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ORIGINAL RESEARCH

Strategic evaluation of silent myocardial ischemia in a group of patients with rheumatoid arthritis and traditional cardiovascular risk factors

Evaluación estratégica de la isquemia miocárdica silenciosa en un grupo de pacientes con artritis reumatoide y factores de riesgo cardiovascular tradicionales

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Palabras clave:
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ABSTRACT

Introduction: IHD has become an important long-term end point for RA patients independent of traditional CVRF. Therefore, cardiovascular injury and mortality might be due to the presence of a chronic systematic inflammatory response. Nonetheless, there is a gap in its diagnosis since symptoms remain silent until major events occur. **Objective:** We aimed to evaluate by gated single-photon emission computed tomography (g-SPECT). Myocardial perfusion in asymptomatic Mexican patients with RA and at least one traditional CVRF, and without history of angina. **Patients and methods:** A prospective study with a total number of 91 patients was conducted. We evaluated CVRF and RA characteristics. We non-invasively assessed them with g-SPECT to reveal ischemia, territories and severity. We calculated relative risks and 95% CI of ischemia given the associated variables. **Results:** 22 (24.2%) patients presented ischemia, half of them in the LAD territory. Regarding CVRF and disease's characteristics; only smokers and patients under a steroid treatment were at more risk to present ischemia (0.49 [0.24 to 0.98] and 2.04 [1.01 to 4.14, respectively) with a p = 0.046. **Conclusion:** We have contributed with additional evidence to strategically diagnose IHD in patients with RA even if they have no symptoms and independently of the existence of cardiovascular risk factors to prevent and reduce cardiovascular mortality.

RESUMEN

Introducción: *La IC se ha convertido en un importante punto de partida a largo plazo para los pacientes con AR independientemente de los FRCV tradicionales. Por lo tanto, las lesiones cardiovasculares y la mortalidad podrían deberse a la presencia de una respuesta inflamatoria sistemática crónica. Sin embargo, hay una brecha en su diagnóstico ya que los síntomas permanecen en silencio hasta que ocurren eventos importantes.* ***Objetivo:*** *Evaluar mediante tomografía computarizada de emisión de un solo fotón (g-SPECT). Perfusión miocárdica en pacientes mexicanos asintomáticos con AR y al menos un FRCV tradicional, sin antecedentes de angina.* ***Pacientes y métodos:*** *Se realizó un estudio prospectivo con un número total de 91 pacientes. Se evaluaron las características FRCV y AR. Los evaluamos de forma no invasiva con g-SPECT para revelar isquemia, territorios y severidad. Se calcularon los riesgos relativos la isquemia de 95% dadas las variables asociadas.* ***Resultados:*** *Veintidós (24.2%) pacientes presentaron isquemia, la mitad de ellos en territorio LAD. Respecto a los FRCV y características de la enfermedad; sólo los fumadores y los pacientes sometidos a un tratamiento con esteroides presentaron mayor riesgo de presentar isquemia (0.49 [0.24 a 0.98] y 2.04 [1.01 a 4.14, respectivamente) con p = 0.046.* ***Conclusión:*** *Hemos aportado pruebas adicionales para diagnosticar la isquemia estratégicamente en los pacientes con AR, incluso si no tienen síntomas y con independencia de la existencia de factores de riesgo cardiovascular para prevenir y reducir la mortalidad cardiovascular.*

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease that leads to progressive joint deformity and disability.[1] affecting approximately 1% of the population worldwide.[2-9] Major cohort studies have demonstrated that patients suffering from RA are 3 to 5 times more likely to experience hospitalization for unrecognized, or silent myocardial infarction (MI) than age- and sex-matched controls.[10,11] Therefore, patients suffering from RA are at a higher risk, ranging from 40 to 65%, to suffer from ischemic heart disease (IHD) without any recognized symptoms. However, before death, the patients were not aware of their cardiovascular risk.[12-14]

A wide range of literature including systematic reviews, meta-analyses and population-based studies with long and complete follow-ups, indicate that the causes of cardiovascular disease (CVD) in patients with many of the traditional cardiovascular risk factors (CVRF) such as hypertension, smoking, diabetes mellitus, obesity and hypercholesterolemia at baseline is similar amongst RA and non-RA patients.[1,15] However, there is no consensus on the correlation between the presence of CVRF and ischemic heart disease as an outcome. Thus, CVD have become an important long-term end point for RA patients independent of traditional CVRF.[16-21]

