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Subclinical impairment of myocardial and endothelial functionality in very early psoriatic and rheumatoid arthritis patients: Association with vitamin D and inflammation

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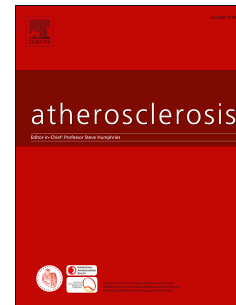
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1       **Subclinical impairment of myocardial and endothelial functionality in very**  
2       **early psoriatic and rheumatoid arthritis patients: Association with vitamin D**  
3       **and inflammation**

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5  
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1 **ABSTRACT**

2

3 *Background and aims:* Cardiovascular (CV) morbidity is increased in inflammatory joint diseases (IJD), as  
4 rheumatoid (RA) and psoriatic arthritis (PsA). Whereas increased prevalence of subclinical atherosclerosis  
5 has been reported in these conditions, whether an early myocardial functionality is also impaired remains  
6 unknown. The aim of this study was to evaluate the myocardial functionality by speckle-tracking  
7 echocardiography (STE) in recent onset RA and PsA patients and its potential associations with the levels  
8 of circulating CD34+ cells, vitamin D, and with disease activity.

9 *Methods:* STE was used to assess the myocardial functionality in patients with very early RA (n=41) and  
10 PsA (n=35) without traditional CV risk factors, and 58 matched healthy controls (HC). Global longitudinal  
11 and circumferential strain (GLS and GCS) were estimated. Pulse wave velocity (PWV), carotid intima-  
12 media thickness (cIMT) were measured as surrogate markers of atherosclerosis. Circulating CD34+  
13 counts were evaluated by flow cytometry and vitamin D levels were quantified by HPLC. Disease activity  
14 was assessed by Disease Activity Score-28 (DAS28).

15 *Results:* RA patients exhibited impaired GLS and GCS (both  $p<0.001$ ) as compared to HC, GLS being  
16 also altered in PsA ( $p=0.020$  vs. HC). DAS28 was correlated to GLS ( $r=0.908$ ,  $p<0.001$ ) and GCS  
17 ( $r=0.868$ ,  $p<0.001$ ) in RA, these findings being confirmed by multivariate regression analyses adjusted for  
18 confounders and Principal Component Analyses. GLS and GCS were impaired in PsA patients with high  
19 disease activity as compared to HC, and GLS was found to be a predictor of cIMT in this condition. On the  
20 other hand, vitamin D was negatively associated with cIMT in HC ( $r=-0.308$ ,  $p=0.026$ ) but not in PsA or  
21 RA, although decreased levels were observed (both  $p<0.001$ ). Vitamin D was an independent predictor of  
22 decreased CD34+ levels in PsA and RA. CD34+ counts negatively correlated DAS28, GLS and GCS in  
23 RA.

24 *Conclusions:* Subclinical myocardial dysfunction is observed in IJD patients with preserved left-ventricular  
25 function and without traditional CV risk factors. Subclinical myocardial dysfunction was found to be a very  
26 early event in IJD. Disease activity was the main predictor of myocardial strain impairment. Interestingly,  
27 myocardial function was altered and associated with cIMT also in PsA patients with high disease activity.

28

29

30 **Keywords:** rheumatoid arthritis, inflammatory joint diseases, speckle-tracking echocardiography, vitamin  
31 D

## 1 INTRODUCTION

2 Patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA) and psoriatic arthritis  
3 (PsA), exhibit increased rates of cardiovascular disease (CVD) morbidity and mortality [1,2], especially  
4 heart failure and myocardial infarction. Traditional CV risk factors cannot fully account for this increased  
5 risk, and chronic inflammation and immune dysregulation are thought to play a substantial role [3,4].

6 The involvement of traditional and non-traditional CV risk factors in IJD has two main consequences. First,  
7 the CVD have a premature development in these patients. Second, the assessment of CV risk solely  
8 based on traditional CV risk factors, as implemented for the general population, is obviously insufficient.  
9 Therefore, there is a clear need for early and appropriate methods for CV risk assessment in IJD [5,6],  
10 which may benefit patient stratification and facilitate the establishment of earlier therapeutic interventions,  
11 in order to improve clinical outcomes.

12 Several non-invasive imaging techniques allows an adequate estimation of CV risk by evaluating  
13 atherosclerosis burden and cardiac function. Although most of the studies have focused on  
14 atherosclerosis, less attention has been paid to myocardial systolic functionality. Two dimensional speckle  
15 tracking echocardiography (STE) is a recent method for detecting ventricular dysfunction by  
16 echocardiographic assessment of myocardial deformation (strain). Strain refers to the deformation or the  
17 relative change of muscle from its original length, expressed as a percentage of change. This technique  
18 provides information about both regional and global myocardial function. It is a very sensitive, load- and  
19 angle-independent technique, which make it superior to angle-dependent 2D Doppler echocardiography  
20 [7,8]. Moreover, strain abnormalities have been reported in a broad range of CV conditions, from heart  
21 failure with preserved EF to myocardial infarction and ischemia-reperfusion lesions [9–12]. Therefore,  
22 impaired ventricular strain can be suited for early detection of CVD in PsA and RA [7,13].

23 The involvement of non-traditional risk factors in IJD is supported by mechanistic insights and may  
24 represent a source of biomarkers and therapeutic targets. Common immune mediators [14–17] drive both  
25 atherosclerosis and joint progression. Chronic activation of immune pathways leads to endothelial  
26 dysfunction, vascular repair failure [18], atherosclerotic plaque formation and, ultimately, CVD  
27 development. Among reparative mechanisms, the case of circulating proangiogenic haematopoietic cells  
28 (CD34+) must be noted. CD34+ precursors are bone marrow-derived, multipotent cells with the ability to  
29 differentiate into different cell types [19,20] that participate in the turnover of damaged endothelium, likely  
30 delaying CVD development [20]. CD34+ cells have been described to improve myocardial  
31 neovascularization and function [21,22], and their number is associated with LV remodeling [23]. Several  
32 factors are known to modulate the number and activity of progenitor cells in rheumatic diseases [18].  
33 Recently, vitamin D receptor has been detected in progenitor CD34+ cells [23], and vitamin D3 has been  
34 described to promote the functionality of endothelial colony-forming cells [24], hence pointing to a role for

1 the vitamin D-CD34+ cells axis in CV homeostasis. Actually, vitamin D levels have been related to arterial  
2 stiffness and progenitor cell numbers in RA [25].

3 Whether myocardial dysfunction can be detected in patients with IJD free of traditional CV risk factors  
4 already in the early phases of the disease remains unknown. Moreover, although circulating CD34+ cells  
5 and vitamin D have been related to ventricular remodelling [23,26] and have been described to be altered  
6 in rheumatic conditions, the associations between STE, circulating CD34+ cells and vitamin D in IJD have  
7 not been investigated so far. Therefore, in the present study, we aimed (i) to evaluate the subclinical  
8 myocardial dysfunction by STE, as well as surrogate markers of subclinical CVD, in patients with very  
9 early IJD without traditional CV risk factors, (ii) to evaluate the associations of STE markers with disease  
10 activity, and (iii) to analyze the associations between myocardial dysfunction and the levels of circulating  
11 CD34+ cells and vitamin D.

12

## 1 MATERIALS AND METHODS

### 2 Ethics statement

3 Written informed consent was obtained from all subjects according to the Helsinki declaration and the  
4 retrospective observation was approved by the Ethics Committee of the University of Messina (Prot. N.  
5 11/17).

### 6 Subjects

7 Between October 2015 and May 2016, 514 outpatients were examined for the first time at the  
8 Rheumatology Division of the University of Messina and were referred for a clinical and instrumental  
9 screening.

10 To be selected for the study, subjects needed to fulfill the following inclusion criteria: (i) to be newly  
11 diagnosed, (ii) not being exposed to immunomodulatory treatments, (iii) to be free of traditional CV risk  
12 factors, and (iv) to meet the classification criteria for PsA or RA [27,28]. Extended definition of traditional  
13 CV risk factors and exclusion criteria can be found in the Supplementary Materials. After applying  
14 inclusion and exclusion criteria, only 35 subjects with PsA and 41 RA patients were considered eligible for  
15 this study. A group of 58 gender- and age-matched healthy subjects were enrolled (institution-based  
16 recruitment) using identical inclusion and exclusion criteria (where applicable) and were studied as the  
17 healthy control (HC) group.

