

# Echocardiographic evaluation of diastolic dysfunction in young and healthy patients with psoriasis: A case-control study

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## Abstract

Psoriasis is a systemic inflammatory disease with a great prevalence in general population. The inappropriate activation of the cellular immune system has been hypothesized to be an independent cardiovascular risk factor, given the higher incidence of cardiovascular disorders in psoriatic patients. Echocardiographic abnormalities have been demonstrated too: the aim of our study was to evaluate the presence of preclinical cardiac dysfunction in a cohort of psoriatic patients without cardiovascular risk factors. We enrolled 52 patients with the diagnosis of chronic plaque psoriasis, compared with a control group not affected by any relevant systemic diseases and inflammatory disorders. In all patients and control group, echocardiographic conventional and tissue Doppler (TDI) studies were conducted. The analysis of echocardiographic parameters revealed normal dimension, mass and systolic

function of the left ventricle. Left ventricular diastolic dysfunction was found in 36.5% patients in the psoriasis group *versus* 0% in control group, and significant reduction of the E/A ratio was found also for the right ventricle. A significant increase of mitral regurgitation has been found in psoriatic patients ( $p=0.005$ ). The early recognition of cardiovascular pre-clinic disease in psoriatic patients may guide a strict follow up and an early treatment, potentially improving cardiovascular prognosis.

## Introduction

Psoriasis is a systemic inflammatory disease that affects 1.5-3% of the general population [1]. Pathophysiology is multifactorial, depending on an association between genetic predisposition and environmental factors that determine an inappropriate activation of the cellular immune system [2].

The role of psoriasis as an independent cardiovascular risk factor (CVRF) is debated: a meta-analysis by Gaeta *et al.* based on 13 studies including patients with psoriasis showed a significant 24% excess risk of overall cardiovascular diseases (CVDs) in patients with psoriasis as compared to controls (RR=1.24 (1.18–1.31);  $P=0.0001$ ) and this risk appears to be independent of smoking, obesity and hyperlipidemia [3]. Several previous reports have also showed a higher incidence of cardiovascular disorders such as arterial hypertension, stroke, coronary artery diseases, heart failure, arrhythmias and valvular disorders in patients with psoriasis than in general population and this association was independent from traditional CVRF [4,5]. Some authors have suggested that the association between psoriasis and CVDs depends on a common chronic inflammatory pathway [6]. Psoriasis is characterized by an overexpression of pro-inflammatory cytokines, such as interleukins, TNF- $\alpha$  and interferon- $\beta$  which play an important role in determining endothelial dysfunction, atherosclerosis promotion and cardiomyocytes toxicity. Psoriasis has been also associated with echocardiographic abnormalities: a study by Biyik *et al.*, including 216 psoriatic patients compared with healthy controls, revealed a significant increase of cardiac abnormalities such as left ventricular hypertrophy, altered left ventricular wall motion and valvular diseases, especially mitral and tricuspidal valve prolapse, and left ventricular diastolic dysfunction in psoriasis group [7]. Diastolic dysfunction has been also observed in patients without cardiovascular risk factors [8].

The aim of our study was to evaluate the presence of preclinical cardiac dysfunction in a cohort of psoriatic patients without CVRFs.

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## Materials and Methods

### Study patients

This was a case-control study to evaluate the presence of echocardiographic anomalies in a population of psoriatic patients without cardiovascular risk factors.

We enrolled patients affected by plaque psoriasis followed-up at the Dermatology Unit of University and Civil Hospital of Brescia. The inclusion criteria were a clinical diagnosis of chronic plaque psoriasis, lasting at least 6 months, in a stable phase of the disease and a psoriasis area severity index (PASI) of at least 10. The type of treatment was not an exclusion criterion. However, it should not have been changed in the 4 weeks preceding the assessment visit. Controls, matched for sex and age, were recruited among healthcare workers of the hospital. Exclusion criteria for both patients and controls were age <18 years, pregnancy, lactation, detection of even a single cardiovascular risk factor (as hypertension, diabetes or dyslipidemia) or any known cardiovascular disease (any coronary syndrome, valvular disease with severity greater than medium, cardiomyopathies, heart rhythm anomalies); familiar history of cardiac or cerebral diseases as of any systemic peripheral arterial disease, in first degree relatives; tobacco use, considering both cigarette and cigar; dyslipidemia diagnosed following cut of value of the European Society of Cardiology (LDL-c >140 mg/dL, tot-c >200 mg/dL, TGL>180 mg/dl, HDL-c <40 mg/dL); diabetes mellitus or impaired fasting glycaemia; obesity (BMI >30) or underweight (BMI< 18); hypertension, diagnosed by values of arterial pressure more than 140/80 mmHg at the clinical evaluation or by the use of antihypertensive drugs. Controls were not affected by any relevant systemic diseases and inflammatory skin or systemic disorders.

