

## Diagnostic Usefulness of Synovial Vascular Morphology in Chronic Arthritis. A Systematic Survey of 100 Cases

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**Objectives:** To assess the diagnostic usefulness of the systematic analysis of synovial vascular morphology in various inflammatory, early, and longstanding arthropathies, and to examine the validity of the vascular patterns in predicting the evolution of a group of patients with undifferentiated arthritis (UA).

**Methods:** One hundred patients who underwent rheumatologic arthroscopy of a symptomatic joint (85 knees, 11 wrists, 3 elbows, 1 metacarpophalangeal joint) were evaluated. The same observer, blinded to patient diagnosis, analyzed the video recordings of the arthroscopies. Vascular morphology was classified into 3 patterns: straight, tortuous, and mixed.

**Results:** Eighty-one patients had inflammatory arthritis: 35 rheumatoid arthritis (RA), 16 psoriatic arthritis (PsA), 13 spondyloarthropathies (SpA), and 17 UA. Forty-nine percent of patients with RA had a straight pattern, 28% a mixed, and 23% a tortuous one. The sensitivity rate of the straight pattern for RA was 77% and the specificity rate was 70%. Seventy-six percent of RA patients with a straight pattern were rheumatoid factor positive (RF+) against 25% of RA patients with a tortuous pattern. The odds ratio for RA associated to straight compared with tortuous pattern was 57.3 (95% confidence interval, 6.6 to 499.5;  $P < .001$ ). Patients with PsA and SpA shared the same pattern and were analyzed as 1 group. Ninety-three percent of patients with PsA/SpA had a tortuous pattern, 4% a straight pattern, and 3% a mixed pattern. The sensitivity rate of the tortuous pattern for PsA/SpA was 61% and the specificity rate was 95%. During 2 years of follow-up, 6 of 17 patients with UA were definitely diagnosed: 4 RA (2 RF+ and straight pattern; 2 with a tortuous pattern, 1 with RF+ and HLA-B27+); 1 SpA and 1 PsA, both with a tortuous pattern. No differences in vascular patterns were observed according to disease duration. Our results indicate that vascular patterns are not modified by disease modifying antirheumatic drug (DMARD) treatment. The other 19 patients had osteoarthritis ( $n = 8$ ) and calcium pyrophosphate dihydrate crystal deposition disease ( $n = 11$ ) and their predominant vascular pattern was tortuous-like.

**Conclusions:** Arthroscopic assessment of synovial vascular changes in chronic arthritis may be of diagnostic and pathogenetic interest, although differences between published studies suggest a need for consensus in evaluating vascular patterns. A straight pattern is strongly associated with RF +

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**RA whereas a tortuous pattern is generally associated with PsA or SpA; these associations are independent of disease duration. The vascular pattern likely does not change qualitatively with DMARD therapy. The application of this technique to the diagnosis or prognosis of patients with UA may be a complementary tool for the treatment of these patients, but larger, prospective studies are necessary to confirm this hypothesis.**

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**I**NFLAMMATION OF synovial tissue (synovitis) is a common final pathway in different inflammatory arthritides. The macro- and microscopic features of synovitis seem to be similar in these arthropathies, and have been defined as non-specific synovitis. However, recent studies have shown differences at either molecular and/or cellular levels (1): a Th1 cytokine pattern of expression is characteristic of rheumatoid arthritis (RA), whereas in spondyloarthropathies (SpA), a Th2 or Th0 cytokine pattern is more frequent (2,3). Furthermore, the CD4/CD8 ratio is higher in RA than in SpA, and macrophages, B cells, and plasma cells are more abundant in RA than in SpA (4,5).

Neovascularization, or growth of new blood vessels from preexisting vessels of the synovium, is 1 of the hallmarks of synovitis (6). The development of rheumatologic arthroscopy represents a significant step forward in investigating joint disease (7), especially the vascular changes characteristic of synovitis. Using this technique, Reece et al (8) assessed the vascular patterns of synovium in early psoriatic arthritis (PsA), reactive arthritis (ReA), and RA, and found that patients with RA had predominantly straight, branching vessels, whereas patients with PsA and ReA had predominantly tortuous, bushy vessels. This study reported that vascularity was the most distinctive and reliable synovial feature scored by 3 observers, and that these different vascular patterns may have important pathogenetic implications (8). Recently, the same authors confirmed their previous findings (9).