18 Patients undergone a complete clinical examination during the clinical appointment, including DAS28-CRP  
19 calculation. In PsA patients, cutaneous lesions were examined and the Psoriasis Area and Severity Index  
20 (PASI) was calculated to assess the severity [29]. The cut-off for low disease activity was established in  
21 2.9 according to the literature [30].

22 At the first clinical evaluation, patients and controls underwent blood sampling by venipuncture and  
23 instrumental examination. Extensive chemical analyses were performed at the medical center after an  
24 overnight fasting in all subjects. Plasma lipids, glucose, fibrinogen, rheumatoid factor (RF) and ACPA were  
25 determined by routine methods. CRP was determined by a commercially available ELISA kit. The levels of  
26 25-hydroxyvitamin D3 (25-OH D) were measured by using high-performance liquid chromatography (Bio-  
27 Rad).

### 28 CD34+ cell count

29 Flow cytometry was used for the quantification of CD34+ frequency in peripheral blood samples as  
30 previously described [25,29]. Briefly, 50  $\mu$ L of peripheral blood was incubated with 10  $\mu$ L of PE-  
31 conjugated anti-human CD34 antibody (BD) in TRUCOUNT tubes (BD) for 15 minutes. Sample acquisition  
32 and analysis were performed by in a FACSCalibur cytometer using CELLQuest as software. Non-viable  
33 cells were excluded according to 7-amino-actinomycin D (7-AAD; BD Pharmingen) staining. Circulating

1 cells that expressed the stem cell antigen CD34 were defined as progenitor haematopoietic CD34+ cells,  
2 and estimated and counted (cells/ $\mu$ L) as absolute count as previously described [25,29].

### 3 **Measurement of cIMT and arterial stiffness indices**

4 Carotid echo Doppler scan and arterial stiffness assessments were performed using a Vivid 3 Expert  
5 ultrasound machine equipped with a 7–15 MHz linear array transducer (GE Healthcare) according to  
6 ESC/ESH guidelines [31] (see Supplementary Materials). The intraobserver/interobserver variability of IMT  
7 and PWV measurements were 1.13/3.51% and 1.23/3.86%, respectively. Intraclass Correlation Coefficient  
8 (ICC) for PWV yielded a value of 0.993 (95% CI: 0.991 – 0.995).

### 9 **Echocardiography study**

10 Echocardiography examination was performed using a VIVID-7 ultrasound machine (GE Vingmed  
11 Ultrasound) equipped with a phased-array transducer, and stored on a dedicated workstation (EchoPAC,  
12 version 8.0.0) for off-line analyses. All measurements (LV, E/A ratio, LVMI and LV mass) were performed  
13 according to the recommendations of the American Society of Echocardiography on three averaged  
14 cardiac cycles [29] (see Supplementary Materials for detailed definitions). To complete the analysis of LV  
15 systolic function, myocardial deformation was assessed by speckle tracking echocardiography and  
16 automated function imaging for the evaluation of global and regional longitudinal (GLS) and circumferential  
17 (GCS) strain, as previously described [29]. Automated function imaging was performed on apical long-  
18 axis, 4-chamber, and 2-chamber views, following an on-screen guided workflow. The results are presented  
19 as a bull's-eye display showing color-coded and numeric values for peak systolic GLS and GCS. A  
20 detailed technique was previously described [29]. A frame rate >70 fps was employed. Strain analysis was  
21 performed offline by using Echopac. Endocardial border was manually traced from apical views,  
22 automatically obtaining the calculation of a region of interest comprised between endocardial and  
23 epicardial layers. Tracking quality was verified for each segment and low quality images were excluded.  
24 Global values of longitudinal strain from each apical view were calculated through an Automated Function  
25 Imaging analysis. LV twist was defined by the difference (in degrees) between apical rotation and basal  
26 rotation at isochronal time points. The intraobserver/interobserver variability of GLS and GCS  
27 measurements were 0.90/3.49% and 1.78/5.97%, respectively. ICC analyses for GLS yielded a value of  
28 0.982 (0.975 – 0.987) whereas that of GCS was 0.971 (0.960 – 0.979).

### 29 **Statistical analysis**

30 Variables were summarized as mean  $\pm$  standard deviation or n(%), unless otherwise stated. Variables  
31 were checked for normality by the Kolmogorov-Smirnov test, and non-parametric tests (Mann-Whitney U  
32 and Kruskal-Wallis tests) were used to analyze differences among groups. Correlations were assessed by  
33 the Spearman's test. Multivariate regression analyses were performed to assess the contribution of  
34 different independent covariates to the dependent variable. Non-normal variables were log-transformed

1 prior to be included in the models. A Principal Component Analysis (PCA) was performed as an integrative  
2 approach to avoid any potential collinearity bias and to retain the maximum of the variance from the  
3 demographical, clinical and traditional risk-related variables. The number of components (correlation  
4 method) retained was based on eigenvalues ( $>1$ ) and loadings greater than 0.5 were used to identify the  
5 variables comprising a component. Principal component scores were calculated for each patient and used  
6 for multivariate regression analysis. Intraclass Correlation Coefficients (ICC) were computed to further  
7 assess the reproducibility of the imaging parameters made by different observers. ICC estimates and their  
8 95% confident intervals were calculated based on a mean-rating ( $k = 3$ ), absolute-agreement, two-way  
9 mixed-effects models. A  $p < 0.050$  was used to denote statistical significance. SPSS 17.0 and R v. 3.3.1  
10 statistical packages were used to perform statistical analyses.

11



## 1 RESULTS

### 2 Subclinical CV disease and myocardial dysfunction in early RA and PsA

3 The characteristics of the subjects recruited for this study are summarized in Table 1. No differences were  
4 observed in age ( $p=0.170$ ), gender ( $p=0.130$ ) or BMI ( $p=0.787$ ) among study groups. Although slight  
5 differences in HDL-cholesterol in RA, the total/HDL-cholesterol ratio (atherogenic index) did not differ  
6 among groups and all individuals were free of previously diagnosed traditional CV risk factors  
7 (hypercholesterolemia/dyslipidemia, hypertension, diabetes, smoking habit and obesity). Similarly, no  
8 differences in creatinine levels and estimated GFR were noted. Finally, both PsA and RA patients were  
9 recruited at onset and they were not exposed to any medication at the time of sampling.

10 cIMT was found to be increased in RA (Table 1): 25 (60.9%) of the RA patients exhibited a cIMT>0.90  
11 mm, compared to 4 (11.4%) and 8 (13.7%) of the PsA and HC groups, respectively ( $p<0.0001$ ).  
12 Additionally, the PWV was found to be impaired in both PsA and RA (Table 1). Moreover, PWV was  
13 correlated with DAS28 ( $r=0.322$ ,  $p=0.055$ ), CRP ( $r=0.446$ ,  $p=0.007$ ) and BASDAI ( $r=0.340$ ,  $p=0.049$ ) in  
14 PsA. Similarly, it was found to parallel DAS28 ( $r=0.371$ ,  $p=0.017$ ), ESR ( $r=0.456$ ,  $p=0.003$ ), CRP ( $r=0.384$ ,  
15  $p=0.013$ ) and duration of the symptoms ( $r=0.337$ ,  $p=0.036$ ) in the RA group.

16 Finally, RA patients exhibited a significant impairment of GLS and GCS compared to HC, whereas GLS  
17 was also altered in PsA. Importantly, DAS28 was positively correlated to GLS ( $r=0.908$ ,  $p<0.001$ ) and  
18 GCS ( $r=0.868$ ,  $p<0.001$ ) in RA. Similar associations were retrieved for ESR, CRP and fibrinogen (data not  
19 shown). Of note, although GCS was not significantly different in PsA compared to HC, a positive  
20 correlation with DAS28 ( $r=0.438$ ,  $p=0.008$ ) was observed. Notably, standard echocardiographic  
21 examination showed no differences in LV diameters, volumes, wall thickness and EF among individuals  
22 (Table 1).

