific overexpression of TNF-α, and heart failure in humans has several enrolled cytokines and ROS due to inflammation. The question "why is TNF-α inhibition harmful?" remains answered. According to some authors, infliximab can cause cell lyses in the presence of a complement[29], as well as a rebound effect of TNF-α toxicity on infliximab infusion[22]. Since the actual cause is not known, there is no evidence regarding the safe dose of infliximab.

Some relevant aspects should be highlighted when analyzing these results, because a number of potential limitations must be considered. First, a small number of RA patients were enrolled in the study. However, even studying a small sample of subjects, the Portapres system allows for continuous recording (beat-to-beat) of hemodynamic variables; the standard errors of means were very small and a test power of 0.72 was achieved. Second, patients did not have a long-term follow-up, so the accumulative dose effects of infliximab on cardiac function could not be analyzed. And finally, due to the small sample of patients studied, there was no standardization of RA duration and severity.

The present findings suggest that a two-hour infliximab infusion decreases cardiac output and stroke volume, even in RA patients without clinical and echocardiographic evidences of previous cardiac dysfunction. The results also demonstrate that, in spite of its possible negative inotropic effect, infliximab may enhance BP, probably by increasing PVR. However, considering the limitations of this study and of others, further investigations on acute and long-term administration of this anti-TNF-α drug, involving a higher number of subjects, should be performed in order to assess the safety of this RA treatment.

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