In this setting, cardiovascular injury and mortality might be due to the presence of a chronic systematic inflammatory response.[2] This is characterized by the release of high levels of pro-inflammatory substances (the cytokines, tumor necrosis factor alpha, interleukin-1, interleukin 2, and adhesion molecules), that causes endothelial dysfunction and the subsequent atherosclerotic disease.[3] Evidence points that the chronic inflammation follows a pathogenesis pathway that occurs in RA and it would lead to increase atherosclerosis as a side effect while acting at a distance on the systemic vascular endothelium.[4]

Strategies that focus solely in the control of CVRF are inadequate since the distribution is generally the same but their impact results in different outcomes; and more relevant, symptoms remain silent for a long time. Consequently, to reduce such gap there is a need to assess IHD in patients with RA even if they have no symptoms and independent of the existence of cardiovascular RF to prevent and reduce cardiovascular mortality.

Objective

We aimed to evaluate myocardial perfusion in asymptomatic by gated single-photon emission computed tomography (g-SPECT) in a group of Mexican patients with rheumatoid arthritis.

Patients and methods

In this prospective observational study, we enrolled 91 consecutive patients with a previous rheumatoid arthritis clinical diagnose, and with at least one traditional cardiovascular risk factor. We excluded those patients with any history of angina or IHD. Patients were referred from the Rheumatology service to the Nuclear Medicine department from March to August 2015. All patients were asked their age, sex, years with RA diagnosis and prescribed treatment.

Assessments

Data were collected on traditional cardiovascular risk factors using established diagnostic criteria. Their body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Diabetes mellitus was defined as a fasting plasma glucose level of 7.0 mmoles/liter (126 mg/dL) or a 2-hour glucose level of 11.1 mmoles/liter (200 mg/dL).[5] Hypertension was defined as systolic blood pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg.[6] Hypercholesterolemia was defined as a fasting plasma cholesterol level of 5 mmoles/liter (200 mg/dL) at baseline. Patients were considered cigarette smokers by current self-report.

In order to measure the activeness of rheumatoid arthritis, we used composite scores of the disease activity (DAS28 Score). DAS28 is validated index scale which provides a number from cero to 10; DAS28 > 5.1 means high disease activity, DAS28 = 3.2 to 5.1 moderate activity, DAS28 3.2 to 2.1 low disease activity, whereas a < 2.1 indicates remission.[7] High

sensitivity C-reactive Protein (hs-CRP) was quantified, where the reference range was as follows: low risk 1.0 mg/L, medium risk 1 to 3.0 mg/L and high risk above 3.0 mg/L.[8] Also, erythrocyte sedimentation rate (ESR) was assessed assuming normal values as 0-22 mm/h for men and 0-29 mm/h for women.[9]

Nuclear screening

All 91 patients were non-invasively assessed trough gated single-photon emission computed tomography (g-SPECT), which is a non-invasive cardiovascular imaging technique.

Image acquisition

The perfusion images were acquired in synchronization with the patient's electrocardiogram (g-SPECT), this allowed us to study not only the left myocardial perfusion, but also the mobility, the systolic wall thickening and left ventricle ejection fraction (left myocardial function).

We utilized a gamma camera SIEMENS®-Symbia-S, with IQ-SPECT technology (dual head) and collimators SMATRZOOM with acquisition of 32 images (in 180º elliptical orbit from 45º right anterior oblique to 45º left anterior oblique, in step and shoot mode); allowing the use of radiotracer lower doses and the acquisition of high quality imaging in less time (4 minutes). Following the guidelines of the *American Society of Nuclear Cardiology* (ASNC)[10] *American College of Cardiology* (ACC),[11] and *American Heart Association* (AHA),[11] SPECT MPI was performed in a 1-Day protocol. The stress examination was done under physical or pharmacological with dipyridamole (according to the physical capacity and clinical condition of the patient). Technetium-99m sestamibi 8 mCi and 16 mCi were injected at rest and stress, respectively.