23 Overall, all these results confirm an increased prevalence of subclinical CV disease and myocardial  
24 dysfunction in the early stages of inflammatory joint diseases in the absence of established traditional CV  
25 risk factors. Surrogate markers of subclinical CV disease and myocardial dysfunction were strongly  
26 associated with the inflammatory burden, hence suggesting a role for inflammation in this scenario.

### 27 Subclinical myocardial dysfunction: role for disease features

28 Further analyses were conducted to evaluate the associations between the subclinical myocardial  
29 dysfunction and disease features in PsA and RA.

30 Because of the previous findings in relation to the disease activity, PsA patients were classified as low  
31 (DAS28<2.9) or high (DAS28>2.9) disease activity (Table 2). High disease activity was associated with  
32 altered GCS and PWV. Moreover, a trend towards an impaired GLS was also noted. PsA patients with  
33 high disease activity exhibited differences in GCS, GLS and PWV when compared to HC, but these

1 differences were not observed in their low disease activity-counterparts. Interestingly, GLS was found to  
2 be a predictor of cIMT in PsA patients (B[95% CI],  $p$ : 0.019 [0.002, 0.035],  $p=0.027$ ) after adjusting for age,  
3 BMI, disease activity and inflammation parameters (ESR, CRP and fibrinogen), PWV and vitamin D.

4 Equivalent results were obtained when RA patients were stratified according to disease activity  
5 (Supplementary Table 1). The association between disease activity and subclinical myocardial dysfunction  
6 was analyzed by multivariate regression analyses in RA patients. Importantly, DAS28 was found to be the  
7 only predictor of GLS and GCS in RA, even after adjusting for potential confounders (Table 3). Therefore,  
8 in order to avoid any potential collinearity bias among the features analyzed, a PCA was conducted  
9 including age, BMI, DAS28, CRP, ESR, fibrinogen, total-, HDL- and LDL-cholesterol, SBP, DBP and  
10 duration on the symptoms (Table 4). PCA revealed a good adequacy of the data (KMO = 0.523, Barlett  
11 sphericity test  $p=2.03 \cdot 10^{-26}$ ) and 4 components were obtained, explaining 69.2% of the total variance.  
12 Variables included in each component based on their loadings were as follows: component 1 (DAS28,  
13 CRP, ESR and fibrinogen), component 2 (age, BMI, total- and LDL-cholesterol), component 3 (SBP and  
14 DBP) and component 4 (HDL-cholesterol and duration of the symptoms). Then, a good separation  
15 between disease-related and other traditional risk-related factors was achieved. Finally, the association  
16 between these components and the myocardial dysfunction was studied by multivariate regression  
17 analyses. Interestingly, only disease-related features (component 1) were predictors of GLS and GCS in  
18 RA patients, hence confirming our previous findings.

19 All these results reinforce the relevance of the inflammatory burden in the subclinical impairment of the  
20 myocardial functionality in IJD already in the very early stage of these conditions. In addition to the strong  
21 association being observed in RA, where GCS and GLS were notably impaired, a clear link was also  
22 found in PsA patients with high disease activity. Moreover, GLS was found to be associated with cIMT in  
23 these patients. Overall, our findings clearly point to disease activity as the driver of STE impairment in IJD,  
24 independently of clinical diagnosis.

### 25 **Altered CD34+ progenitor cells and vitamin D: associations with subclinical myocardial** 26 **dysfunction**

27 Finally, we studied whether altered circulating CD34+ progenitor cells or vitamin D levels may underlie the  
28 subclinical myocardial dysfunction in IJD.

29 Vitamin D was negatively associated with cIMT in HC ( $r=-0.308$ ,  $p=0.026$ ) but not in IJD patients, where  
30 decreased levels were found (Table 1), hence pointing to a link between vitamin D and subclinical  
31 atherosclerosis. This correlation was also observed in PsA patients with low disease activity (DAS28<2.9)  
32 ( $r=-0.636$ ,  $p=0.035$ ), but not in those with higher disease activity ( $r=0.185$ ,  $p=0.387$ ).

33 Moreover, vitamin D levels and DAS28 were independent predictors of CD34+ cells in PsA, whereas  
34 vitamin D and duration of the symptoms did in RA (Table 5). Circulating CD34+ cells were decreased in

- 1 RA (Table 1), negative correlations with STE parameters being disclosed (GCS:  $r=-0.291$ ,  $p=0.068$ ; GLS:
- 2  $r=-0.301$ ,  $p=0.057$ ).
- 3 All these results suggest that vitamin D was independently associated with circulating CD34+ levels in IJD.
- 4 CD34+ cells paralleled STE parameters in RA, but additional studies are required.
- 5

ACCEPTED MANUSCRIPT

## 1 DISCUSSION

2 Chronic rheumatic conditions, such as RA and PsA, are associated with enhanced atherosclerosis and  
3 impaired endothelial function [32]. Since these alterations occur shortly after disease onset and traditional  
4 CV risk factors cannot solely account for this increased risk, a role for inflammation has been proposed  
5 [33]. In the present report, we have demonstrated an association between the disease activity and  
6 biomarkers of endothelial function, atherosclerosis and subclinical myocardial function in PsA and RA  
7 during the early phase of the disease. These alterations were linked to the inflammatory burden, disease  
8 activity being the main predictor of impaired myocardial dysfunction irrespectively of disease diagnosis.  
9 Importantly, altered levels of CD34+ cells and vitamin D were found in both conditions. Overall, our results  
10 clearly confirm a role for the inflammatory burden in both subclinical endothelial and myocardial  
11 dysfunction in these patients, hence providing a rationale for the utilization of STE assessment for the CV  
12 risk assessment in IJD.

13 The most interesting result from our study was the impaired myocardial functionality in both RA and PsA  
14 patients in the very early phase of the disease. This finding suggests that patients with IJD exhibit not only  
15 an accelerated atherosclerosis development in the peripheral vasculature but also myocardial dysfunction  
16 already at disease onset. Although some authors have previously reported a reduced LV myocardial  
17 deformation in RA patients [7,34,35], most of these studies have been focused on patients with long-  
18 standing disease and increased prevalence of traditional CV risk factors. Midtbø and colleagues reported  
19 an impaired myocardial function in RA patients with respect to controls, but active RA was related to a  
20 higher prevalence of hypertension and diabetes as compared with patients in remission and controls [36].  
21 Therefore, it is likely that the impairment in GLS observed in patients with active RA or PsA in that study  
22 may be a consequence of accumulated myocardial damage in the context of these risk factors. Therefore,  
23 our results expand the current knowledge of myocardial dysfunction in IJD by confirming its very early  
24 onset in these conditions, independently of disease duration, traditional CV risk factors and treatment-  
25 related effects. Moreover, we observed for the first time that patients with a more pronounced  
26 inflammatory status, assessed by CRP, ESR and fibrinogen, and mainly with a more activity status, had a  
27 stronger alteration in myocardial function irrespectively of their IJD (RA or PsA), suggesting that  
28 inflammation could be the principal driver in impairing myocardial function. Interestingly, other studies  
29 have found an association between the exposure to different immunomodulatory drugs and improved  
30 myocardial LV strain markers [7,34,35].

31 Disease activity was found to be associated with GLS and GCS in both RA and PsA in univariate and  
32 multivariate analysis, therefore confirming a crucial role of the inflammatory burden in the development of  
33 such functional alterations. This idea is in line with the protective effect of the low disease activity to  
34 reduce CV risk burden in these conditions [5]. In fact, Solomon and colleagues have revealed that an  
35 accumulated high disease activity over time was associated with the development of CV disease in RA  
36 [37]. Interestingly, despite exhibiting a comparable duration of the symptoms, a stronger impairment of the

1 endothelial and myocardial function was observed in RA compared to PsA. Moreover, the duration of the  
2 symptoms itself was found to be associated with PWV and CD34+ count in RA, but not in PsA. Overall,  
3 our findings are in line with an enhanced inflammatory burden in RA compared to PsA. However, the  
4 relevance of the inflammatory burden in PsA cannot be underestimated. Although a lower CV risk has  
5 been attributed to this condition compared to other IJD [6,38], a substantial increased risk is still found  
6 compared to the general population. Actually, PsA patients with high disease activity exhibited impaired  
7 PWV and myocardial dysfunction compared to HC in our study. Of note, GLS was found to be a predictor  
8 of cIMT in PsA patients, in line with previous studies in psoriasis [39]. Like arterial stiffness, STE  
9 parameters are functional surrogate markers of CV risk. As functional measurements, their alteration is  
10 likely to be reversible. Taking into account the association between myocardial dysfunction and disease  
11 activity, an appropriate control of the inflammatory burden would be advisable in IJD patients. This is  
12 especially relevant during the very early stage of the disease, in line with the concept of the therapeutic  
13 'window of opportunity'. Taken together, our results support the need of a prompt and effective control of  
14 disease activity for CVD prevention in IJD.

