

Multiparametric analysis of coronary flow in psoriasis using a coronary flow reserve companion

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Abstract

Background: Coronary microvascular dysfunction (CMD) is usually evaluated measuring coronary flow velocity reserve (CFVR). A more comprehensive analysis of CFVR including additional consideration of the associated logical companion-CFVR, where hyperemic diastolic coronary flow velocity may act as surrogate, was applied in this study to elucidate the mechanism of CMD in psoriasis.

Methods and results: Coronary flow velocity reserve was analysed using transthoracic echocardiographs of 127 psoriasis patients (age 36 ± 8 years; 104 males) and of 52 sex- and age-matched healthy controls. CFVR determination was repeated in the patient subgroup ($n = 78$) receiving anti-inflammatory therapy. Baseline and hyperemic microvascular resistance (MR) were calculated. CMD was defined as $CFVR \leq 2.5$. Four endotypes of CMD were identified referring to concordant or discordant impairments of hyperemic flow or CFVR. We evaluated the companion-CFVR, as derived from the quadratic mean of hyperemic and diastolic flow velocity at rest. Coronary flow parameters, including CFVR ($p = 0.01$), were different among the two endotypes having $CFVR > 2.5$. Specifically, all 11 (14%) patients with CFVR deterioration despite therapy, belonged to endotype 1, and had higher baseline and hyperemic MR ($p < 0.0001$, both). Interestingly, while CFVR was comparable in patients with worsened versus those with improved CFVR, the companion-CFVR could discriminate by being lower in patients with worsened CFVR ($p = 0.01$).

Conclusions: The reduced CFVR in psoriasis is driven by decreased companion-CFVR, combined with increased hyperemic MR. Adoption of the mandatory companion-CFVR enables a personalized characterization superior to that achieved by exclusive consideration of CFVR.

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KEYWORDS

anti-inflammatory therapy, coronary flow reserve, coronary microcirculation, coronary microvascular dysfunction, Doppler echocardiography, psoriasis

1 | INTRODUCTION

Psoriasis affects 2%–3% of the population and decreases patient quality of life similarly to major illnesses such as cancer and heart failure.¹ Psoriasis is recognized as a systemic inflammatory syndrome associated with serious comorbidities, in particular coronary artery disease (CAD),² which is the leading cause of death in psoriasis patients.

Psoriasis confers an independent risk of myocardial infarction beyond traditional risk factors leading to an elevated incidence of cardiovascular events.¹ Young patients with severe psoriasis carry the highest cardiovascular risk, with up to 8.2% increased mortality compared to the control population.³ We and others found that coronary flow velocity reserve (CFVR) decreases with increased psoriasis skin disease severity as reflected by the psoriasis area and severity index (PASI).^{4,5}

Coronary flow velocity reserve, defined as the ratio of the maximal diastolic coronary flow velocity measured during hyperemic conditions (CFV_h) and the maximal diastolic coronary flow velocity at rest (CFV_r), describes the ability to increase coronary flow to dynamically match myocardial metabolic requirements.⁶ Impaired CFVR was demonstrated in psoriasis patients without epicardial coronary disease,^{7,8} suggesting the existence of microvascular structural and/or functional impairment. Thus, when epicardial arteries are normal, an impaired CFVR indicates coronary microvascular dysfunction (CMD), which may result from two main mechanisms: (1) increased CFV_r and concomitant reduced coronary microvascular resistance at baseline (BMR) or (2) reduced CFV_h due to high microvascular resistance under maximal hyperaemia (HMR), attributable to impaired vasodilatory function of the coronary microcirculation.⁹ The traditional metric CFVR is a dimensionless ratio; therefore, similar proportional changes of the numerator and denominator, for example concomitant doubling of CFV_h and CFV_r , will result in identical CFVR values. To overcome this limitation, we apply a mathematically derived companion to CFVR (cCFVR) to complement the ratio and allow a better appraisal of variations of CFV_h and CFV_r .^{10–13}

Mechanisms underlying impaired CFVR in psoriatic patients are not yet elucidated. Therefore, we aimed to determine which of the two above-mentioned pathophysiological mechanisms of CMD contributes to reduced CFVR in

psoriasis patients. Additionally, we tested in these patients the clinical relevance of the newly introduced cCFVR and the effect of anti-inflammatory therapy on coronary flow parameters.

2 | METHODS

2.1 | Study populations

In this single-centre cross-sectional study, among 185 psoriasis patients with available CFVR evaluation, we selected patients ($n = 127$) affected by moderate-severe psoriasis before the beginning of treatment. Baseline evaluation included a physical examination and collection of clinical and echocardiographic data. The median time from psoriasis diagnosis to CFVR determination was 4.3 years (range 0.25–9.3 years). Patients aged >50 years, or with a history or clinical evidence of cardiopulmonary, renal, hepatic, malignant or infectious disease were excluded as well as patients with psoriatic arthritis or any other systemic inflammatory disorder. Patients with cardiovascular risk factors, such as diabetes, hypertension, dyslipidaemia, smoking and obesity, were also excluded.

The control group consisted of 52 healthy volunteers recruited from institutional personnel, who were matched for age and sex. The control subjects did not undergo any cardiovascular conditioning programme. Exclusion criteria for all subjects were any of the following: cerebral vascular disease, carotid artery bruit, peripheral bruit or abnormal pulse, history of anginal pain, any presence of fixed coronary stenosis, any previous myocardial infarction, any previous percutaneous coronary intervention or previous aorto-coronary by-pass grafting surgery, or alcohol intake >10 oz per week.

All participants had a normal electrocardiogram at rest and during adenosine-induced hyperaemia. The absence of CAD was evaluated by clinical history, physical examination and electrocardiogram. Further characteristics of the control and the patient groups are presented in [Table 1](#). In addition, patients with $CFVR \leq 2.5$ underwent coronary multi-slice computed tomography to exclude angiographically significant epicardial stenosis. The study protocol was approved by the institutional ethical committee. All participants provided written informed consent.

