International Journal of Cardiology 167 (2013) 2031–2038

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heart involvement in Rheumatoid Arthritis: Systematic review and meta-analysis ☆,☆☆

Salvatore Corrao [a,b,*], Silvia Messina [a], Giovanni Pistone [b], Luigi Calvo [a], Rosario Scaglione [a], Giuseppe Licata [a]

[a] Centre of Research for Effectiveness and Appropriateness in Medicine (CREAM), Biomedical Department of Internal Medicine and Subspecialties [DiBiMIS], University of Palermo, Palermo, Italy

[b] National Relevance Hospital Trust, Unit of Internal Medicine II, Outpatient Rheumatology Clinic, ARNAS Civico, Di Cristina e Benfratelli, Palermo, Italy

ARTICLE INFO

Article history:
Received 20 April 2012
Received in revised form 7 May 2012
Accepted 11 May 2012
Available online 15 June 2012

Keywords:
Rheumatoid Arthritis
Systematic review
Meta-analysis
Echocardiography assessment
Pericardial disease
Cardiac valvular calcification

ABSTRACT

Objective: The aim of our study was to conduct a systematic review with meta-analysis of the current case–control studies about the valvular and pericardial involvement in patients with Rheumatoid Arthritis (RA), asymptomatic for cardiovascular diseases.

Methods: Case–control studies were identified by searching PubMed (1975–2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) (1975–2010). Participants were adult patients with RA asymptomatic for cardiovascular diseases, and the outcome measure was the presence of cardiac involvement.

Results: Quantitative synthesis included 10 relevant studies out of 2326 bibliographic citations that had been found. RA resulted significantly associated to pericardial effusion (OR 10.7; 95% CI 5.0–23.0), valvular nodules (OR 12.5; 95% CI 2.8–55.4), tricuspidal valve insufficiency (OR 5.3; 95% CI 2.4–11.6), aortic valve stenosis (OR 5.2; 95% CI 1.1–24.1), mitral valve insufficiency (OR 3.4; 95% CI 1.7–6.7), aortic valve insufficiency (OR 1.7; 95% CI 1.0–2.7), combined valvular alterations (OR 4.3; 95% CI 2.3–8.0), mitral valve thickening and/or calcification (OR 5.0; 95% CI 2.0–12.7), aortic valve thickening and/or calcification (OR 4.4; 95% CI 1.1–17.4), valvular thickening and/or calcification (OR 4.8; 95% CI 2.2–10.5), and mitral valve prolapse (OR 2.2; 95% CI 1.2–4.0).

Conclusions: Our systematic review pointed out the strength and the grade of both pericardial and cardiac valvular involvement in RA patients. Our findings underscore the importance of an echocardiographic assessment at least in clinical research when RA patients are involved. Moreover, further research is needed to understand the possible relationship of our findings and the increased cardiovascular mortality.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that affects joints causing deformities, severe disability and premature mortality [1,2]. This disease has a high social and economic burden. Indeed, about 1.3 million adults are affected by RA in the United States [3]. The world prevalence of RA might be around 0.3–1.2% [4]. Recently the Swedish patients register [5] has shown a RA cumulative prevalence of 0.77% (women 1.16% men 0.44%) confirming above mentioned assumptions. In this disease, the synovial membrane is the main target, although extra-articular manifestations can be found including the cardiac ones. Pericarditis is the cardiac manifestation most readily recognized, but myocardial disease, coronary vasculitis, diastolic dysfunction, accelerated atherosclerosis and valvular lesions of the heart have also been reported [6]. The premature mortality among patients with RA is frequently due to cardiovascular disease [7], primarily ischemic heart disease [8] and congestive heart failure [9]. A recent meta-analysis of our team showed that rheumatoid patients have a higher left ventricular mass than controls [10]. Moreover, in rheumatoid patients without overt cardiovascular disease, we previously reported pericardial, valvular, and aortic root involvement that we clinically defined as “silent rheumatoid heart disease” [11]. Recently, Yiu et al. [12] have found out a significant association between Rheumatoid Arthritis and valvular calcifications. This study used multidetector computed tomography and has also pointed out that the presence of mitral valve calcification independently predicted the occurrence of premature atherosclerosis. On the other hand, several echocardiographic studies have been published in the last two decades on this issue. So that, summarizing evidence from all these studies may be useful to understand the effect of the

☆ This work was made with the institutional, financial support of University of Palermo, Italy.