15 It is noteworthy that among STE parameters, GLS was impaired in both PsA and RA, whereas GCS was  
16 only altered in RA. Interestingly, GLS was reported to be a more sensitive marker than circumferential or  
17 radial strains [12]. Upon pathological traits, subendocardial myocardial fibers (longitudinally orientated and  
18 thus responsible of the longitudinal contraction) are affected earlier than subepicardial fibers (hence  
19 accounting for unchanged circumferential and radial strains). Then, a more pronounced systemic  
20 inflammation in RA patients can explain the impairment of both STE parameters compared to their PsA  
21 counterparts. Equivalent results were observed when PsA patients were classified by disease activity.  
22 These results reinforce our previous findings on inflammatory burden and myocardial dysfunction. The  
23 elucidation of the best LV myocardial strain marker according to IJD progression warrant further studies.

24 Our findings stress the need of an appropriate monitoring of disease activity-mediated myocardial  
25 dysfunction in IJD and, presumably, other inflammatory conditions. Recently, other authors have reported  
26 that subclinical alterations in the myocardium can be present in other autoimmune rheumatic diseases,  
27 such as sarcoidosis [40,41]. Although a number of techniques for CV risk assessment and management  
28 have been proposed [32,42,43], most of them are focused on endothelial dysfunction and atherosclerosis,  
29 whereas myocardial functionality has not received enough attention. Despite the recent advances in the  
30 CV risk management, there is still a considerable room for improvement, hence supporting the need for  
31 additional tools. Actually, the research agenda of latest EULAR recommendations for CV risk  
32 management in IJD proposes the study of cardiac abnormalities as well as the inclusion of additional CV  
33 risk biomarkers to assist in the clinical setting [5]. Taking into account all these ideas, strain imaging by  
34 STE can be proposed as a promising tool to address this clinical unmet need. Strain imaging has proved  
35 to be a valuable non-invasive opportunity for identifying subclinical CVD [8,44,45], being able to detect  
36 subtle LV myocardial dysfunction in an objective and angle-independent fashion. In fact, we have

1 previously reported that STE was able to identify very early mechanical changes in hypertensive patients  
2 prior to the occurrence of LV hypertrophy [46], thereby reinforcing its applicability for early assessment  
3 and patient stratification.

4 Finally, the role of CD34+ cells and vitamin D as biomarkers was analyzed. Interestingly, vitamin D was a  
5 predictor of circulating CD34+ cells levels in IJD, even after adjusting for disease activity, hence  
6 suggesting that vitamin D levels can be a surrogate marker of impaired CD34+ levels. Our findings pose  
7 the question as whether vitamin D supplementation could counteract the disease activity-mediated  
8 detrimental effects on CD34+ cells and myocardial dysfunction. Chronic inflammation leads to oxidative  
9 stress, myocyte dysfunction and increased fibroblast activity causing myocardial collagen deposition and  
10 interstitial fibrosis [47–49], hence hampering myocardial contraction [50]. Furthermore, vitamin D  
11 deficiency has been related to cardiac tissue remodeling [51] and LV hypertrophy [52]. Since inflammatory  
12 pathways and oxidative stress seems to underlie the myocardial dysfunction, and taken into account the  
13 effects of vitamin D on tissue remodeling [52] and on anti-inflammatory and anti-oxidative pathways  
14 [53,54], the potential beneficial effects of vitamin D on myocardial dysfunction warrants future studies.

15 In conclusion, the results herein presented expand the current knowledge about the subclinical CV  
16 alterations in IJD. To the best of our knowledge, this is the first study where myocardial alterations are  
17 analyzed in patients with very early IJD, which represents a major strength of our study. Although a  
18 number of previous studies have described an increased prevalence of atherosclerosis and endothelial  
19 dysfunction, our results went further by reporting the LV myocardial strain alterations in IJD patients,  
20 regardless of disease diagnosis. Additionally, these pathological findings were found in middle-aged  
21 patients already at disease onset with preserved LVEF, in the absence of traditional CV risk factors and  
22 related to disease activity. Being our patients not exposed to any DMARD at recruitment allowed us to rule  
23 out a potential medication-related confounding effect in our findings. A number of limitations of the present  
24 study must also be remarked. First, although stringent criteria were used to control for traditional CV risk  
25 factors, lifestyle factors such as diet [55] or physical activity were not appraised. However, there is not a  
26 strong evidence pointing to these factors as potential bias for STE in the current literature. Second,  
27 because of the cross-sectional design of our study, our findings require confirmation in prospective follow-  
28 up studies to evaluate the clinical relevance of the subclinical myocardial impairment in IJD patients. Third,  
29 although our data support a good reliability and reproducibility of the STE assessments, certain variability  
30 may be expected for multi-centric comparisons [56]. Then, standardization of the image processing and  
31 analysis algorithms as well as the validation of appropriate cut-off values are required to guide its routine  
32 clinical utilization in the future.

33

34

**1 Conflict of interest**

2 The authors declared they do not have anything to disclose regarding conflict of interest with respect to  
3 this manuscript.

4

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9

**10 Author contributions**

11 ALG, JRC and GM conceived the study, analyzed and interpreted the data and drafted the manuscript.  
12 COA, GD, CZ, SL and MA were in charge of patient recruitment, clinical data collection and clinical data  
13 analyses. AS (Ana Suárez) and AS (Antonino Saitta) participated in the conception, design and critical  
14 revision of the results. All the authors participated in the discussion of the results and literature search. All  
15 authors approved the final version of the manuscript.