TABLE 1 Characteristics of the study population (n = 179)

	Whole study population (n = 179)	Healthy subjects (n = 52)	Psoriasis patients (n = 127)	p
Age \pm SD, years	39 \pm 2	40 \pm 3	36 \pm 8	0.618
Male sex, n (%)	147 (82)	43 (82)	104 (82)	0.821
Echocardiographic characteristics				
IVSd \pm SD, mm	9.4 \pm 2.1	9.0 \pm 2.2	9.8 \pm 1.8	0.225
PWTd \pm SD, mm	9.5 \pm 1.9	8.4 \pm 1.4	8.9 \pm 1.0	0.510
LVIDd \pm SD, mm	52 \pm 1.7	53 \pm 4.9	50 \pm 3.9	0.423
LV mass \pm SD, g	167 \pm 48	170 \pm 50	165 \pm 44	0.222
LV mass index \pm SD, g/m ²	101 \pm 19	102 \pm 22	100 \pm 20	0.552
LV mass/height ^{2.7} \pm SD, g/m ^{2.7}	45 \pm 9	46 \pm 11	43 \pm 9	0.310
Relative WT \pm SD	0.32 \pm 0.04	0.32 \pm 0.06	0.31 \pm 0.04	0.712
LV hypertrophy, LVMI, n (%)	2 (1)	2 (4)	0 (0)	0.152
LV hypertrophy, LVMH, n (%)	2 (1)	2 (4)	0 (0)	0.152
LVEF \pm SD, %	62 \pm 3	62 \pm 3	61 \pm 3	0.725
E/A ratio \pm SD	1.50 \pm 0.22	1.51 \pm 0.21	1.49 \pm 0.32	0.861
DT \pm SD, ms	174 \pm 15	172 \pm 15	177 \pm 17	0.541
IVRT \pm SD, ms	77 \pm 5	70 \pm 5	78 \pm 4	0.621
PVs/PVd ratio \pm SD	1.29 \pm 0.12	1.33 \pm 0.11	1.13 \pm 0.18	0.201
E/E' ratio septal \pm SD	7.51 \pm 1.29	7.41 \pm 1.42	7.53 \pm 1.23	0.774
E/E' ratio lateral \pm SD	6.59 \pm 1.11	6.51 \pm 1.34	6.64 \pm 1.21	0.810
Grade of diastolic dysfunction, n (%)				
None	121 (67)	45 (86)	76 (60)	0.031
Mild	54 (30)	7 (14)	51 (40)	0.023
Moderate	0 (0)	0 (0)	0 (0)	1.000
Severe	0 (0)	0 (0)	0 (0)	1.000
Microvascular Coronary Flow Parameters				
CFV _r median (Q1–Q3), cm/s	23 (19–27)	26 (20–29)	21 (19–25)	<0.001
CFV _h median (Q1–Q3), cm/s	77 (57–83)	90 (74–103)	65 (56–77)	<0.0001
CFVR median (Q1–Q3)	3.2 (2.7–3.6)	3.5 (3.0–4.0)	3.0 (2.6–3.5)	<0.0001
BMR median (Q1–Q3), mmHg·s/cm	4.1 (3.3–5.1)	4.1 (3.5–5.1)	4.2 (3.5–5.0)	0.911
HMR median (Q1–Q3), mmHg·s/cm	1.3 (1.08–2.03)	1.1 (1.0–1.4)	1.4 (1.1–1.7)	<0.0001
ARI median (Q1–Q3), mmHg·s/cm	2.8 (2.1–3.3)	3.0 (2.3–3.8)	2.7 (2.1–3.4)	0.035
ARI median (Q1–Q3), %	69 (67–75)	72 (69–76)	66 (61–71)	<0.0001
cCFVR median (Q1–Q3), cm/s	80 (68–94)	93 (78–108)	68 (59–80)	<0.0001

Note: A wave indicates the flow velocity during atrial contraction.

Abbreviations: ARI, arteriole resistance index; BMR, basal microvascular resistance; cCFVR, companion coronary flow velocity reserve; CFV_h, hyperemic coronary flow velocity; CFVR, coronary flow velocity reserve; CFV_r, rest coronary flow velocity; DT, deceleration time; E wave, early transmitral diastolic flow velocity; E/E', ratio of early transmitral diastolic flow velocity (E) and early diastolic velocity recorded by Doppler tissue imaging (E') in the mitral annulus; HMR, hyperemic microvascular resistance; IVRT, isovolumetric relaxation time; IVSd, diastolic interventricular septal thickness; LV, left ventricular; LVEF, LV ejection fraction; LVIDd, LV internal diameter in diastole; LVIDs, LV internal diameter in systole; LVMH, LV mass/ height; LVMI, LV mass index; PVd, diastolic pulmonary vein velocity; PVs, systolic pulmonary vein velocity; PWTd, diastolic posterior wall thickness; PWTs, systolic posterior wall thickness; WT, wall thickness.

2.2 | Treatment of psoriasis

In 78 patients (age 38 ± 8 years; range, 19–50; 66 males), CFVR determination was repeated after 6 months of anti-inflammatory treatment with adalimumab ($n = 22$), etanercept ($n = 20$), infliximab ($n = 15$), ustekinumab ($n = 14$) or cyclosporine ($n = 7$). Treatment choice and administration mode for psoriasis are detailed in online [Supplementary Material Online](#).

2.3 | Echocardiography and CFVR

Transthoracic Doppler echocardiography (Vivid 7, GE Medical System, Inc.) was performed as detailed in [Supplementary Material Online](#).

Coronary images were obtained in the distal part of the left anterior descending artery with a 7 MHz transducer. After recordings the CFV_r , adenosine was intravenously infused ($140 \mu\text{g kg}^{-1} \text{min}^{-1}$) for 3 min, to obtain CFV_h , yielding $CFVR = CFV_h/CFV_r$. All patients abstained from caffeine-containing drinks for at least 48 h before testing.

$CFVR \leq 2.5$ was considered abnormal and a marker of CMD, and the population was dichotomized according to this cut-off point.^{14,15} We evaluated heart rate and systolic and diastolic arterial pressure at rest and during hyperaemia, as well as the CFV_r , CFV_h , $cCFVR$ and $CFVR$.

2.4 | Resistance indices

The mean pressure in coronary arteries without stenosis is considered equal to the mean aortic pressure and, thus, can be approximated using a sphygmomanometer. The BMR and HMR were calculated as the ratio between the respective mean blood pressure ($0.67 \cdot$ diastolic arterial pressure + $0.33 \cdot$ systolic arterial pressure) and CFV ,¹⁶ assuming that distal pressure in the microvascular bed can be neglected. The difference between the BMR and HMR defines the arteriolar resistance index (ARI)¹⁶ and indicates the arteriolar vasodilatory capacity under hyperaemia. Finally, $ARI\% = (ARI/BMR) \cdot 100$.