Other investigators also have studied the macroscopic morphology of synovial blood vessels in RA and SpA. Whereas 1 study confirmed the previously described vascular pattern for RA and PsA (10), another reported that straight vessels are

most characteristic of RA, even though they are not the most prevalent (11).

Until now, there has been no systematic study of synovial vascular morphology in patients with specific inflammatory arthropathies of diverse duration, including the heterogeneous group of patients with undifferentiated arthritis (UA). Patients with UA comprise a significant percentage of patients seen in early arthritis clinics (12). Therefore, the development of diagnostic and prognostic markers for these patients is of interest (13). The study and follow-up of patients with UA, some of whom develop a definitive diagnosis over time, may clarify the role of arthroscopy in the diagnosis of inflammatory joint disease.

The aims of the present study are to assess the diagnostic usefulness of the systematic analysis of synovial vascular patterns in various inflammatory, early, and longstanding arthropathies; to confirm the vascular patterns in joints other than the knee; and to examine the validity of the vascular morphology as a predictor of the evolution of patients with UA. The study of vascular morphology in patients with chronic, noninflammatory arthropathies, osteoarthritis (OA) and calcium pyrophosphate dihydrate crystal deposition (CPPD) disease, also is considered.

## PATIENTS AND METHODS

### *Patients*

The first consecutive 100 patients from the database of the Rheumatological Arthroscopy Unit were selected: 81 patients with active inflammatory arthritis (39 with early arthritis), 8 patients with OA, and 11 patients with CPPD disease. CPPD disease was diagnosed by radiologic chondrocalcinosis and episodic monoarthritis with CPPD crystals in synovial fluid.

In the inflammatory group, 35 patients had RA according to American College of Rheumatology (formerly, American Rheumatology Association) 1987 criteria (18 with early arthritis), 16 had PsA according to Moll and Wright criteria (6 with early arthritis), and 13 had SpA according to European Spondyloarthropathies Study Group (ESSG) criteria (8 with early arthritis, 4 ankylosing spondylitis, 1 ReA, 6 undifferentiated SpA [uSpA], all HLA-B27 positive; 1 ReA and 1 Crohn disease SpA, both HLA-B27 negative). Seventeen patients were classified as UA (7 with early arthritis). Patients with early arthritis (disease duration  $\leq 12$  months) had undergone arthroscopy examination before introduction of disease modifying antirheumatic drug (DMARD) therapy, whereas most of patients with  $>12$  months disease duration were on DMARDs.

#### Arthroscopy

All patients underwent rheumatologic arthroscopy (diagnostic and/or therapeutic indication) of a symptomatic joint between January and December 1999, at the Rheumatological Arthroscopy Unit, Hospital Clinic of Barcelona, after informed consent was obtained. A 2.7-mm diameter (knee, wrist, and elbow) or a 1.9-mm diameter metacarpophalangeal (MCP) arthroscope (Storz, Tuttlingen, Germany) was inserted into the joint, under local anesthesia. The joint was systematically explored in all cases. The full arthroscopy exploration was video recorded. The video recording was analyzed by the same, blinded observer (J.D.C.), using a computerized analysis system (Studio PCTV; Pinnacle Systems, Braunschweig, Germany) that allows direct single-image analysis, magnification, and storage of the recorded images. This system allows detailed analysis of vascular morphology, but the assignation of the pattern is

made by the investigator according to the distribution of vascular morphology throughout the joint. The vascular morphology was further classified in 3 patterns: straight, tortuous, and mixed. In this study, the compensated  $\kappa$  value of intraobserver reliability for the 3 patterns in the 60 first consecutive patients was 0.79. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona.