16

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## 1 REFERENCES

- 2 [1] A. Jamnitski, I.M. Visman, M.J.L. Peters, M. Boers, B.A.C. Dijkmans, M.T. Nurmohamed,  
3 Prevalence of cardiovascular diseases in psoriatic arthritis resembles that of rheumatoid arthritis.,  
4 *Ann. Rheum. Dis.* 70 (2011) 875–6. doi:10.1136/ard.2010.136499.
- 5 [2] C. Han, D.W. Robinson, M. V Hackett, L.C. Paramore, K.H. Fraeman, M. V Bala, Cardiovascular  
6 disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing  
7 spondylitis., *J. Rheumatol.* 33 (2006) 2167–72. <http://www.ncbi.nlm.nih.gov/pubmed/16981296>.
- 8 [3] E. Bartoloni, Y. Shoenfeld, R. Gerli, Inflammatory and autoimmune mechanisms in the induction of  
9 atherosclerotic damage in systemic rheumatic diseases: Two faces of the same coin, *Arthritis*  
10 *Care Res.* 63 (2011) 178–183. doi:10.1002/acr.20322.
- 11 [4] I.D. del Rincón, K. Williams, M.P. Stern, G.L. Freeman, a Escalante, High incidence of  
12 cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk  
13 factors., *Arthritis Rheum.* 44 (2001) 2737–2745. doi:10.1002/1529-0131(200112)44:12<2737::AID-  
14 ART460>3.0.CO;2-#.
- 15 [5] R. Agca, S.C. Heslinga, S. Rollefstad, M. Heslinga, I.B. McInnes, M.J.L. Peters, T.K. Kvien, M.  
16 Dougados, H. Radner, F. Atzeni, J. Primdahl, A. Södergren, S. Wallberg Jonsson, J. van Rompay,  
17 C. Zabalán, T.R. Pedersen, L. Jacobsson, K. de Vlam, M.A. Gonzalez-Gay, A.G. Semb, G.D.  
18 Kitas, Y.M. Smulders, Z. Szekanecz, N. Sattar, D.P.M. Symmons, M.T. Nurmohamed, EULAR  
19 recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis  
20 and other forms of inflammatory joint disorders: 2015/2016 update., *Ann. Rheum. Dis.* 76 (2017)  
21 17–28. doi:10.1136/annrheumdis-2016-209775.
- 22 [6] S.L. Kristensen, I.B. McInnes, N. Sattar, Psoriasis, psoriatic arthritis and cardiovascular risk: are  
23 we closer to a clinical recommendation?, *Ann. Rheum. Dis.* 74 (2015) 321–322.  
24 doi:10.1136/annrheumdis-2014-206617.
- 25 [7] N.M. Fine, C.S. Crowson, G. Lin, J.K. Oh, H.R. Villarraga, S.E. Gabriel, Evaluation of myocardial  
26 function in patients with rheumatoid arthritis using strain imaging by speckle-tracking  
27 echocardiography., *Ann. Rheum. Dis.* 73 (2014) 1833–9. doi:10.1136/annrheumdis-2013-203314.
- 28 [8] S. Langeland, J. D'hooge, P.F. Wouters, H.A. Leather, P. Claus, B. Bijnens, G.R. Sutherland,  
29 Experimental validation of a new ultrasound method for the simultaneous assessment of radial  
30 and longitudinal myocardial deformation independent of insonation angle., *Circulation.* 112 (2005)  
31 2157–62. doi:10.1161/CIRCULATIONAHA.105.554006.
- 32 [9] A.M. Shah, B. Claggett, N.K. Sweitzer, S.J. Shah, I.S. Anand, L. Liu, B. Pitt, M.A. Pfeffer, S.D.  
33 Solomon, Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved  
34 Ejection Fraction and the Impact of Spironolactone., *Circulation.* 132 (2015) 402–14.  
35 doi:10.1161/CIRCULATIONAHA.115.015884.
- 36 [10] C.-L. Hung, A. Verma, H. Uno, S.-H. Shin, M. Bourgoun, A.H. Hassanein, J.J. McMurray, E.J.  
37 Velazquez, L. Kober, M.A. Pfeffer, S.D. Solomon, VALIANT investigators, Longitudinal and  
38 circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction., *J.*  
39 *Am. Coll. Cardiol.* 56 (2010) 1812–22. doi:10.1016/j.jacc.2010.06.044.
- 40 [11] C.G. Santos-Gallego, T.P. Vahl, G. Goliash, B. Picatoste, T. Arias, K. Ishikawa, I.U. Njerve, J.  
41 Sanz, J. Narula, P.P. Sengupta, R.J. Hajjar, V. Fuster, J.J. Badimon, Sphingosine-1-Phosphate  
42 Receptor Agonist Fingolimod Increases Myocardial Salvage and Decreases Adverse  
43 Postinfarction Left Ventricular Remodeling in a Porcine Model of Ischemia/Reperfusion.,  
44 *Circulation.* 133 (2016) 954–66. doi:10.1161/CIRCULATIONAHA.115.012427.
- 45 [12] K.H. Haugaa, T. Edvardsen, Global longitudinal strain: the best biomarker for predicting prognosis  
46 in heart failure?, *Eur. J. Heart Fail.* 18 (2016) 1340–1341. doi:10.1002/ehfj.632.



- 1 [13] Q. Shang, L.-S. Tam, J.E. Sanderson, J.-P. Sun, E.K.-M. Li, C.-M. Yu, Increase in ventricular-  
2 arterial stiffness in patients with psoriatic arthritis., *Rheumatology (Oxford)*. 51 (2012) 2215–23.  
3 doi:10.1093/rheumatology/kes213.
- 4 [14] V. Abella, M. Scotece, J. Conde, V. López, V. Lazzaro, J. Pino, J.J. Gómez-Reino, O. Gualillo,  
5 Adipokines, metabolic syndrome and rheumatic diseases., *J. Immunol. Res.* 2014 (2014) 343746.  
6 doi:10.1155/2014/343746.
- 7 [15] E. Choy, K. Ganeshalingam, A.G. Semb, Z. Szekanecz, M. Nurmohamed, Cardiovascular risk in  
8 rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk  
9 predictors and the impact of treatment., *Rheumatology (Oxford)*. 53 (2014) 2143–54.  
10 doi:10.1093/rheumatology/keu224.
- 11 [16] I.A. Ku, J.B. Imboden, P.Y. Hsue, P. Ganz, Rheumatoid arthritis: model of systemic inflammation  
12 driving atherosclerosis., *Circ. J.* 73 (2009) 977–85.  
13 <http://www.ncbi.nlm.nih.gov/pubmed/19430165>.
- 14 [17] R. Ramonda, A. Lo Nigro, V. Modesti, L. Nalotto, E. Musacchio, L. Iaccarino, L. Punzi, A. Doria,  
15 Atherosclerosis in psoriatic arthritis., *Autoimmun. Rev.* 10 (2011) 773–8.  
16 doi:10.1016/j.autrev.2011.05.022.
- 17 [18] J. Rodríguez-Carrio, P. López, A. Suárez, Endothelial Progenitor Cells as mediators of the  
18 crosstalk between vascular repair and immunity: lessons from systemic autoimmune diseases.,  
19 *Curr. Med. Chem.* (2017). doi:10.2174/0929867324666170428110311.
- 20 [19] Y. Yamaguchi, M. Kuwana, Proangiogenic hematopoietic cells of monocytic origin: roles in  
21 vascular regeneration and pathogenic processes of systemic sclerosis., *Histol. Histopathol.* 28  
22 (2013) 175–83. doi:10.14670/HH-28.175.
- 23 [20] C.O. Aragona, E. Imbalzano, F. Mamone, V. Cairo, A. Lo Gullo, A. D'Ascola, M.A. Sardo, M.  
24 Scuruchi, G. Basile, A. Saitta, G. Mandraffino, Endothelial Progenitor Cells for Diagnosis and  
25 Prognosis in Cardiovascular Disease., *Stem Cells Int.* 2016 (2016) 8043792.  
26 doi:10.1155/2016/8043792.
- 27 [21] K. Jujo, M. Ii, D.W. Losordo, Endothelial progenitor cells in neovascularization of infarcted  
28 myocardium., *J. Mol. Cell. Cardiol.* 45 (2008) 530–44. doi:10.1016/j.yjmcc.2008.08.003.
- 29 [22] T. Takahashi, C. Kalka, H. Masuda, D. Chen, M. Silver, M. Kearney, M. Magner, J.M. Isner, T.  
30 Asahara, Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial  
31 progenitor cells for neovascularization., *Nat. Med.* 5 (1999) 434–8. doi:10.1038/7434.
- 32 [23] S. Maltais, L.P. Perrault, H.Q. Ly, The bone marrow-cardiac axis: role of endothelial progenitor  
33 cells in heart failure., *Eur. J. Cardiothorac. Surg.* 39 (2011) 368–74.  
34 doi:10.1016/j.ejcts.2010.04.022.
- 35 [24] M. Grundmann, M. Haidar, S. Placzko, R. Niendorf, N. Darashchonak, C.A. Hubel, F. von Versen-  
36 Höynck, Vitamin D improves the angiogenic properties of endothelial progenitor cells., *Am. J.*  
37 *Physiol. Cell Physiol.* 303 (2012) C954-62. doi:10.1152/ajpcell.00030.2012.
- 38 [25] A. Lo Gullo, G. Mandraffino, G. Bagnato, C.O. Aragona, E. Imbalzano, A. D'Ascola, F. Rotondo, A.  
39 Cinquegrani, E. Mormina, C. Saitta, A.G. Versace, M.A. Sardo, R. Lo Gullo, S. Loddo, A. Saitta,  
40 Vitamin D Status in Rheumatoid Arthritis: Inflammation, Arterial Stiffness and Circulating  
41 Progenitor Cell Number., *PLoS One.* 10 (2015) e0134602. doi:10.1371/journal.pone.0134602.
- 42 [26] H.B. Assalin, B.P. Rafacho, P.P. dos Santos, L.P. Ardisson, M.G. Roscani, F. Chiuso-Minicucci,  
43 L.F. Barbisan, A.A.H. Fernandes, P.S. Azevedo, M.F. Minicucci, L.A. Zornoff, S.A.R. de Paiva,  
44 Impact of the length of vitamin D deficiency on cardiac remodeling., *Circ. Heart Fail.* 6 (2013) 809–  
45 16. doi:10.1161/CIRCHEARTFAILURE.112.000298.
- 46 [27] D. Aletaha, T. Neogi, A.J. Silman, J. Funovits, D.T. Felson, C.O. Bingham, N.S. Birnbaum, G.R.