2.5 | Companion to CFVR in the velocity domain

CFVR as a simple ratio refers to only two variables, CFV_h and CFV_r , expressed in the velocity domain, (Figure 1).¹¹ However, we can also interpret each point in the graph by a set of two alternative components: (1) the slope (angle) as CFVR and (2) the corresponding distance from the origin,

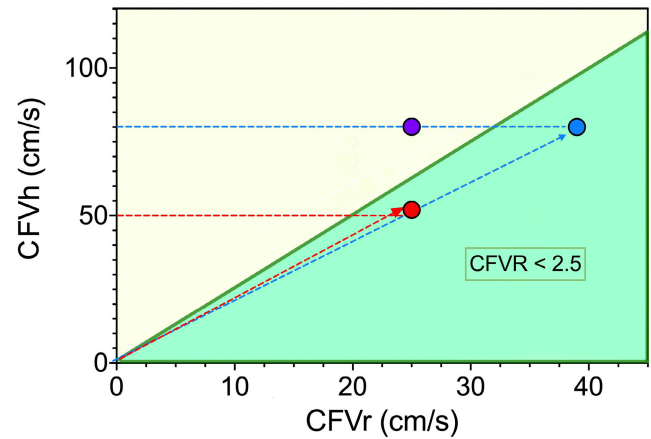


FIGURE 1 Cartesian and polar coordinates in the flow velocity domain. The coronary flow velocity reserve (CFVR) is defined by the ratio of the maximal coronary diastolic flow velocity during hyperaemia (CFV_h) and the maximal coronary diastolic flow velocity at rest (CFV_r). Reportedly, coronary microvascular dysfunction (CMD) is present when $CFVR \leq 2.5$ (see green marked triangular area). The graph shows the CFV_h (cm/s) versus CFV_r (cm/s) for three hypothetical patients: Red dot with Cartesian coordinates $\{25, 50\}$ and slope $CFVR = 50/25 = 2.0$. Blue dot with Cartesian coordinates $\{40, 80\}$ and slope $CFVR = 80/40 = 2.0$. Purple dot with Cartesian coordinates $\{25, 80\}$ and slope (not shown) $CFVR = 80/25 = 3.2$. Clearly, the CFVR values for the red and blue dots are identical, although the flow velocity levels both at rest and during hyperaemia are substantially different. This discrepancy indicates that CFVR alone cannot adequately define (normal nor impaired) myocardial perfusion conditions. The CFV_h level for the blue dot is similar to that for the purple dot, which is located outside the CMD zone, with a “healthy” $CFVR = 3.2$. The difference between various (patho)physiological states can be further quantified by calculating their individual distance to the origin, that is, the length of the red line with the arrowhead and the blue stippled line with the arrowhead. The companion (c), denoted as $cCFVR$ (cm/s), equals the hypotenuse: Red dot: $cCFVR = \sqrt{(50 \times 50 + 25 \times 25)} = 55.9$ cm/s with $CFVR = 2.0$. Blue dot: $cCFVR = \sqrt{(80 \times 80 + 40 \times 40)} = 89.4$ cm/s with $CFVR = 2.0$. $CFVR$ and $cCFVR$ are combined to form polar coordinates equivalent to the Cartesian coordinates. Within this context, CFV_h may be viewed as a surrogate for $cCFVR$, as the value for $cCFVR$ approaches $(\sqrt{2}) \cdot CFV_h$ when the difference between CFV_r and CFV_h is relatively small

here referred to as “companion” ($cCFVR$) (Figure 1), which is numerically defined as¹¹:

$$cCFVR = \sqrt{(CFV_r^2 + CFV_h^2)}$$

As CFV_h is the dominant component in the formula of the companion, CFV_h may act as a surrogate for $cCFVR$ (Figure 1).

2.6 | Coronary multi-slice computed tomography

Patients with CMD underwent coronary multi-slice computed tomography to exclude angiographically significant epicardial CAD and to measure the calcium score. Coronary multi-slice computed tomography was performed using a 64-slice dual-source scanner (Definition, Siemens Medical System), as previously detailed.¹⁷

2.7 | Laboratory methods

Fasting serum samples were collected at baseline and at the end of the study and stored at -80°C until their analysis. In all individuals, anthropometric measures and blood samples for the biochemical parameters were obtained in the morning, on the day of the CFVR study. Laboratory methods are reported in online [Supplementary Material Online](#).

2.8 | Psoriasis area severity index evaluation

Psoriasis area severity index evaluation (PASI) grades psoriatic plaques based on three criteria: redness, thickness and scaliness. Severity is rated for each feature on a 0–4 scale (0 for skin integrity, up to 4 for severe involvement). Currently, PASI is considered the gold standard method used to assess psoriasis severity and is widely accepted as an outcome measure in clinical research and by health authorities.¹⁸ For detailed PASI evaluation and psoriasis treatment, see [Supplementary Material Online](#).

2.9 | Statistical analysis

Continuous variables with no/mild skew were presented as the mean \pm standard deviation; skewed measures were represented as the median with the first and third quartiles (Q1–Q3). Categorical variables were summarized as frequencies and percentages. The distribution of the data was analysed with a one-sample Kolmogorov-Smirnov test. Categorical variables were compared by the chi-square test or Fisher's exact test, as appropriate. Continuous data were compared by use of the two-tailed paired or unpaired *t* test (for normally distributed data sets) or the Mann-Whitney U or Wilcoxon signed-rank test (for skewed variables). Multiple comparisons of coronary flow parameters among groups were assessed by Kruskal-Wallis with the Dunn multiple comparisons

test. The sensitivity, specificity, accuracy and predictive values were calculated according to standard definitions. Evidence of CFVR worsening (defined as its decrease) was taken as the positive reference standard, and receiver operating characteristic curves were generated for analysis. Spearman's rho correlation coefficient was used to assess the relationship between microvascular coronary flow parameters, PASI and the time from diagnosis. Integration of CFVR and CFV_h (as surrogate for cCFVR) permits identification of four endotypes based on whether concordant or discordant impairment of these indices occurred. $\text{CFVR} \leq 2.5$ was considered abnormal and a marker of coronary microvascular dysfunction.¹⁵ As the median CFV_h was 65 cm/s in our cohort of psoriasis patients and previous studies showed a median CFV_h of approximately 65 cm/s in normal coronary arteries, we used 65 cm/s as a threshold for our analysis.¹⁹ The intraobserver and interobserver reproducibilities of CFVR were evaluated by linear regression analysis and expressed as correlation coefficients (*r*), the standard error of estimates (SEE) and the intraclass correlation coefficient (ICC). These reproducibilities were assessed by repeating the CFVR evaluation twice, 1 h apart, by the same operator (G.F.) in all patients and by another operator (F.T.) in all patients, before and after treatment. Reproducibility was considered satisfactory if the intraclass correlation coefficient was between 0.81 and 1.0.

All tests were two-sided, and the statistical significance was set at $p < 0.05$. The data were analysed with SPSS v.24.0 (SPSS, Inc.). The authors had full access to and take full responsibility for the integrity of the data. All authors read and agreed to the manuscript as written.