#### Statistical Analysis

The Chi-square test or Fisher exact tests were used to analyze qualitative variables in the univariate analysis. For the quantitative variables, either Student *t* test or Mann-Whitney U test was used to compare 2 categories. Variance analysis or the Kruskal-Wallis test was used to compare more than 2 categories. To estimate the risk of developing RA associated with a specific vascular pattern, we used a multivariate logistic regression model. The specificity and sensitivity of these vascular patterns in both RA and SpA/PsA also were analyzed.

## RESULTS

Thirty-nine of 81 patients with inflammatory arthritis had  $\leq 12$  months duration. Eighty-five knees, 11 wrists, 3 elbows, and 1 MCP joint were studied. The distribution of patients according to diagnosis showed no significant differences in disease duration, and no differences were found in the distribution of the vascular patterns (straight, tortuous, and mixed) between patients with less or more than 12 months of disease (Table 1).

#### Clinical and Demographic Characteristics of Patients

Thirty-five patients had RA: 83% women; mean age, 47 years (range, 35 to 76 years); mean disease

**Table 1: Distribution of Diagnosis of Chronic Arthritis and Vascular Pattern According to Disease Duration**

	Diagnosis			Vascular Patterns	
	$\leq 12$ mo	$> 12$ mo		$\leq 12$ mo	$> 12$ mo
RA (n = 35)	18	17	Straight	12	10
PsA (n = 16)	6	10	Tortuous	21	23
SpA (n = 13)	8	5	Mixed	6	9
UA (n = 17)	7	10			

duration 68 months (range, 1.5 to 240 months); 63% rheumatoid factor positive (RF+). Sixteen patients had PsA: 45% women; mean age, 36 years (range, 19 to 57 years); mean disease duration, 38 months (range, 3 to 60 months); and all were RF negative (RF-) and HLA-B27 negative (HLA-B27-). Thirteen patients had SpA: 27% women; mean age, 30 years (range, 18 to 55 years); mean disease duration, 57 months (range, 2 to 284 months); and 85% were HLA-B27 positive (HLA-B27+). Seventeen patients had UA: 57% women; mean age, 55 years (range, 22 to 69 years); mean disease duration, 38 months (range, 3 to 42 months); and 29% were RF+ and 12% were HLA-B27+. Eleven patients had CPPD disease: 65% women; mean age, 72 years (range, 67 to 80 years); mean disease duration, 62 months (range, 36 to 88 months). Eight patients had OA: 40% women; mean age, 73 years (range, 69 to 77 years); mean disease duration, 55 months (range, 44 to 64 months).

#### *Vascular Patterns of the Different Diagnostic Groups of Chronic Arthritis*

Although the vascular morphology was diverse, 2 principal morphologic traits were identified: straight and tortuous. The straight pattern is composed of straight, branching vessels not ending in loops. The tortuous pattern includes tortuous, bushy vessels, and meandering or ring-shaped vessels. When a defined vascular pattern, either straight or tortuous, was predominant (>75% vessels in 1 patient displaying either morphology), the patient was classified according to this predominant pattern. Patients with similar proportions of straight and tortuous patterns were classified as mixed pattern. Figure 1 shows examples of straight and tortuous patterns.

Seventy-seven percent of patients with a straight pattern had RA, 18% UA, and 5% SpA. Forty-nine percent of RA patients had a straight pattern, 28% a mixed pattern, and 23% a tortuous pattern. Because patients with PsA and SpA shared the same vascular patterns, the 2 categories were pooled (PsA/SpA group). Sixty-two percent of patients with a tortuous pattern had PsA/SpA, 20% had UA, and 18% had RA. However, 93% of patients with PsA/SpA had a tortuous pattern, 4% had a straight pattern, and 3% had a mixed pattern. Fifty-three percent of patients with UA displayed a

tortuous pattern, 24% a mixed pattern, and 23% a straight pattern.