- 1 Burmester, V.P. Bykerk, M.D. Cohen, B. Combe, K.H. Costenbader, M. Dougados, P. Emery, G.  
 2 Ferraccioli, J.M.W. Hazes, K. Hobbs, T.W.J. Huizinga, A. Kavanaugh, J. Kay, T.K. Kvien, T. Laing,  
 3 P. Mease, H.A. Ménard, L.W. Moreland, R.L. Naden, T. Pincus, J.S. Smolen, E. Stanislawski-  
 4 Biernat, D. Symmons, P.P. Tak, K.S. Upchurch, J. Vencovský, F. Wolfe, G. Hawker, 2010  
 5 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European  
 6 League Against Rheumatism collaborative initiative, *Arthritis Rheum.* 62 (2010) 2569–2581.  
 7 doi:10.1002/art.27584.
- 8 [28] W. Taylor, D. Gladman, P. Helliwell, A. Marchesoni, P. Mease, H. Mielants, CASPAR Study  
 9 Group, Classification criteria for psoriatic arthritis: development of new criteria from a large  
 10 international study., *Arthritis Rheum.* 54 (2006) 2665–73. doi:10.1002/art.21972.
- 11 [29] G. Mandraffino, C.O. Aragona, G. Basile, V. Cairo, F. Mamone, C. Morace, A. D'Ascola, A.  
 12 Alibrandi, A. Lo Gullo, S. Loddo, A. Saitta, E. Imbalzano, CD34+ cell count predicts long lasting life  
 13 in the oldest old., *Mech. Ageing Dev.* 164 (2017) 139–145. doi:10.1016/j.mad.2017.03.003.
- 14 [30] R.M. Fleischmann, D. van der Heijde, P. V Gardiner, A. Szumski, L. Marshall, E. Bananis, DAS28-  
 15 CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not  
 16 interchangeable, *RMD Open.* 3 (2017) e000382. doi:10.1136/rmdopen-2016-000382.
- 17 [31] G. Mancía, G. De Backer, A. Dominiczak, R. Cifkova, R. Fagard, G. Germano, G. Grassi, A.M.  
 18 Heagerty, S.E. Kjeldsen, S. Laurent, K. Narkiewicz, L. Ruilope, A. Rynkiewicz, R.E. Schmieder,  
 19 H.A.S. Boudier, A. Zanchetti, ESH-ESC Task Force on the Management of Arterial Hypertension,  
 20 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task  
 21 Force on the Management of Arterial Hypertension., *J. Hypertens.* 25 (2007) 1751–62.  
 22 doi:10.1097/HJH.0b013e3282f0580f.
- 23 [32] S. Castañeda, M.T. Nurmohamed, M.A. González-Gay, Cardiovascular disease in inflammatory  
 24 rheumatic diseases., *Best Pract. Res. Clin. Rheumatol.* 30 (2016) 851–869.  
 25 doi:10.1016/j.berh.2016.10.006.
- 26 [33] P.H. Dessen, B.I. Joffe, M.G. Veller, B. a Stevens, M. Tobias, K. Reddi, A.E. Stanwix, Traditional  
 27 and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid  
 28 arthritis., *J. Rheumatol.* 32 (2005) 435–42. doi:0315162X-32-435 [pii].
- 29 [34] I. Ikonomidis, S. Tzortzis, I. Andreadou, I. Paraskevidis, C. Katseli, P. Katsimbri, G. Pavlidis, J.  
 30 Parissis, D. Kremastinos, M. Anastasiou-Nana, J. Lekakis, Increased benefit of interleukin-1  
 31 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary  
 32 artery disease and coexisting rheumatoid arthritis., *Circ. Cardiovasc. Imaging.* 7 (2014) 619–28.  
 33 doi:10.1161/CIRCIMAGING.113.001193.
- 34 [35] I. Ikonomidis, S. Tzortzis, J. Lekakis, I. Paraskevidis, I. Andreadou, M. Nikolaou, T. Kaplanoglou,  
 35 P. Katsimbri, G. Skarantavos, P. Soucacos, D.T. Kremastinos, Lowering interleukin-1 activity with  
 36 anakinra improves myocardial deformation in rheumatoid arthritis., *Heart.* 95 (2009) 1502–7.  
 37 doi:10.1136/hrt.2009.168971.
- 38 [36] H. Midtbø, A.G. Semb, K. Matre, T.K. Kvien, E. Gerds, Disease activity is associated with reduced  
 39 left ventricular systolic myocardial function in patients with rheumatoid arthritis., *Ann. Rheum. Dis.*  
 40 76 (2017) 371–376. doi:10.1136/annrheumdis-2016-209223.
- 41 [37] D.H. Solomon, G.W. Reed, J.M. Kremer, J.R. Curtis, M.E. Farkouh, L.R. Harrold, M.C. Hochberg,  
 42 P. Tsao, J.D. Greenberg, Disease Activity in Rheumatoid Arthritis and the Risk of Cardiovascular  
 43 Events, *Arthritis Rheumatol.* 67 (2015) 1449–1455. doi:10.1002/art.39098.
- 44 [38] B. Fernández-Gutiérrez, P.P. Perrotti, J.P. Gisbert, E. Domènech, A. Fernández-Nebro, J.D.  
 45 Cañete, C. Ferrándiz, J. Tornero, V. García-Sánchez, J. Panés, E. Fonseca, F. Blanco, J.  
 46 Rodríguez-Moreno, P. Carreira, A. Julià, S. Marsal, L. Rodríguez-Rodríguez, IMID Consortium,  
 47 Cardiovascular disease in immune-mediated inflammatory diseases: A cross-sectional analysis of  
 48 6 cohorts., *Medicine (Baltimore).* 96 (2017) e7308. doi:10.1097/MD.0000000000007308.