3 | RESULTS

3.1 | Clinical features and CFVR evaluation

Clinical characteristics of 127 psoriasis patients (mean age 36 ± 8 years; range, 18–50; 104 males) and 52 healthy subjects (mean age 40 ± 3 years; range, 25–54; 43 males) are presented in [Table 1](#), along with a comparison. The echocardiographic assessment of CFVR was always well tolerated. In psoriasis patients, the median CFVR was 3.0 (2.6–3.5), median cCFVR was 68 (59–80) cm/s, and median CFV_h was 65 (56–77) cm/s. CMD was present in 26 patients (20.4%). Severe impairment ($\text{CFVR} < 2$) was found in 10 patients (7.8%). All 26 patients with CMD had normal coronary arteries at coronary multi-slice computed tomography with calcium score < 10 , and their characteristics are presented in [Table S1](#).

3.2 | CFVR versus diastolic hyperemic flow

Four endotypes were identified in psoriasis patients based on the concordant or discordant variation of CFVR and CFV_h (Figure 2). Figure 3 shows the haemodynamic and microvascular coronary flow parameters relative to each endotype and in healthy subjects. CFVR was preserved (>2.5) in both endotypes 1 and 2. However, endotype 1 showed different coronary flow parameters compared to endotype 2 (A-F), in particular lower CFVR (Figure 3C, $p = 0.01$) and $cCFVR$ (Figure 4, $p < 0.001$). Indeed, endotype 1 had a higher BMR (Figure 3D, $p < 0.001$) and HMR (Figure 3E, $p < 0.001$) and consequently lower CFV_r and CFV_h compared to endotype 2. These findings allow a better characterization of patients with preserved CFVR. Along this notion, PASI was higher in endotype 1 compared to endotype 2 (13.5 [10–18] vs. 10 [7–15], $p = 0.02$) despite both having $CFVR > 2.5$.

Of note, endotypes 1 and 3 presented a similar PASI (13 [10–18] vs. 15 [13–20], $p = 0.2$) and both had impaired CFV_h . However, CFVR was >2.5 (i.e. no CMD) in

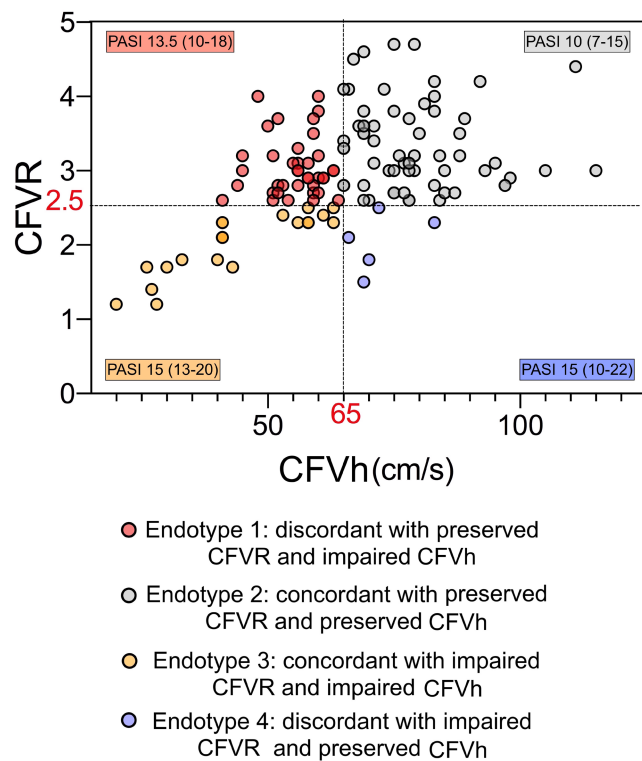


FIGURE 2 Scatter plot of the coronary flow velocity reserve and hyperemic diastolic coronary flow velocity. Concordant and discordant impairment of the coronary flow velocity reserve (CFVR) and hyperemic diastolic coronary flow velocity (CFV_h) identified four endotypes of patients. $CFVR \leq 2.5$ and $CFV_h \leq 65$ cm/s were defined as abnormal. The PASI of the individual endotypes is shown in the smaller boxes (median and interquartile range)

endotype 1 compared to endotype 3 with CMD. Notably, endotype 1 had a higher BMR ($p = 0.003$, Figure 3D) but a lower HMR ($p = 0.008$, Figure 3E), with a lower CFV_r ($p = 0.007$, Figure 3A) but higher $cCFVR$ ($p = 0.008$, Figure 4) and CFV_h ($p = 0.002$, Figure 3B) compared to endotype 3 accounting for higher CFVR.

As expected, PASI was higher in endotype 3 compared with endotype 2 (15 [13–20] vs. 10 [7–15], $p = 0.001$). These results suggest that a combined evaluation of CFVR with $cCFVR$ and the PASI may facilitate the identification of CMD and offer a better phenotyping of psoriasis patients. Age was slightly different between endotypes. Specifically, patients in endotype 2 were younger than patients in endotype 1 (34 ± 6 vs. 38 ± 8 , $p = 0.007$). No other differences were found between groups. Figure 5 shows the differences between the endotypes and healthy subjects.

3.3 | Subpopulation after treatment

The CFVR improved after 6 months of therapy compared to baseline ($p < 0.0001$) in all except for 11 patients (14%) with worsened and for 3 (4%) with unchanged CFVR at follow-up. Table 2 presents the microvascular coronary flow parameters of 78 patients assessed before and after treatment. There were significant improvements in all coronary haemodynamic parameters, except for BMR after treatment. No relationship between the CFVR change and interleukin 6 or vascular endothelial growth factor was found. Only 15 (19%) patients failed to attain a 75% improvement from the baseline score (PASI 75), 32 (41%) patients reached PASI 75 but not PASI 90, 13 (17%) patients achieved PASI 90 but not PASI 100 (complete clearance of psoriasis), and 18 (23%) showed a complete favourable response. No difference among the therapies was found.

3.4 | Effect of therapy for the four endotypes

PASI generally improved without differences among endotypes ($p = 0.2$). CFVR after 6 months of therapy improved less in patients belonging to endotype 1 compared with those in endotype 2 (6 [–28 to 26] % vs. 33 [18–64] %, $p = 0.02$) and in endotype 3 (6 [–28 to 26] % vs. 77 [39–100] %, $p < 0.001$; Figure 6). CFVR raised >2.5 in all but 1 endotype 3 patient ($CFVR = 2.4$).