Image processing and data analysis

All g-SPECT myocardial perfusion imaging (MPI) studies were analyzed by two experienced nuclear cardiologist physicians who were blinded to perfusion results (Kappa intra e inter-observer 0.92). Reconstruction and image processing was generated in the usual levels: short axis, vertical long axis and horizontal long axis. For qualitative analysis, perfusion SPECT studies were assessed visually, using the 17-segment model which were rated based on the severity of perfusion defects in visual 5-point scale, where 0 denotes normal perfusion; 1 mild perfusion defect; 2 moderate defects; 3 severe perfusion defect and 4 denotes absence perfusion. Necrosis was indicated at the presence of a perfusion defect in the rest images, and was defined as transmural (severe defect or absence of perfusion) and nontransmural (moderate perfusion defect). Ischemia was indicated where the presence of a reversible defects, which refers to a perfusion defect present in stress that resolved at rest in the same segment, and was rated as mild, moderate and severe.

Statistical analysis

Descriptive data were generated for all variables. In order to test whether or not ischemia was statistically significantly associated with traditional CV risk factors and characteristics of RA, we calculated the relative risk, odds ratio and 95% CI. All analyses were carried out using SPSS, version 21.

RESULTS

The sample consisted of 91 patients presenting RA diagnosis and without any history of angina or coronary artery disease. Eight were men and 83 women. Mean age was 59 ± 12, with a range of 27 and 84. The median number of years with diagnosis was 18.5 ± 7.9, the minimum number of years was 2 and the maximum was 36. Body mass index mean was 27.6 ± 4.8; 65 (71.4%) patients were obese, 17 (18.7%) classified as normal weight and 9 (9.1%) were overweight. The majority of patients (95.6%) underwent disease modifying antirheumatic drugs (DMARD) alone or combined with other modality of treatment. The median DAS28 score was 1.5 (IQR 1.0-5.2); 44 patients (48.4%) had a low severity, 29 (31.9%) had medium severity, and the remaining 18 (19.8%) had a high severity. According to the analyses of inflammation markers, hs-CRP mean was 11.14

± 12.0 mg/L, whereas ESR mean was 26.5 ± 13.4 mm/h. *Table I* presents the distribution of clinical characteristics associated to RA, and risk factors, divided into two groups; with and without ischemia assessed by g-SPECT.

In general, 22 (24.2%) patients presented ischemia when assessed by the g-SPECT.

The severity of the ischemia was mostly mild ischemia. The more frequent location of the myocardial perfusion alteration was in the territory of the anterior descending coronary artery (DA) as is presented in *table II*.

Regarding traditional cardiovascular risk factors, hypertension was the most common; found in 29 (31.9%) patients, followed by smoking found in 13 (14.3%) and lastly diabetes mellitus in 9 (9.8%). *Table III* shows the distribution of risk factors as well as the relative risk for ischemia and odds ratios. Smoking steroid treatment were statistically significant risk factors for presenting ischemia. Since the 95% CI for the rest of risk factors span 1.0, the odds of having a diagnosed risk factor and presenting ischemia do not reach statistical significance.

DISCUSSION

The present study was designed to assess with a non-invasive cardiovascular imaging technique, the existence of ischemia in asymptomatic patients with rheumatoid arthritis and traditional cardiovascular risk factors. The development of quantitative methods

Table I. Characteristics of patients with RA with and without ischemia assessed by gated-SPECT.

	Ischemia n = 22 (24.2)	No ischemia n = 69 (75.8)	Total n = 91 (100)
Sex			
Woman	17 (18.7)	65 (71.4)	82 (90.1)
Men	5 (5.5)	4 (4.4)	9 (9.9)
Risk factors			
Obesity	7 (7.7)	29 (31.9)	36 (39.6)
Hypercholesterolemia	7 (7.7)	23 (25.3)	30 (33.0)
Hypertension	9 (9.9)	20 (29)	29 (31.9)
Smoking	5 (5.5)	8 (8.8)	13 (14.3)
Diabetes mellitus	4 (18.2)	5 (7.2)	9 (9.8)
Type of treatment			
DMARD + steroids	8 (8.8)	39 (42.9)	47 (51.6)
DMARD + steroids + bio	4 (18.2)	17 (18.7)	21 (23.1)
DMARD	8 (8.8)	11 (12.1)	19 (20.9)
Biological + steroids	0 (0)	2 (2.2)	2 (2.2)
Biological	2 (2.2)	0 (0)	2 (2.2)
ESR (mm/h)			
Normal	11 (12.1)	29 (31.9)	40 (44.0)
Abnormal	11 (12.1)	40 (44.0)	51 (56.0)
hs-PCR (mg/L)			
Low	7 (7.7)	9 (9.8)	15 (16.5)
Medium	9 (9.9)	26 (28.6)	35 (38.5)
High	7 (7.7)	43 (47.3)	50 (55.0)
DAS28 Score			
Low	9 (9.9)	36 (39.6)	45 (49.5)
Medium	7 (7.7)	21 (23.1)	28 (30.8)
High	6 (6.5)	12 (13.2)	18 (19.8)