- 1 [39] I. Ikonomidis, G. Makavos, E. Papadavid, M. Varoudi, I. Andreadou, K. Gravanis, K.  
 2 Theodoropoulos, G. Pavlidis, H. Triantafyllidi, J. Parissis, I. Paraskevaidis, D. Rigopoulos, J.  
 3 Lekakis, Similarities in coronary function and myocardial deformation between psoriasis and  
 4 coronary artery disease: the role of oxidative stress and inflammation., *Can. J. Cardiol.* 31 (2015)  
 5 287–95. doi:10.1016/j.cjca.2014.11.002.
- 6 [40] S. Kul, G.A. Kutlu, T.S. Guvenc, M. Kavas, K. Demircioglu, Y. Yilmaz, H.I. Yakar, A. Kanbay, S.  
 7 Boga, M. Caliskan, Coronary flow reserve is reduced in sarcoidosis., *Atherosclerosis.* 264 (2017)  
 8 115–121. doi:10.1016/j.atherosclerosis.2017.05.005.
- 9 [41] C.G. Santos-Gallego, A.J. Weiss, J. Sanz, Non-cardiac sarcoid actually affects the heart by  
 10 reducing coronary flow reserve., *Atherosclerosis.* 264 (2017) 74–76.  
 11 doi:10.1016/j.atherosclerosis.2017.07.006.
- 12 [42] M.A. González-Gay, C. González-Juanatey, J. Llorca, Carotid ultrasound in the cardiovascular risk  
 13 stratification of patients with rheumatoid arthritis: when and for whom?, *Ann. Rheum. Dis.* 71  
 14 (2012) 796–8. doi:10.1136/annrheumdis-2011-201209.
- 15 [43] G.J. Fent, J.P. Greenwood, S. Plein, M.H. Buch, The role of non-invasive cardiovascular imaging  
 16 in the assessment of cardiovascular risk in rheumatoid arthritis: where we are and where we need  
 17 to be., *Ann. Rheum. Dis.* 76 (2017) 1169–1175. doi:10.1136/annrheumdis-2016-209744.
- 18 [44] J. Gorcsan, H. Tanaka, Echocardiographic assessment of myocardial strain., *J. Am. Coll. Cardiol.*  
 19 58 (2011) 1401–13. doi:10.1016/j.jacc.2011.06.038.
- 20 [45] D. Bellavia, P.A. Pellikka, T.P. Abraham, G.B. Al-Zahrani, A. Dispenzieri, J.K. Oh, K.R. Bailey,  
 21 C.M. Wood, M.Q. Lacy, C. Miyazaki, F.A. Miller, Evidence of impaired left ventricular systolic  
 22 function by Doppler myocardial imaging in patients with systemic amyloidosis and no evidence of  
 23 cardiac involvement by standard two-dimensional and Doppler echocardiography., *Am. J. Cardiol.*  
 24 101 (2008) 1039–45. doi:10.1016/j.amjcard.2007.11.047.
- 25 [46] E. Imbalzano, C. Zito, S. Carerj, G. Oreto, G. Mandraffino, M. Cusmà-Piccione, G. Di Bella, C.  
 26 Saitta, A. Saitta, Left ventricular function in hypertension: new insight by speckle tracking  
 27 echocardiography., *Echocardiography.* 28 (2011) 649–57. doi:10.1111/j.1540-8175.2011.01410.x.
- 28 [47] I. Ikonomidis, G. Athanassopoulos, K. Stamatelopoulos, J. Lekakis, I. Revela, K. Venetsanou, M.  
 29 Marinou, C. Monaco, D. V Cokkinos, P. Nihoyannopoulos, Additive prognostic value of interleukin-  
 30 6 at peak phase of dobutamine stress echocardiography in patients with coronary artery disease.  
 31 A 6-year follow-up study., *Am. Heart J.* 156 (2008) 269–76. doi:10.1016/j.ahj.2008.03.020.
- 32 [48] H. Maradit-Kremers, P.J. Nicola, C.S. Crowson, K. V Ballman, S.E. Gabriel, Cardiovascular death  
 33 in rheumatoid arthritis: a population-based study., *Arthritis Rheum.* 52 (2005) 722–32.  
 34 doi:10.1002/art.20878.
- 35 [49] I. Ikonomidis, J.P. Lekakis, M. Nikolaou, I. Paraskevaidis, I. Andreadou, T. Kaplanoglou, P.  
 36 Katsimbri, G. Skarantavos, P.N. Soucacos, D.T. Kremastinos, Inhibition of interleukin-1 by  
 37 anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis.,  
 38 *Circulation.* 117 (2008) 2662–9. doi:10.1161/CIRCULATIONAHA.107.731877.
- 39 [50] R.A. Frieler, R.M. Mortensen, Immune cell and other noncardiomyocyte regulation of cardiac  
 40 hypertrophy and remodeling., *Circulation.* 131 (2015) 1019–30.  
 41 doi:10.1161/CIRCULATIONAHA.114.008788.
- 42 [51] D.G. Gardner, S. Chen, D.J. Glenn, Vitamin D and the heart., *Am. J. Physiol. Regul. Integr. Comp.*  
 43 *Physiol.* 305 (2013) R969-77. doi:10.1152/ajpregu.00322.2013.
- 44 [52] H. Tamez, C. Zoccali, D. Packham, J. Wenger, I. Bhan, E. Appelbaum, Y. Pritchett, Y. Chang, R.  
 45 Agarwal, C. Wanner, D. Lloyd-Jones, J. Cannata, B.T. Thompson, D. Andress, W. Zhang, B.  
 46 Singh, D. Zehnder, A. Pachika, W.J. Manning, A. Shah, S.D. Solomon, R. Thadhani, Vitamin D  
 47 reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease.,

- 1 Am. Heart J. 164 (2012) 902–9.e2. doi:10.1016/j.ahj.2012.09.018.
- 2 [53] B. Prietl, G. Treiber, T.R. Pieber, K. Amrein, Vitamin D and immune function., *Nutrients*. 5 (2013)  
3 2502–21. doi:10.3390/nu5072502.
- 4 [54] P.E. Norman, J.T. Powell, Vitamin D and cardiovascular disease., *Circ. Res.* 114 (2014) 379–93.  
5 doi:10.1161/CIRCRESAHA.113.301241.
- 6 [55] J. Gambardella, G. Santulli, Integrating diet and inflammation to calculate cardiovascular risk.,  
7 *Atherosclerosis*. 253 (2016) 258–261. doi:10.1016/j.atherosclerosis.2016.08.041.
- 8 [56] S.P. Costa, T.A. Beaver, J.L. Rollor, P. Vanichakarn, P.C. Magnus, R.T. Palac, Quantification of  
9 the variability associated with repeat measurements of left ventricular two-dimensional global  
10 longitudinal strain in a real-world setting., *J. Am. Soc. Echocardiogr.* 27 (2014) 50–4.  
11 doi:10.1016/j.echo.2013.08.021.
- 12

## 1 TABLES

2 Table 1: Characteristics of the subjects recruited in the present study.

	HC (n=58)	PsA (n=35)	RA (n=41)	<i>p</i> <sup>#</sup>	<i>p</i> (Dunn-Bonferroni)		
					C vs. PsA	C vs. RA	PsA vs. RA
Age, median (range)	45 (24 – 66)	45 (23 – 59)	46 (32 – 62)	ns			
Gender, f/m	35/23	26/9	32/9	ns			
<b>CV risk-related parameters</b>							
BMI, kg/m <sup>2</sup>	24.79±2.73	24.70±2.61	25.15±3.71	ns			
Total cholesterol, mg/dl	181.84±20.88	185.00±22.84	198.05±36.43	ns			
HDL-cholesterol, mg/dl	50.41±9.91	58.00±19.81	58.00±12.87	0.020	0.070	0.021	1.000
LDL-cholesterol, mg/dl	114.00±20.88	106.29±34.94	116.56±35.53	ns			
Total/HDL-cholesterol ratio	3.73±0.80	3.12±0.89	3.62±0.85	ns			
Glucose, mg/dl	88.00±7.04	89.50±10.76	89.00±14.09	ns			
Creatinine, mg/dl	0.66±0.14	0.71±0.16	0.65±0.16	ns			
SBP, mm	122.09±8.85	120.50±11.34	124.27±10.03	ns			
DBP, mm	70.06±6.29	72.00±8.64	74.15±10.94	ns			
CD34+ cell count, cell/μl	2.35±1.14	2.12±0.80	1.58±0.58	<0.001	0.380	0.002	0.024
<b>Clinical features</b>							
DAS28		3.33±0.55	3.61±0.88	ns			
Duration of the symptoms, months		9.37±7.75	6.43±6.00	ns			
Fibrinogen, mg/dl	264.56±50.88	297.26±72.61	321.76±58.91	<0.001	0.068	<0.001	0.343
Vitamin D, ng/ml	31.75±5.05	23.53±4.84	23.68±6.42	<0.001	<0.001	<0.001	0.699
CRP, mg/dl	0.34±0.16	0.50±0.50	0.95±1.18	0.049	1.000	0.011	0.167
ESR, mm		25.06±10.60	27.02±20.40	ns			
HAQ (0-3)		0.52±0.61	1.15±0.64	<0.001			
VAS (0-100)		48.82±15.12	59.42±18.01	0.034			
RF, UI/ml		7.6±2.9	100±100.4	<0.001			
ACPA, n (%)			20 (49.0)				
BASDAI		1.76±2.14					

PASI 0.91±1.31

**Subclinical CVD and myocardial dysfunction parameters**

cIMT, mm	0.79±0.18	0.82±0.19	0.98±0.16	<0.001	1.000	<0.001	<0.001
PWV, m/s	5.11±0.83	6.42±1.39	7.91±1.93	<0.001	<0.001	<0.001	0.009
GLS, %	-23.25±1.80	-21.57±2.59	-18.13±1.36	<0.001	0.020	<0.001	<0.001
GCS, %	-24.50±.70	-24.97±2.50	-20.15±1.34	<0.001	1.000	<0.001	<0.001

**Echocardiographic assessment**

Septum, mm	10.20±1.00	10.20±1.76	11.20±1.90	ns
LV mass index	77.40±12.00	77.80±15.50	82.90±10.70	ns
Posterior wall thickness, mm	9.00±1.20	8.90±1.70	8.70±1.50	ns
LV DD, mm	50±6.75	52.71±3.5	50.6±2.8	ns
LV ESD, mm	36.20±2.20	37.00±5.24	35.6±3.90	ns
E/A	1.10±0.34	1.25±0.10	1.20±0.29	ns
EF, %	62.88±3.30	61.9±4.79	60.0±4.47	ns

1

2 Variables are summarized as mean ± standard deviation or n (%) unless otherwise stated. Differences  
3 were assessed by Kruskal-Wallis tests (with Dunn's Bonferroni correction for multiple comparisons' tests),  
4  $\chi^2$  or Mann-Whitney U tests, as appropriate.