Of note, all 11 patients with worsened CFVR belonged to endotype 1. These 11 patients showed lower CFV_r (18 [16–19] vs. 20 [19–21] cm/s, $p = 0.01$) and CFV_h (52 [48–54] vs. 58 [56–60] cm/s, $p = 0.01$) with higher BMR (5.1 [4.7–5.5] vs. 4.4 [4.2–4.9] mm Hg·s/cm, $p = 0.04$) compared with the other patients into the same endotype ($n = 14$). Moreover,

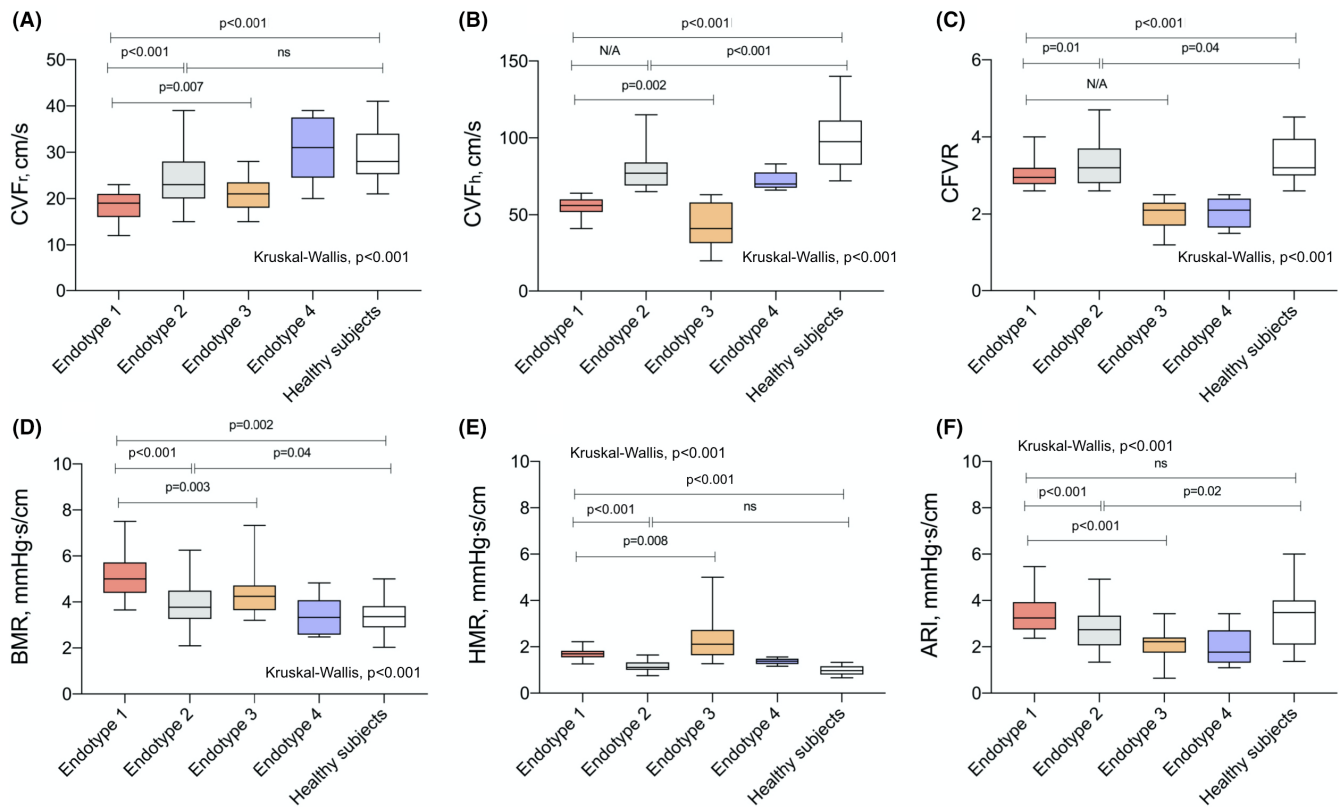


FIGURE 3 Haemodynamic and microvascular coronary flow parameters relative to each endotype and in healthy subjects. Coronary flow velocity reserve was preserved (CFVR) (>2.5) in both endotype 1 and 2. However, endotype 1 showed different coronary flow parameters compared to endotype 2, in particular lower CFVR (C, $p = 0.01$) with lower CVF_r (A) and higher BMR (D)

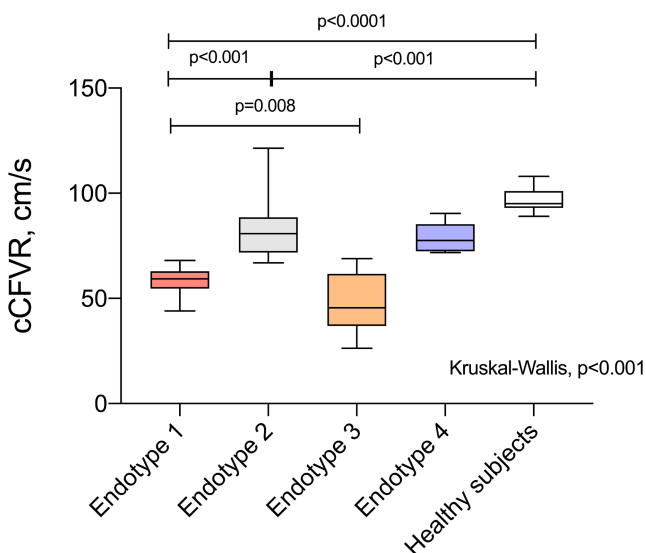


FIGURE 4 cCFVR in each endotype and in healthy subjects. cCFVR was lower in endotype 1 than in endotype 2 ($p < 0.001$) and healthy subjects ($p < 0.0001$)

these 11 patients in endotype 1, who experienced worsening CFVR, had a first CFVR not unlike patients in whom CFVR would later improve (2.8 [2.7–3.1] vs. 2.9 [2.7–3.0], $p = 0.7$).

Instead, the cCFVR was lower in the 11 patients with worsened CFVR compared with those improving their CFVR (55 [50–57] vs. 61 [59–64] cm/s, $p = 0.01$). PASI improvement was similar in the two groups and comparable to findings in all other endotypes ($p = 0.2$). It is remarkable how, in endotype 1, a significant reduction in disease activity after therapy indicated by lower PASI was not always translating into an improvement of CFVR. This observation suggests the hypothesis regarding the presence in some patients in this endotype of more advanced coronary microvascular damage, possibly structural, resistant to inflammation-lowering approaches.