The study was conducted in the Cardiology Unit of University and Civil Hospital of Brescia, Italy. We certified that the study complied with the ethical standards of the Declaration of Helsinki [9] and all patients gave their written, informed consent to participate.

### Study protocol

Patients eligible for the study underwent a complete clinical assessment, electrocardiogram and transthoracic echocardiography.

They underwent 2-dimensional and Doppler transthoracic echocardiography. Based on our previous study [10], echocardiograms were performed using Vivid 7 (GE) with a 3.5 transducer. Subjects were examined in the left decubitus position according to the standardization of the American Society of Echocardiography. Left ventricular dimensions and ejection fraction (LVEF) were estimated according to LV volumes evaluated by biplane Simpson's method [11].

Mitral and tricuspid valve regurgitation grade were assessed semi-quantitatively according to the current guidelines and classified as mild, moderate and severe [12]. By placing the 2-mm PWD at the mitral inflow, the early diastolic (E) and atrial (A) velocities were measured and

E/A ratio was calculated. The deceleration time (DT) was measured according to the recommendations of the American Society of Echocardiography [13]. Myocardial systolic and diastolic velocities were recorded using the PW tissue Doppler Imaging (TDI). Systolic (S'), early (E') and late (A') diastolic waves velocities were measured by placing the sample volume, underneath the mitral annulus, on the lateral and on the septal myocardial wall of the LV from the apical 4-chamber view and on the tricuspidal lateral annulus. The E/E' ratio was also obtained; we used the average of E' left sides velocities for the prediction of LV filling pressures [14]. According to the recommendations of the American Society of Echocardiography [14], LV diastolic dysfunction was defined as septal E' less than 8 cm/sec or lateral E' less than 10 cm/sec; different rates of diastolic dysfunction were classified in mild or grade 1 (impaired relaxation pattern), moderate or grade 2 (pseudonormal filling pattern), and severe or grade 3 (restrictive filling pattern). Conventional PW echocardiography has been used to derive left ventricular and RV myocardial performance indexes (MPIs) as previously described by Tei and colleagues, considering as normal LV MPI less than 0.40 and RV MPI less than 0.30 [15]. Patients had to answer to a specific questionnaire for the assessment of cardiovascular risk factors with the help of trained nurse.

### Statistical analysis

Continuous variables were visually tested for normality using Q-Q plots and expressed as mean  $\pm$  standard deviation, while categorical variables as frequency (n) and percentage of the sample. After Levene's test for homoscedasticity, independent samples Welch's *t*-test was performed to analyze the difference between means for continuous variables. The  $\chi^2$  test was used for assessing differences between proportions. Statistical analysis was performed using IBM SPSS Statistics 20 for Windows (SPSS, Inc., Chicago, IL, USA). All values were two-tailed; statistical significance was set at  $p < 0.05$ .

### Results

From January 2015 to December 2015 we evaluated 424 patients followed by the Dermatology Unit with a diagnosis of chronic plaque psoriasis. After evaluation for inclusion and exclusion criteria we enrolled 52 patients. The expected 6 months' enrollment period has required an extension due to the difficulty encountered in finding patients corresponding to inclusion and exclusion criteria. Baseline characteristics are shown in Table 1. At study entry, the two groups were balanced with respect to demographic and clinical variables. The analysis of echocardiographic parameters reveals normal dimension, mass and systolic function of the left ventricle, according to the clinical characteristics of patients (Table 2). The only difference in dimensions was telesystolic diameter (DTS), which was larger in cases respect to controls ( $p < 0.001$ ).

The most interesting result was about left ventricle diastolic dysfunction, defined as E/A <1 and deceleration time >220 msec and E/E' <10,

Table 1. Clinical and demographic characteristics of the study population.

Variable	Group 1 Psoriasis (n=52)	Group 2 Controls (n=52)	p
Age (years)	44.3 $\pm$ 14.8	39.7 $\pm$ 10.5	0.792
Sex	Male: 27 (51.9%) Female: 25 (48.1%)	Male: 25 (48.1%) Female: 27 (51.9%)	0.845
SBP (mmHg)	120.6 $\pm$ 13.2	118.2 $\pm$ 13.0	0.382
DBP (mmHg)	73.3 $\pm$ 7.4	70.1 $\pm$ 9.7	0.046
Heart rate (bpm)	76.5 $\pm$ 9.7	70.1 $\pm$ 13.0	0.009

found in 19 (36.5%) patients in the psoriasis group *versus* 0% in control group (Table 3). However, left atrial dimensions were not statistically different among the two groups. Differences were also found in right ventricle diastolic function between case and controls (MPI:  $0.23 \pm 0.07$  *vs*  $0.41 \pm 0.04$ ,  $p < 0.01$ ; E/A  $1.27 \pm 0.32$  *vs*  $2.26 \pm 0.90$ ,  $p < 0.001$ ), but not in systolic function (TAPSE  $25,00$  mm *vs*  $24,40$  mm,  $p = 0.460$ ) (Table 4).