With respect to the clinical and immunologic characteristics of the patients (Table 2), we observed that 76% of RA patients with a straight pattern and 70% of RA patients with a mixed pattern were RF+, against only 25% of RA patients with a tortuous pattern. Twenty-seven of 29 patients with PsA/SpA had a tortuous vascular pattern: 10 were SpA HLA-B27+ (4 AS, 1 ReA, and 5 uSpA), 2 were SpA HLA-B27- (1 ReA and 1 Crohn disease SpA), and 15 had PsA (oligo-, mono-, and polyarthritis). One patient had a straight pattern and uSpA (knee arthritis) HLA-B27+, and another had a mixed pattern and PsA (oligoarthritis).

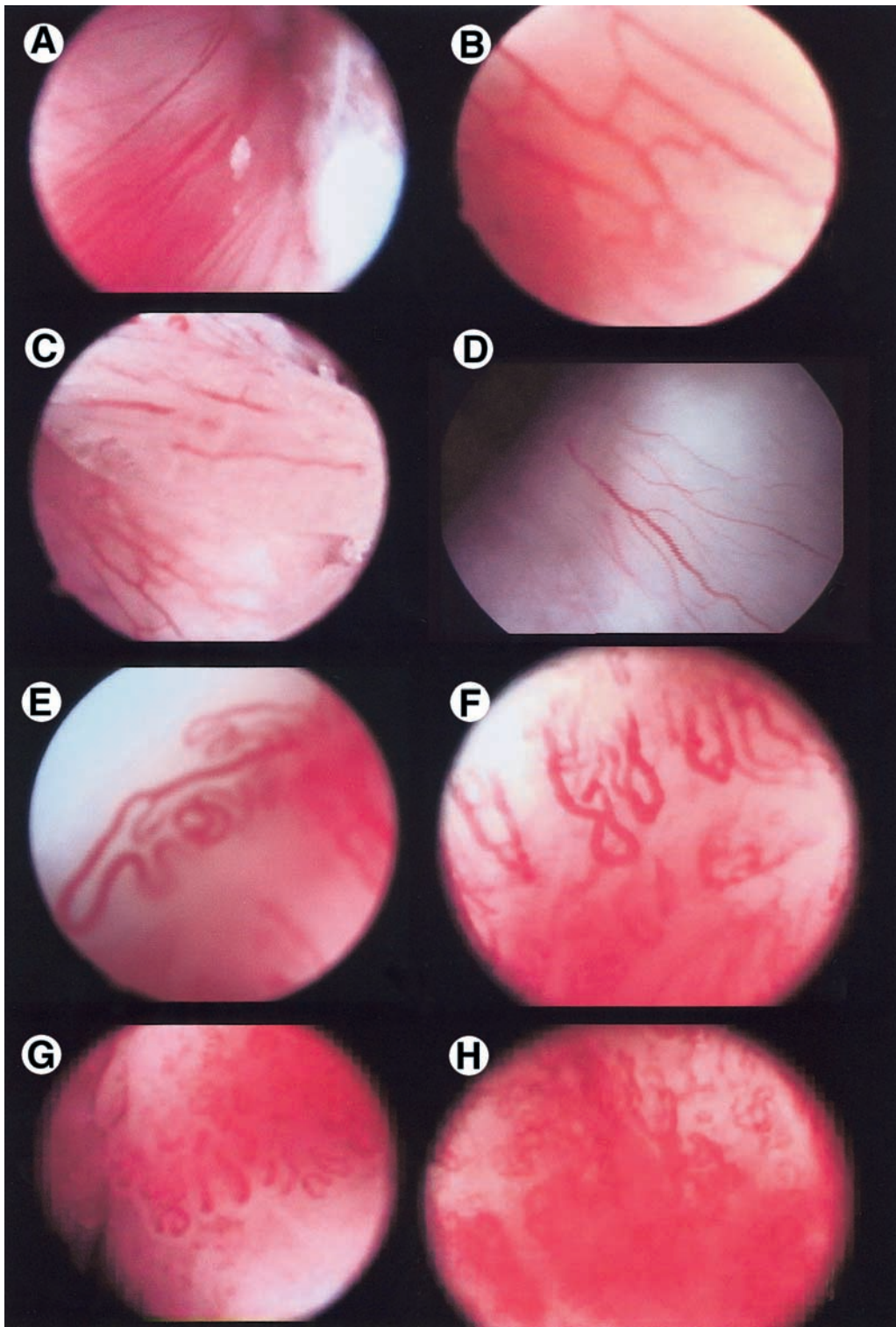
#### *Sensitivity and Specificity of the Vascular Pattern for Diagnosis of RA and PsA/SpA*