3.5 | Microvascular parameters in patients with normal CFVR (endotypes 1 and 2, $n = 55$), worsened after therapy but remained in the normal range (>2.5)

CVF_r and CVF_h were lower in endotype 1 patients and worsened in CFVR after therapy ($n = 11$) compared with patients having a normal CFVR who featured improved values after therapy ($n = 44$) (19 [16–20] vs. 23 [20–30] cm/s, $p = 0.001$, and 52 [51–55] vs. 71 [60–83] cm/s, $p = 0.003$, respectively). The BMR and HMR were higher

	BMR, mmHG*s/cm	p	HMR, mmHG*s/cm	p	ARI, mmHG*s/cm	p	ARI%	p
Healthy Subjects*	4.1 (3.5-5.1)	/	1.1 (1.0-1.4)	/	3.0 (2.3-3.8)	/	72 (69-76)	/
Endotype 1	5.0 (4.4-5.6)	0.002	1.7 (1.5-1.8)	<0.001	3.2 (2.7-3.9)	ns	65 (64-68)	<0.0001
Endotype 2	3.8 (3.3-4.3)	0.04	1.1 (1.0-1.3)	ns	2.7 (2.0-3.3)	0.02	69 (66-73)	0.004
Endotype 3	4.2 (3.6-4.6)	ns	2.1 (1.6-2.6)	<0.001	2.2 (1.8-2.3)	<0.0001	51 (42-57)	<0.0001
Endotype 4	3.3 (2.6-3.4)	0.04	1.1 (1.0-1.4)	ns	1.7 (1.5-1.9)	<0.0001	56 (53-59)	<0.0001

*reference

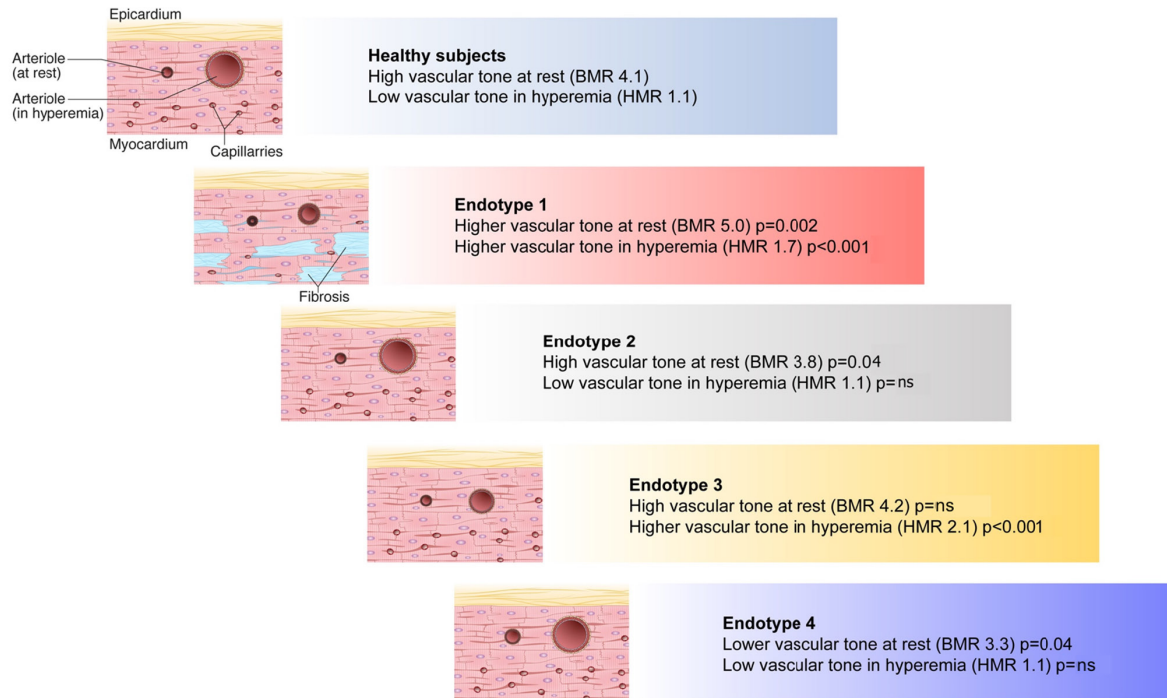


FIGURE 5 Comparison between various endotypes and healthy controls. The table specifies the differences in the baseline (BMR) and hyperemic microvascular resistance (HMR), arteriolar resistance index (ARI) and ARI% between four endotypes ($n = 38, 63, 21$ and 5 , respectively) and healthy controls ($n = 52$). The lower part visualizes the possible patho-physiological mechanism underlying the different endotypes, compared with healthy subjects

in patients with a normal CFVR and showed worsening after therapy ($5.0 [4.6-5.6]$ vs. $3.7 [3.0-4.4]$ mmHg-s/cm, $p = 0.002$, and $1.7 [1.6-1.8]$ vs. $1.2 [1.0-1.5]$ mmHg-s/cm, $p = 0.001$, respectively). The CFVR was comparable between the two groups ($2.7 [2.3-3.0]$ vs. $2.9 [2.7-3.1]$, $p = 0.6$), whereas the cCFVR was lower in patients with normal CFVR yet worsened after therapy ($57 [54-79]$ vs. $66 [58-82]$ cm/s, $p = 0.03$).

Additionally, we generated receiver operating characteristic curves to determine the optimal cut-off value of the CFVR and other haemodynamic parameters for the prediction of deteriorating CFVR in patients with normal CFVR (endotypes 1 and 2). Table S2 shows the prognostic value of each coronary flow parameter for the detection of declining CFVR. As shown in Figure 7A, a lower CFVR was not associated with worsened CFVR at follow-up. The area under the curve was 0.582 with a standard error of 0.108, yielding a 95% confidence interval of 0.371–0.793 ($p = 0.4$). A CFVR cut-off point of 3.1, identified as optimal

by receiver operating characteristic curves analysis, was only 20% specific and 60% sensitive (positive predictive value 14%, negative predictive value 69%; $p = 0.2$), with an accuracy of 27%. On the contrary, Figure 7B indicates that a lower cCFVR was associated with declining CFVR. The area under the curve was 0.809 with a standard error of 0.088, yielding a 95% confidence interval of 0.636–0.982 ($p = 0.002$). The cCFVR cut-off point at 59 cm/s was 93% specific and 70% sensitive (positive predictive value 70%, negative predictive value 93%; $p < 0.0001$), with an accuracy of 90%. This supports the use of cCFVR as a better marker of advanced and irreversible CMD.

3.6 | Intraobserver and interobserver reproducibilities of CFVR

Before treatment, the intraobserver reproducibility was high ($r = 0.94$, $SEE = 0.10$); the mean difference was

−0.005; the upper and lower limits of agreement between the measurements were +0.17 (95% CI, +0.09 to +0.21) and −0.18 (95% CI, −0.24 to −0.13), respectively; and the ICC was 0.976. The interobserver reproducibility was also high ($r = 0.91$, $SEE = 0.11$); the mean difference was −0.016; the upper and lower limits of agreement between the two measurements were +0.30 (95% CI, +0.23 to +0.43) and −0.33 (95% CI, −0.41 to −0.21), respectively; and the ICC was 0.969.