Table II. Frequency of patients for each level and location of myocardial perfusion abnormalities.

Myocardial perfusion	LAD	LCX	RCA	Total n (%)
Mild ischemia	10	5	1	16 (72.7)
Moderate ischemia or infarct	1	3	2	6 (27.3)
Total	11 (50)	8 (36)	3 (14)	22 (100)

LAD = Left anterior descending artery, LCX = Left circumflex coronary artery, RCA = Right coronary artery.
Numbers in parentheses are the % of the total number of ischemia cases.

Table III. Risk factors of ischemia with relative risks at 95% CI and p-values.

Risk factor	n (%)	RR (95% Confidence interval)	p
Smoking	13 (14.3)	0.49 (0.24 to 0.98)	0.046*
Diabetes mellitus	9 (9.9)	2.02 (0.87 to 4.67)	0.098
Hypertension	9 (9.9)	1.48 (0.72 to 3.06)	0.290
Hypercholesterolemia	65 (71.4)	1.67 (0.56 to 3.30)	0.492
Obese or overweight	12 (13.2)	0.83 (0.47 to 1.46)	0.636
High or medium DAS28	13 (14.3)	1.35 (0.64 to 2.84)	0.426
Abnormal ESR levels	11 (12.08)	1.27 (0.61 to 2.63)	0.656
High hs-PCR	10 (11.0)	0.62 (0.30 to 1.29)	0.206
Underwent steroids Tx	69 (75.8)	2.04 (1.01 to 4.14)	0.046*

* Statistically significant variable; p-values < 0.05 significant.

in the attempt to diagnose IHD by nuclear imaging test, has provided a more objective measure, reducing operator bias compared with traditional diagnostic approaches.[12] We have presented evidence to fill the gap for screening myocardial perfusion in patients with RA with more accuracy, since we have also presented the injured territory and the severity of the disease. These results support previous research regarding the non-relation between traditional CVRF and ischemia in this type of patients (5-9, 11-15). In fact, the most important clinically relevant finding of our study was that only one traditional CVRF, which was smoking, was statistically significantly associated with the presence of ischemia. The other significant relative risk, was treatment with steroids, which has also been topic of discussion because it has been related to endothelial dysfunction and atherosclerosis development.[13] This means that neither the relevant clinical symptoms of the rheumatologic disease, as pain in articulations and inflammation evaluated with the DAS28 score, counted as a statistically significant association to the presence of ischemia. It is worth noting, that even when hs-CRP and ESR values were higher than the normal mean, there was not statistically significant correlation with ischemia. Therefore, the value of the myocardial perfusion assessment by g-SPECT is of enormous relevance, since it reveals the exact location and severity of myocardial perfusion defects, as a final outcome for asymptomatic patients (silent myocardial ischemia) with intermediate to high cardiovascular risk. This strategic diagnosis goes beyond what it is explained by traditional CVRF and the clinical rheumatologic disease's characteristics. In fact, a striking observation is that our youngest patient; a woman aged 27, with two years of diagnosed RA and with DM as a risk factor, presented ischemia already.

Therefore, because the presence of myocardial perfusion defects could not be attributable to CVRF, we suggest that the abnormalities (ischemia or infarction) in gated-SPECT MPI can be explained by the persistence of a systemic inflammation PROCESS and endothelial dysfunction, as an inherent side effect of rheumatoid disease; explaining an accelerated atherosclerosis process.[14]

A non-invasive strategic diagnosis was possible because of the use of novel and updated software programs, which allow a non-invasive, automatic, quantitative, and without operator bias assessment of the left myocardial perfusion. Thus, the sensibility (90%) and accuracy (100%) of the method makes it a reproducible tool, since it allows the detection of perfusion abnormalities and the existence of functional coronary significant obstructions in the different anatomical territories (LAD, LCX and RCA), as well as the severity and the extension of the coronary artery disease.