Pulmonary arterial systolic pressure was slightly higher in psoriatic patients than in controls, even without pulmonary hypertension ( $p = 0.008$ ). Moreover, considering cardiac valves function, we evidenced a significant increase of mitral regurgitation in the psoriatic cohort: 27% of psoriatic patient have a mild mitral regurgitation *versus* 3.8% of control ( $p = 0.005$ ) (Table 5).

Table 2. Echocardiographic characteristics of left ventricle, left atrium, right ventricle.

Variable	Group 1 Psoriasis (n=52)	Group 2 Controls (n=52)	p
EDD (mm)	$45.6 \pm 5.3$	$47.1 \pm 3.8$	0.102
ESD (mm)	$28.8 \pm 6.0$	$25.1 \pm 3.5$	<0.001
IVST (mm)	$10.3 \pm 1.1$	$9.4 \pm 1.1$	0.527
PWT (mm)	$8.4 \pm 1.5$	$8.7 \pm 1.2$	0.360
Mass (g)	$166.4 \pm 22.1$	$127.9 \pm 26.7$	0.216
RWT	$0.373 \pm 0.076$	$0.369 \pm 0.056$	0.759
LVEF (%)	$61.8 \pm 6.5$	$63.2 \pm 4.5$	0.189
LA AP diameter (mm)	$31.5 \pm 4.8$	$30.4 \pm 2.1$	0.164
TAPSE (mm)	$25.0 \pm 4.5$	$24.4 \pm 3.5$	0.460
sPAP (mmHg)	$23.8 \pm 4.2$	$22.1 \pm 1.7$	0.008
RV MPI	$0.235 \pm 0.079$	$0.420 \pm 0.041$	<0.001

Table 3. Left ventricle diastolic function.

Variable	Group 1 Psoriasis (n=52)	Group 2 Controls (n=52)	p
E (m/s)	$0.70 \pm 0.21$	$0.68 \pm 0.15$	0.708
A (m/s)	$0.59 \pm 0.21$	$0.38 \pm 0.07$	<0.001
E/A	$1.36 \pm 0.62$	$1.87 \pm 0.61$	<0.001
DT (msec)	$209.9 \pm 63.8$	$187.5 \pm 56.2$	0.060
E' (m/s)	$0.08 \pm 0.02$	$0.11 \pm 0.02$	0.032
A' (m/s)	$0.05 \pm 0.04$	$0.08 \pm 0.04$	0.040
S' (m/s)	$0.08 \pm 0.03$	$0.06 \pm 0.17$	0.003
E/E'	$7.00 \pm 6.06$	$6.34 \pm 1.72$	0.452
E'/A'	$1.65 \pm 1.00$	$1.98 \pm 1.12$	0.118
Grade I diastolic dysfunction	19 (36.5%)	0 (0.0%)	<0.001
- E/A < 1			
- DT > 220 msec			
- E/e' < 10			

Table 4. Right ventricle diastolic function.

Variable	Group 1 Psoriasis (n=52)	Group 2 Controls (n=52)	p
E (m/s)	$0.40 \pm 0.15$	$0.64 \pm 0.14$	<0.001
A (m/s)	$0.34 \pm 0.14$	$0.31 \pm 0.10$	0.299
E/A	$1.27 \pm 0.32$	$2.26 \pm 0.90$	<0.001

Table 5. Valvular abnormalities.

Variable	Group 1 Psoriasis (n=52)	Group 2 Controls (n=52)	p
MR	14 (26.9%)	2 (3.8%)	0.005
MVP	4 (7.7%)	0 (0.0%)	0.112
MS	0 (0.0%)	0 (0.0%)	-
AoR	5 (9.6%)	0 (0.0%)	0.057
AoS	0 (0.0%)	0 (0.0%)	-
AoEct	4 (7.7%)	0 (0.0%)	0.118
TR	7 (13.5%)	2 (3.8%)	0.160

MR, mitral regurgitation; MVP, mitral valve prolapse; MS, mitral stenosis; AoR, aortic regurgitation; AoS, aortic stenosis; AoEct, aortic ectasia; TR, tricuspid regurgitation.