After treatment, the intraobserver reproducibility was high ($r = 0.98$, $SEE = 0.12$); the mean difference was 0.011; the upper and lower limits of agreement between the measurements were +0.19 (95% CI, +0.1 to +0.24) and −0.17 (95% CI, −0.21 to −0.12), respectively; and the ICC was 0.991. The interobserver reproducibility was also high ($r = 0.95$, $SEE = 0.13$); the mean difference was 0.021;

TABLE 2 Characteristics of Patients before and after Anti-Inflammatory Therapy (N = 78)

	Before therapy	After therapy	<i>p</i>
CFV _r , cm/s	21 (20–26)	20 (18–22)	<0.0001
CFV _h , cm/s	61 (52–77)	67 (58–78)	0.006
CFVR	2.8 (2.4–3.0)	3.6 (3.1–4.1)	<0.0001
BMR, mmHg-s/cm	4.1 (3.3–4.8)	3.4 (2.9–4.5)	0.2
HMR, mmHg-s/cm	1.5 (1.1–1.8)	1.2 (1.1–1.5)	0.001
ARI, mmHg-s/cm	2.4 (1.9–3.0)	3.1 (2.6–3.6)	<0.0001
ARI%	64 (60–66)	88 (71–99)	<0.0001
cCFVR, cm/s	64 (55–81)	70 (61–82)	0.004
PASI	13 (10–18)	2 (1–3)	<0.0001
hs-CRP, mg/L	1.8 (0.3–3.3)	0.3 (0.12–2.6)	<0.0001
TNF- α , pg/ml	9.9 (7.8–10.5)	4.4 (3–5)	<0.0001

Abbreviations: hs-CRP, high-sensitive C-reactive protein; PASI, psoriasis area severity index; TNF- α , tumour necrosis factor- α .

Other abbreviations as in Table 1.

the upper and lower limits of agreement between the two measurements were +0.23 (95% CI, +0.19 to +0.38) and −0.19 (95% CI, −0.23 to −0.15), respectively; and the ICC was 0.971.

4 | DISCUSSION

Our findings document that in psoriasis an impaired CFVR, which is a marker of CMD, was predominantly driven by the combination of decreased CFV_h (as primarily reflected by cCFVR) and increased HMR. This evidence points to the reduction of CFV_h due to high HMR (pathophysiological mechanism 2) as the main driver of the impaired vasodilation of the coronary microcirculation in this disease. Accordingly, a blunted coronary arteriolar dilatory reserve is indicated by the ARI and ARI% in patients with CMD compared to those without it as well as in psoriasis patients compared to healthy subjects. Some authors ascribed this haemodynamic phenotype as a consequence of microvascular structural remodelling,²⁰ whereas others reported improvements after therapy,²¹ suggesting a functional microvascular alteration. Our findings support the existence of a functional component in the decrease of arteriolar vasodilatory capacity and, thus, the ability to recruit CFVR. This view is supported by the normalization of the CFVR in the overwhelming majority of our patients, in the absence of other cardiovascular risk factors, after 6 months of therapy with specific immune-inflammatory modulators,^{21,22} such as inhibitors of tumour necrosis factor- α , interleukin 17A and interleukin 12/23.

Inflammation profoundly influences arterial physiology leading to vascular dysfunction, such as atherosclerosis and arterial stiffening.²³ Psoriasis is accompanied by diffuse arterial dysfunction, proportional to the severity of the immune-inflammatory alterations.⁵ At the core of

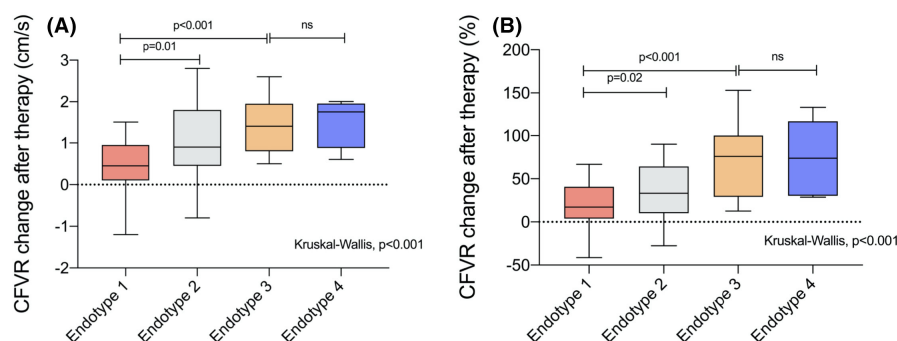


FIGURE 6 Coronary flow velocity reserve was preserved (CFVR) change after therapy across the different endotypes. The CFVR was unchanged in 3 (4%) patients with endotype 2 and worsened after 6 months of therapy only in 11 patients (14%), all of which were of endotype 1 (endotype 1, $n = 25$; endotype 2, $n = 30$; endotype 3, $n = 19$; endotype 4, $n = 4$). Groups were compared by Kruskal-Wallis with the Dunn multiple comparisons test