The sensitivity of the straight pattern in the diagnosis of RA was 77%, and the specificity 70%. The sensitivity of the tortuous pattern for the diagnosis of PsA/SpA was 61% and the specificity 95%. In a gender-adjusted model, taking the tortuous vascular pattern as a reference, a higher risk of RA was associated with the straight pattern (odds ratio [OR] = 57.3; 95% confidence interval [CI], 6.6 to 499.5;  $P < .001$ ), and with the mixed pattern (OR = 33.7; 95% CI, 3.7 to 305.1;  $P = .002$ ).

#### *Vascular Patterns in Patients With UA Initially and at Follow-up*

Four of 17 UA patients had a straight pattern, of which 2 (50%) had erosive RF+ oligoarthritis and the other 2 had intermittent HLA-B27- monoarthritis. Nine had a tortuous pattern and only 2 (22%) were RF+ (oligoarthritis, 1 of whom was also HLA-B27+). The other 7 had bilateral knee (n = 2), intermittent oligoarthritis (n = 1), or monoarthritis (n = 4) and were all RF- and 1 was HLA-B27+. The remaining 4 patients with UA had a mixed pattern and only 1 (25%) was RF+ (knee arthritis); the others had mono- or oligoarthritis. During the 2 years of follow-up after arthroscopy, 6 of 17 patients with UA developed a definite diagnosis. Four of these 6 patients eventually met the American College of Rheumatology criteria for RA: 2 had a straight pattern (both RF+ oligoarthritis) and the other 2 had a tortuous pattern (1 of them RF+ and HLA-B27+ oligoarthritis). Of the remaining 2 patients, 1 developed uSpA





**Fig 1.** Examples of synovitis from different patients, showing the straight, branching vessels that are seen predominantly in patients with RA (A-D), and the tortuous, bushy vessels that predominate in patients with PsA/SpA (E-H).

**Table 2: Immunologic Features of Chronic Arthritis Patients According to Vascular Pattern**

Diagnostic Group	Straight	Tortuous	Mixed
Rheumatoid arthritis (n = 35)			
RF+	13 (76)	2 (25)*	7 (70)
RF-	4 (24)	6 (75)	3 (30)
Psoriatic arthritis (n = 16)	0	15 (94)	1 (6)
All RF- and HLA-B27-			
Spondyloarthropathies (n = 13)			
HLA-B27+	1 (100)	10 (83)	0
HLA-B27-	0	2 (17)	0
Undifferentiated arthritis (n = 17)			
RF+	2 (50)	2 (22)*	1 (25)
RF-	2 (50)	7 (78)*	3 (75)

NOTE. Percents in parentheses.

\*1 patient HLA-B27+.

HLA-B27+ and the other developed PsA oligoarthritis; both patients had a tortuous vascular pattern at the time of arthroscopy.

#### *Vascular Patterns in Patients With and Without DMARD Therapy*

The patients in the early arthritis group were not receiving DMARD treatment at the time of arthroscopy. However, 31 patients with >12 months of disease duration (17 RA, 9 PsA, 3 SpA, and 2 UA) were receiving treatment with methotrexate (22), intramuscular gold (7), chloroquine (5), salazopyrine (3), or combination therapy. There were no significant differences in the distribution of patterns between the 2 groups (Table 1).

#### *Vascular Patterns in Joints Other Than the Knee*

Fifteen patients underwent arthroscopy in joints other than the knee. The vascular patterns according to the diagnosis were: 11 RA (5 straight, 2 tortuous, and 4 mixed); 3 PsA/SpA (all tortuous); and 1 UA RF+ (straight).