## Discussion

Chronic inflammation is an established cardiovascular risk factor. The latest ESC guidelines in this regard have included a specific chapter for autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis and psoriasis are in fact identified as diseases associated with an increased risk of myocardial infarction [16]. Psoriasis is an immune-modulated inflammatory disorder [5,17] and precisely this pro-inflammatory state has been linked to the increased incidence of diseases such as atherosclerosis, myocardial infarction, heart failure and cerebrovascular events [18,19]. The risk seems to increase with the degree of severity of the disease. Both psoriasis and cardiovascular disease are characterized by a T helper-1 cell mediated immune impairment [20-22] with involvement of cytokines such as interferon- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$  [23,24], and interleukin-2 [25]. They stimulate keratinocytes to produce IL-6, IL-7, IL-8, IL-12, IL-15, and IL-18 [25], and interferon- $\gamma$  [26] that can stimulate the expression of major histocompatibility complex class II molecules and intracellular adhesion molecule (ICAM)-1 [26,27]. In addition, vascular endothelial growth factor (VEGF), a potent pro-angiogenic, has been found up-regulated both in psoriasis and atherosclerosis [28,29]. How this common inflammatory pattern interacts remains poorly understood but we could state that it provides a common background to both diseases.

However, data from many recent trials about the correlation between psoriasis and cardiovascular diseases are inconsistent even because cardiovascular risk factors are highly under-diagnosed and consequently under treated [30].

The aim of our decision to conduct a study on a population without CVRFs was to reduce the possibility of potential confounders. Then, even excluding CVRFs, we found the presence of pre-clinical cardiovascular disease in the majority of asymptomatic psoriatic patients.

Echocardiographic evaluation revealed an increased prevalence of diastolic dysfunction in psoriatic patients compared to control population. Diastolic dysfunction, prevalently represented by abnormalities of early to late ventricular filling velocities ratio (E/A), early flow deceleration time (DT) and isovolumic relaxation time (IVRT), may be the first abnormality in heart disease, which involve not only the left, but also the right ventricle (MPI, E/A).

Alterations of matrix metalloproteinases, related to the enhanced inflammatory pathways, lead to an increased stiffness of the extracellular matrix [31,32]. Oxidative stress could instead act on the structure of cardiomyocytes [33] with consequent alteration of Titin isoform and increased myocardial stiffness [34]. Both these mechanisms, together with subclinical atherosclerosis promoted by the above mentioned dysregulated inflammatory state, are able to explain the incremented stiffness of psoriatic hearts revealed by alterations of diastolic function at echocardiography.

The finding of diastolic dysfunction in young patients (completely free from any known common CV risk factor) sustains the importance of chronic inflammation as an independent CV factor.

This also supports the modern hypothesis of heart failure with preserved ejection fraction as a systemic disease correlated to the presence of metabolic syndrome, hypertension, obesity, atrial fibrillation and renal failure: the common pathway between those diseases appear to be the enhanced inflammatory state.

Our study confirms also the greater presence of valvular defects in psoriatic patients. Mitral valve is the most affected (27% vs 3.8%;  $p=0.005$ ), followed by aortic valve (9.6% vs 0%,  $p=0.05$ ). These data agree with what previously emerged in literature: valvular defects were found in a range between 40% and 26% compared to 20 to 18% in control groups [7,35].

Pathophysiology of this alteration remains unknown but an autopsy study of Kakturskii *et al.* revealed mucoid edema and diffuse mononuclear cell infiltration of the mitral and aortic valves suggesting chronic valvulitis [36].

## Conclusions

Our findings support the importance of chronic inflammation as an independent CV factor, irrespectively from traditional cardiovascular risk factors, such as hypertension, age and lipid disorders, which, on the other hand, surely act like enhancer of the inflammatory balance.

The early recognition of cardiovascular pre-clinic disease in psoriatic patients, thanks to validated echocardiographic parameters which can be obtained easily in most centers, may guide a strict follow up and an early treatment, potentially improving cardiovascular prognosis.

Moreover, psoriatic patients should be controlled more than normal population: this will be reflected in a more careful management of conditions like hypertension, diabetes and dyslipidemia. The dermatologic surgery should become the preferred place for implementation of this primary prevention strategy, allowing the management of psoriatic patients in a holistic way with a 360 degrees promotion of healthy lifestyle by cooperation between cardiologists and dermatologists.

## Limitations

Our study has several limitations. First the small simple size of recruited patients. Anyway, this is certainly balanced by the accurate selection of patients without cardiovascular risk factors. Our trial has been completed in a single institute and this could have determined selection bias due to unknown specific characteristics of the patients from the Dermatology Unit of University and Civil Hospital of Brescia.

Second, we did not evaluate the prognostic value of diastolic dysfunction. This should be evaluated through a specific prospective study.

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