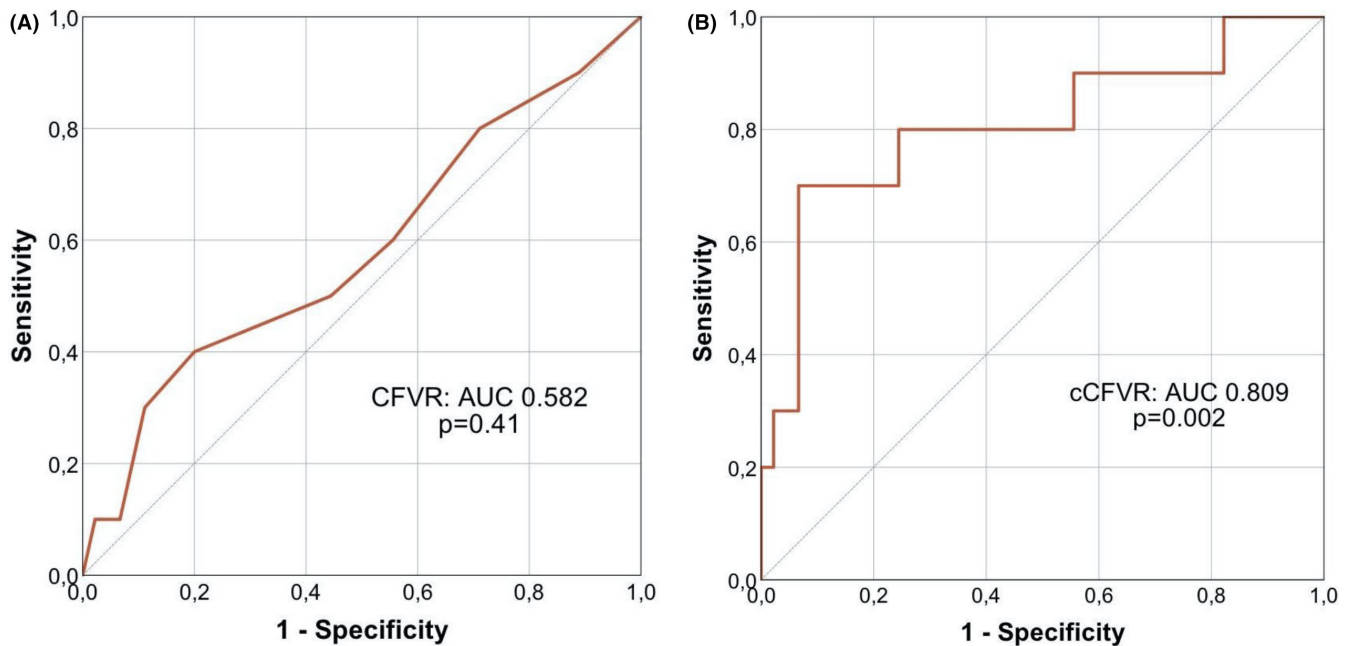


FIGURE 7 Ability of Coronary flow velocity reserve was preserved (CFVR) and cCFVR to predict depressed CFVR by receiver operating characteristic (ROC) curve analysis. (A) A lower CFVR at baseline is not associated with worse CFVR at follow-up. The area under the curve was 0.582 with a standard error of 0.108, yielding a 95% confidence interval (CI) of 0.371 to 0.793 ($p = 0.4$). (B) A lower cCFVR was associated with worse CFVR at follow-up. The area under the curve was 0.809 with a standard error of 0.088, yielding a 95% CI of 0.636–0.982 ($p = 0.002$)

many of these processes, there is an increased production of radical oxygen species, particularly superoxide anions and hydrogen peroxide, in addition to the activation of noxious redox-sensitive signalling pathways.^{24,25} Additionally, inflammation-driven endothelial dysfunction may result in functional coronary microvascular stiffening due to a concomitant reduction of NO bioavailability and increased activity of the opposing mediator, endothelin 1.²⁶ Recent findings suggest that the treatment of inflammation by targeted drugs leads to the regression of arterial dysfunction.²⁷ All these factors may explain how, in most of our patients, a reduced CFVR normalized after specific anti-inflammatory therapy while significantly improving the PASI, a validated marker of disease activity and inflammation. We employed five different therapeutic interventions, each having different mechanisms of effect, although generally modulating inflammation.

Another remarkable finding of our study is that the CFVR may worsen despite the improvement in psoriasis as judged by reduced PASI. All patients with worsened CFVR despite anti-inflammatory therapy belonged to endotype 1 (discordant with preserved CFVR and abnormal CFV_h) and exhibited low flow velocities at rest and during hyperaemia with high microvascular resistance. Based on these results, the presence of a different remodelling of coronary microcirculation with structural features such as partial loss of the vascular bed capacity, capillary

rarefaction and fibrosis may be speculated (Figure 2). The latter suggests, even if it does not prove, irreversible structural damage with worsening of the coronary flow parameters despite anti-inflammatory therapy. These findings highlight the fact that in the presence of high microvascular resistance, CFVR may remain normal despite a dysfunctional microvasculature. This happens because the CFVR metric is dimensionless and, therefore, not always able to capture structural CMD with low flow velocities and high resistances. Consequently, we propose a companion metric (cCFVR), calculated as the “quadratic mean”.¹¹ Ratios are not ideal for exploring differences between groups, as changes in the numerator and denominator occurring in the same direction may readily cancel each other out.¹⁰ Therefore, cCFVR may be better suited to identify differences at similar CFVR values, using CFV_h as a surrogate marker. In contrast to ratio-based metrics, the associated companion carries sound physical units (namely cm/s).¹¹ The companion can also be identified as being associated with physiologically relevant quantities, for example, cCFVR relates to hyperaemia-recruited coronary flow velocity.^{10,11} Notably, cCFVR in combination with CFVR and other microvascular coronary flow parameters investigated in this study permitted elucidation of underlying pathophysiologic mechanism of CMD.

Moreover, our findings highlight the importance of successfully treating systemic inflammation to improve

CMD in psoriasis, and add to the growing body of literature regarding the beneficial therapeutic role of immune-inflammatory modulation to decrease the cardiovascular disease risk. Larger prospective studies with longer follow-up periods should be conducted to understand how changes in CFVR and cCFVR may translate into a reduction in the future cardiovascular events in psoriasis and whether elevated resting flow in functional microvascular dysfunction precedes changes that lead to structural microvascular dysfunction. Future therapeutic studies should stratify patients with CMD based on impairment of resting or hyperemic coronary diastolic flow and considering the proposed patient endotypes.

Some important limitations of the present study must be taken into account. Firstly, the relatively small sample size makes it a hypothesis-generating study. Secondly, this was a retrospective study that included only a few patients with severely worsened CFVR. A key methodological limitation of this work is the lack of gold standard invasive data (invasive CFVR and microvascular resistance measurements in response to intracoronary or intravenous adenosine) that would evidence which patients definitively had CMD. Obviously, such an invasive study would ethically not be permissible in healthy controls, and therefore, we relied on non-invasive studies such as the present investigation. However, our group described the close relationship between invasive and noninvasive measurement of CFVR.²⁸ Unfortunately, to the best of our knowledge, no correlation data are available between invasive and non-invasive measurement of microvascular resistance indices. However, we can say with reasonable certainty that low coronary flow velocities underlie high microvascular resistances and high velocities are associated with low resistances. We do not have histological data to validate our hypothesis on the relationship between coronary flow endotypes and a specific coronary microvascular remodelling process as it would be unethical to submit psoriasis patients to cardiac catheterization and endomyocardial biopsy. Moreover, additional measurements of circulating biomarkers suggestive of inflammation, fibrosis or collagen turnover, or evaluation of myocardial fibrosis with magnetic resonance imaging were not performed. Finally, most of our patients and controls were males and thus results cannot be with certainty extrapolated to women.

5 | CONCLUSIONS

We demonstrated that the newly introduced cCFVR may contribute to better characterization of CMD in psoriasis patients. Particularly, a lower cCFVR was associated with worse CFVR at follow-up after treatment.

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CONFLICT OF INTEREST

Nothing to disclosure and no conflict of interest.

DISCLOSURES

None.

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