☆☆ There was no relationship with industry.

* Corresponding author at: Centre of Research for Effectiveness and Appropriateness in Medicine (CREAM), Biomedical Department of Internal Medicine and Subspecialties [DiBiMIS], Piazza delle Cliniche 2, 90127 Palermo, Italy. Tel./fax: +39 091 6552165.
E-mail address: s.corrao@tiscali.it (S. Corrao).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.05.057

disease on cardiac structures of rheumatoid patients almost partially in the pre-biological era.

The aim of our study was to perform a systematic review and meta-analysis of the current case–control studies based on echocardiographic assessment of valvular and pericardial involvement in patients with RA.

2. Materials and methods

2.1. Search strategy for identification of studies

The review was achieved following the Cochrane Collaboration Steps [13] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standard of reporting [14].

Sources of published data included electronic database such as PubMed-Medline (1975–July 2010) [15] and the Cochrane Central Register of Controlled Trials (CENTRAL) (1975–July 2010) [16]. The search strategy was as follows: "rheumatoid arthritis AND (heart OR ventricle OR ventricular OR valvular)" without any other restriction for reaching maximum recall. We controlled for the terms "pericardial or pericardium" but it did not add any further citation recall compared to the above mentioned search string.

2.2. Criteria for considering studies for this review

Retrieved citations were screened independently by two adjudicators (SC, SM) using titles of papers and abstracts. Once pertinent studies (that is according to the aim of this systematic review) were identified, the full publication was retrieved and reviewed independently by the two investigators to determine the suitability for final inclusion.

The reviewers were blinded to the names of authors, institutions or journals, and articles were independently selected for inclusion according to the prespecified selection criteria. No prejudice in study evaluation was made.

The type of studies considered to be included was controlled clinical trial with case–control design. Series of case, descriptive reports, cohort and uncontrolled studies were excluded from the analysis. Participants in the studies were adult patients with RA, asymptomatic for cardiovascular diseases.

Measured outcome was the proportion of patients with valvular and pericardial involvement.

2.3. Quality assessments

Methodological quality was assessed independently by two reviewers (SC, SM) using the STROBE (Strengthening the Reporting of Observational studies in Epidemiology Statement) recommendations [17], with special consideration on selection bias and detection bias. Performance bias was not considered because it concerns pharmacological studies. Moreover, loss to follow-up was not considered basing on the design of the included studies in this review (only case–control ones).

2.4. Data extraction and statistical analysis

Data on patients, methods, outcomes and results were extracted using a data extraction form (SM, LC). Disagreement was resolved by other adjudicator (SC). Data were analyzed using the STATA Version 9.0 and were presented as odds ratio (OR) along with their corresponding 95% confidence intervals (CI). Heterogeneity was investigated by using the I^2 statistic with significance set at $p<0.05$. Pooled ORs and 95% CIs were calculated using a random effect model or a fixed effect model according to heterogeneity. Bias of publication was evaluated by the Egger Regression Asymmetry Test and the Regression Asymmetry Plot.

3. Results

The search string that we used recalled 2326 bibliographic citations. They were screened, and 55 papers were retrieved because they were recognized as pertinent. Then, 16 studies were excluded because they were not case–control studies, 1 because it was a pharmacological study and 28 because they were not pertinent. So we identified 10 relevant papers. All of them were used for this systematic review. All the patients were asymptomatic for cardiovascular disease, and, after echocardiographic assessment, none was reported affected by more than slight–moderate hemodynamic valvular alterations (as regurgitation as stenosis). Fig. 1 shows the flow-diagram of the study selection process. Appendix 1 shows characteristics of studies that were included in this systematic review [11,18–26]. Appendix 2 shows the list of studies that were excluded.