In asymptomatic patients with suspicion or an intermediate to high risk to develop atherosclerotic coronary disease, as the case of patients with RA, g-SPECT technique is highly safe and reliable since it is credited for less than 1% of complications. In addition, it is the most used method in nuclear cardiology.

CONCLUSION

The present study will serve as a base for considering arthritis rheumatoid as a risk factor to develop atherosclerotic coronary artery disease. We have confirmed previous findings and have contributed additional evidence that suggests the need to explore CVD in patients with RA even if they have no symptoms and independently of the existence of cardiovascular risk factors to prevent and reduce cardiovascular mortality. We enhance the value of the g-SPECT as a non-invasive cardiovascular imaging evidence-based technique to perform strategic early assessments in asymptomatic patients with intermediate to high cardiovascular risk.

Limitations and suggestions

Due to the large prevalence of one or more cardiovascular risk factors within the Mexican population, more research is required to determine economic considerations and clinical implications to implement diagnosis protocols. Further investigation should focus on the role of steroid doses.

REFERENCES

1. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008; 59 (12): 1690-1697.
2. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004; 109 (Suppl II): II2-II10.
3. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: a multifactorial process. Exp Clin Cardiol. 2002; 7 (1): 40-53.
4. Del Rincón I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001; 44 (12): 2737-2745.
5. ADA. Diabetes care. Diabetes Care. 2014; 37 (1): S21-S22.
6. James PA, Oparil S, Carter BL, Cushman WC, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults. JAMA. 2014; 311 (5): 507-520.
7. Van Riel PL, Schumacher HR Jr. How does one assess early rheumatoid arthritis in daily clinical practice? Best Pract Res Clin Rheumatol. 2001; 15 (1): 67-76.
8. Casas J, Shah T, Hingorani A, Danesh J, Pepys M. C-reactive protein and coronary heart disease: a critical review. J Inrtern Med. 2008; 264 (4): 295-314.
9. Kurec AS, Lifshitz MS. General concepts and administrative issues, Philadelphia: Saunders Elsevier, 2011.
10. Hendel R, Corbett J, Cullom S, DePuey EG, Garcia EV, Bateman T. The value and practice of attenuation correction for myocardial perfusion SPECT imaging. a joint position statement from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine. J Nucl Cardiol. 2002; 9: 135-143.
11. Ryan T, Antman E, Brooks N. American College of Cardiology. [En línea]. [Último acceso: 28 October 2015] Available: http://www.acc.org/clinical/guidelines/nov96/1999/amipdf99.pdf
12. Chin D, Battistoni A, Tocci G, Passerini J, Parati G, Volpe M. Non-invasive diagnostic testing for coronary artery disease in the hypertensive patient: Potential advanages of a risk estimation-based algorithm. Am J Hypertens. 2012; 25 (12): 1226-1235.
13. Patt H, Bandgar T, Lila A, Shah N. Management issues with exogenous steroid therapy. Indian J Endocrinol Metab. 2013; 17 (3): 612-616.
14. Wolfe F, Mitchell D, Dibley JS, Bloch D, Williams C. The mortality of rheumatoid arthritis. Arthritis Rheum. 1994; 37: 481-494.
15. Monson RR, Hall AP. Mortality among arthritics. J Chronic Dis. 1976; 29: 459-467.

16. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011; 365 (23): 2205-2219.
17. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012; 18: S295-S302.
18. Peláez-Ballestas I, Sanin LH, Moreno-Montoya J, Álvarez-Nemegyei J, Burgos-Vargas R, Garza-Elizondo M et al. Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. J Rheumatol Suppl. 2011; 86: 3-8.
19. Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis. 2005; 64: 1595-1601.
20. Kaplan MJ. Cardiovascular complications of rheumatoid arthritis-assessment, prevention and treatment. Rheum Dis Clin North Am. 2010; 36 (2): 405-426.
21. Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatopid arthritis: results from a community based study. Ann Rheum Dis. 2004; 63: 952-955.

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