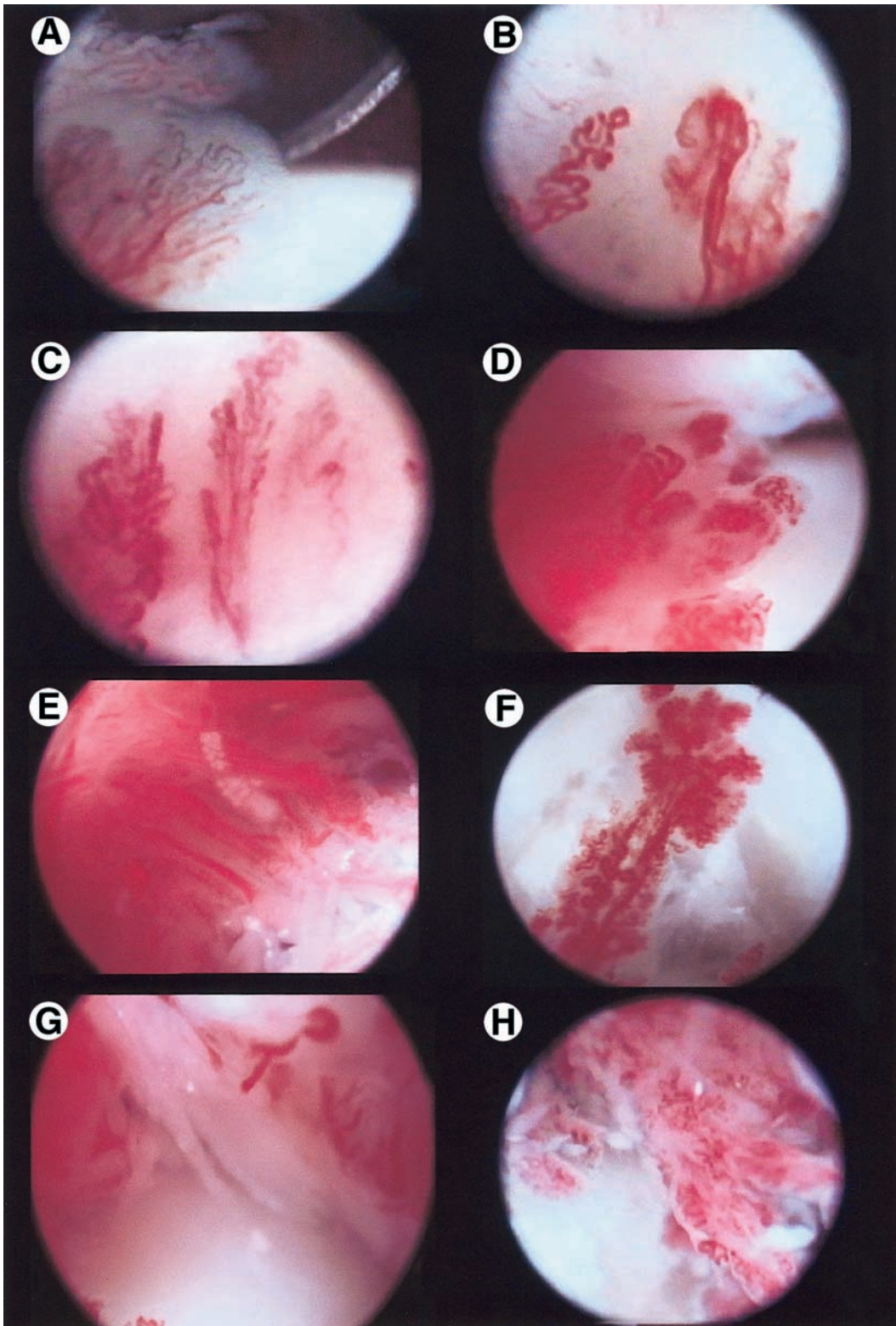
As for the noninflammatory arthropathies, both CPPD disease and OA patients had mild synovitis, characterized by fewer and finer villae, with fewer and smaller ring- and loop-shaped vessels, compared with cases of inflammatory arthritis. Ninety-one percent of patients with CPPD disease and 89% of patients with OA had a tortuous-like vascular pattern (Fig 2). The remaining patients in both groups had a mixed pattern.