We performed a meta-analysis for each of the following abnormalities: pericardial effusion, valvular nodules, valvular thickening and/or calcification (Fig. 2), tricuspidal valve insufficiency, aortic valve insufficiency, aortic valve stenosis, mitral valve stenosis, mitral valve prolapse

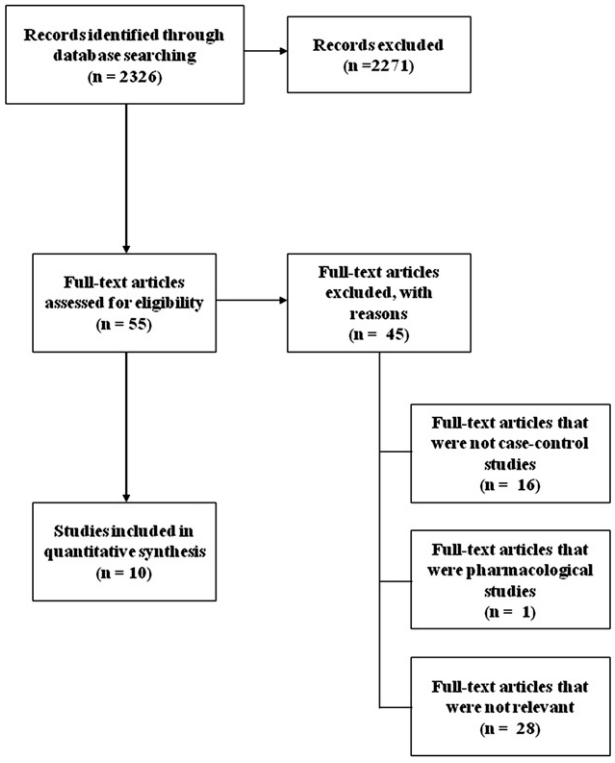

Fig. 1. Systematic review flow diagram according to the MOOSE standard: the flow chart shows the selection process regarding the retrieved citations; trials on treatment and studies not pertinent were excluded such as all the studies that were not controlled ones.

(Fig. 3), and combined valvular alterations (Fig. 4). Fig. 5 shows other four meta-analyses that were preformed about mitral valve thickening/calcification, aortic valve thickening/calcification, mitral valve prolapse, and mitral valve insufficiency. Pulmonary valve insufficiency and aortic valve prolapse were reported by only one study [18]. Thus, in this case, we did not perform any meta-analysis.

The fixed model was used for the following abnormalities: pericardial effusion, valvular nodules, valvular thickening and/or calcification, tricuspidal valve insufficiency, aortic valve insufficiency, aortic valve stenosis, mitral valve stenosis, and combined valvular alterations.

The random model was used for the following abnormalities: mitral valve insufficiency, mitral valve thickening and/or calcification, aortic valve thickening and/or calcification.

We preferred to use fixed and random models for mitral valve prolapse since the high I^2 (51.8%; $p<0.081$) even if not significant.

Table 1 shows the summary data of all the performed meta-analyses, including the Egger's test statistic for evaluation of the publication bias. Only in the case of aortic valve stenosis, we found a significant p value by the Egger's test (this test states a probable publication bias in this field of knowledge).

Our meta-analyses showed a higher risk of pericardial effusion and valvular nodules more than ten times in patients with RA compared with controls. Concerning data about tricuspidal valve insufficiency, aortic valve stenosis, and mitral valve thickening/calcification, meta-analyses showed an increased risk about five times more in patients with RA compared with controls. Moreover, data about valvular thickening and/or calcification, combined valvular alterations, and aortic valve thickening and/or calcification showed an increased risk about four times in patients with RA compared with controls. Data about mitral valve insufficiency showed an increased risk about three times in patients with RA compared with controls. A risk about twice in patients with RA compared with controls emerged from data about aortic valve insufficiency. Finally, data of meta-analyses did not show an increased risk about mitral valve stenosis,