5 #p-values: p-values obtained in Kruskal-Wallis,  $\chi^2$  or Mann-Whitney tests, depending on the distribution of  
6 the variables and the groups included in the analyses. When Kruskal-Wallis tests achieved a p-  
7 value<0.050, multiple comparisons' tests were performed and p-values are indicated in the last columns.

8 BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol;  
9 HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein cholesterol; CRP: C-reactive  
10 protein.; GLS: global longitudinal strain; GCS: global circumferential strain; PWV: pulse wave velocity;  
11 cIMT: carotid intima-media thickness; DAS 28: Disease Activity Score; HAQ: Health assessment  
12 questionnaire; VAS: visual analogic scale; PASI: Psoriasis Area Severity Index. LV: left ventricular; EDD:  
13 end diastolic diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic  
14 diameter; ns: non-significant

15

1 Table 2: Characteristics of PsA patients classified according to disease activity.

	DAS28 $\leq$ 2.9	DAS28 $>$ 2.9	<i>p</i>
Age	45.91 $\pm$ 7.13	42.71 $\pm$ 9.84	0.409
Gender, f/m	8/3	18/6	0.636
<b>CV risk-related parameters</b>			
BMI	24.58 $\pm$ 1.68	24.61 $\pm$ 2.98	0.875
Total cholesterol	178.00 $\pm$ 25.71	180.76 $\pm$ 22.35	0.804
HDL-cholesterol	55.14 $\pm$ 8.05	59.00 $\pm$ 22.63	0.455
LDL-cholesterol	104.00 $\pm$ 33.55	93.27 $\pm$ 3.95	0.423
Total/HDL-cholesterol ratio	3.32 $\pm$ 0.84	3.04 $\pm$ 0.92	0.494
Glucose	91.00 $\pm$ 12.11	86.00 $\pm$ 10.14	0.336
Creatinine	0.68 $\pm$ 0.18	0.72 $\pm$ 0.16	0.451
SBP	112.00 $\pm$ 10.36	123.33 $\pm$ 10.46	0.066
DBP	69.00 $\pm$ 11.42	73.00 $\pm$ 7.74	0.497
<b>Clinical features</b>			
Duration of symptoms	6.90 $\pm$ 3.08	9.00 $\pm$ 8.9	0.174
Fibrinogen	252.00 $\pm$ 43.90	318.00 $\pm$ 74.37	<b>0.008</b>
CRP	0.21 $\pm$ 0.14	0.45 $\pm$ 0.56	<b>0.016</b>
ESR	17.91 $\pm$ 6.48	28.33 $\pm$ 10.60	<b>0.002</b>
HAQ	0.22 $\pm$ 0.37	0.66 $\pm$ 0.61	0.038
BASDAI	0.79 $\pm$ 1.76	2.19 $\pm$ 2.17	0.098
PASI	1.49 $\pm$ 1.53	0.72 $\pm$ 1.14	0.123
<b>Subclinical CVD parameters</b>			
cIMT	0.80 $\pm$ 0.14	0.84 $\pm$ 0.34	0.612
PWV	5.50 $\pm$ 1.24	6.85 $\pm$ 1.27	<b>0.005</b>
GLS	-22.35 $\pm$ 1.98	-21.04 $\pm$ 2.85	0.066
GCS	-27.00 $\pm$ 15.74	-24.30 $\pm$ 2.37	<b>0.007</b>

2 Differences between PsA patients with low and high disease activity were evaluated by Mann-Whitney U  
3 tests or  $\chi^2$  tests, as appropriate. Variables with significant differences are highlighted in bold.

Table 3: Multivariate regression analysis of myocardial dysfunction parameters in RA.

		<b>B</b>	<b>95% CI</b>	<b>p</b>
GLS	Age	0.033	-0.006, 0.071	0.091
	BMI	0.021	-0.069, 0.112	0.631
	CRP	0.142	-0.095, 0.379	0.229
	ESR	0.005	-0.013, 0.022	0.580
	DAS28	8.075	4.439, 11.710	<b>&lt;0.0001</b>
	SBP	0.011	-0.035, 0.057	0.628
	DBP	0.008	-0.031, 0.048	0.672
	Vitamin D	-0.711	-3.150, 1.727	0.554
	CD34+ cells	0.425	-1.298, 2.148	0.617
	Duration of the symptoms	-0.138	-0.965, 0.689	0.735
GCS	Age	0.015	-0.029, 0.060	0.486
	BMI	-0.007	-0.112, 0.097	0.889
	CRP	0.105	-0.169, 0.379	0.440
	ESR	0.015	-0.005, 0.036	0.131
	DAS28	7.214	3.013, 11.415	<b>0.002</b>
	SBP	0.030	-0.023, 0.083	0.260
	DBP	-0.019	-0.064, 0.027	0.409
	Vitamin D	-1.860	4.678, 0.959	0.187
	CD34+ cells	0.742	-1.249, 2.733	0.451



Duration of symptoms	0.072	-0.883, 1.028	0.878
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Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

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**Table 4: Multivariate regression analysis of PCA components on GLS and GCS in RA**

		<b>B</b>	<b>95% CI</b>	<b>p</b>
GLS	Component 1	0.989	0.713, 1.265	<b>&lt;0.0001</b>
	Component 2	-0.021	-0.304, 0.261	0.878
	Component 3	-0.262	-0.560, 0.036	0.083
	Component 4	0.118	-0.190, 0.426	0.442
GCS	Component 1	1.067	0.812, 1.323	<b>&lt;0.0001</b>
	Component 2	-0.002	-0.263, 0.260	0.988
	Component 3	-0.175	-0.451, 0.100	0.205
	Component 4	0.160	-0.125, 0.445	0.261

Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

**Table 5: Multivariate regression analysis of CD34+ frequency in PsA and RA.**

		<b>B</b>	<b>95% CI</b>	<b>p</b>
PsA	Age	-0.002	-0.010, 0.006	0.613
	BMI	0.009	-0.017, 0.035	0.491
	CRP	0.154	-0.045, 0.352	0.124
	ESR	-0.001	-0.010, 0.009	0.905
	DAS28	-0.152	-0.307, -0.001	<b>0.050</b>
	cIMT	-0.079	-0.674, 0.517	0.788
	PWV	0.002	-0.043, 0.048	0.920
	Vitamin D	0.019	0.005, 0.033	<b>0.009</b>
	Duration of symptoms	-0.003	-0.011, 0.006	0.512
RA	Age	0.001	-0.007, 0.008	0.911
	BMI	-0.003	-0.022, 0.016	0.734
	CRP	-0.015	-0.064, 0.033	0.520
	ESR	-0.001	-0.004, 0.003	0.520
	DAS28	0.011	-0.075, 0.097	0.792
	cIMT	-0.258	-0.983, 0.467	0.472
	PWV	-0.029	-0.065, 0.007	0.105
	Vitamin D	0.010	0.001, 0.019	<b>0.028</b>
	Duration of the symptoms	0.016	0.004, 0.028	<b>0.010</b>

Multiple linear regression analysis including CD34+ frequency as dependent variable. Variables found to be significant predictors are highlighted in bold.

**HIGHLIGHTS**

- Subclinical myocardial dysfunction is found in very early rheumatoid arthritis (RA) and psoriatic arthritis (PsA) with normal ejection fraction (EF)
- Inflammatory burden is associated with altered myocardial functionality in inflammatory joint diseases (IJD)
- Speckle-tracking echocardiography may be useful for CV risk stratification in IJD