## DISCUSSION

This study systematically analyzed the vascular changes that occur in the synovial membrane in early and longstanding inflammatory arthritis, as well as noninflammatory arthropathies. Our results suggest that vascular changes in inflammatory arthritis do not depend on disease duration or DMARD therapy. Rather, the synovial vessel morphology seems to be more related to the type of arthritis. This also seems to be true in joints other than the knee, but the number of cases is too low to for definite conclusions to be drawn.

In our patients, the straight vascular pattern had a specificity rate of 70% and a sensitivity rate of 77% for RA diagnosis, and was associated with a higher risk of RA (OR = 57.3) than the tortuous pattern. The proportion of RA patients with a mixed pattern, and the higher risk of RA associated to this pattern (OR = 33.7), as compared with the tortuous pattern, also is of interest. The high prevalence of RF+ in the RA patients with straight and mixed patterns compared to the tortuous pattern suggests that this vessel morphology may be related to the pathogenesis of RA. Our study confirms the results of earlier studies (8-11) and extends them to SpA patients with AS and uSpA. However, some differences with previous studies were found (Table 3).

The pioneering study by Reece et al (8) found a prevalence of the straight pattern in RA of 89%, as opposed to 49% in the present study. In that study,



**Fig 2.** Examples of synovitis from different patients, showing the tortuous-like vessels that are seen in patients with OA (A-D) and in patients with CPPD disease (E-H).



**Table 3: Studies Evaluating Synovial Vascular Morphology**

Study Diagnosis	Duration (yr)	Straight (%)	Tortuous (%)	Mixed (%)
Reece et al (8)				
RA (n = 18)	<1	89		11*
PsA (n = 14)	<1		73	27*
ReA (n = 12)	<1		73	27*
Baeten et al (11)				
RA (n = 18)	<1 and >1.5	28	28	44
SpA (n = 13)	<1 and >1.5	0	62	38
Fiocco et al (10)				
RA (n = 19)	<2 and >2	100*		
PsA (n = 20)	<2 and >2		100*	
Fraser et al (9)				
RA (n = 12)	<1	100*		
PsA (n = 12)	<1		100	
Cañete et al				
RA (n = 35)	≤1 and >1	49	23	28
PsA (n = 16)	≤1 and >1	0	94	6
SpA (n = 13)	≤1 and >1	8	92	0
UA (n = 17)	≤1 and >1	23	53	24

\*Extrapolated percentage from the articles.

11% of RA patients had “a mixed pattern, but predominantly straight vessels,” while in our study 28% of RA patients had a mixed and, perhaps more unexpectedly, 23% had a tortuous pattern. Another study (10) comparing vascular patterns in RA and PsA concludes that “the prevailing synovial vascular pattern in RA knee joints was straight branching,” but gave no exact percentage for this pattern, or for mixed or tortuous patterns in their RA patients. Baeten et al (11), found 28% RA patients with a straight pattern, 28% with a tortuous pattern, and 44% with a mixed pattern, results more in line with our own. Recently, Fraser et al (9) studied 12 patients with early RA, none of whom had a tortuous pattern, although the mixed pattern was not specifically mentioned.

The differences between these studies may be due to patient selection or to a different definition of patterns. With respect to patient selection, 2 studies (8,9) included only patients with early RA, whereas the other 2 (10,11) included patients with early and late RA, with no apparent differences in synovial pattern related to duration of arthritis. Our study included 51% of early RA patients and we observed no differences in the prevalence of the different vascular patterns compared to longstanding RA. Our RA patients with straight and mixed

patterns were predominantly RF+, but, unfortunately, none of the previous studies give details of the prevalence of RF+ according to the vascular pattern.

Another explanation for differences between studies could be the definition of the vascular pattern, the mixed pattern probably being the most variable between studies. The study by Reece et al (8) found a good correlation between 3 observers in assigning straight or tortuous patterns to RA or PsA patients, although the mixed pattern was not expressly defined. In our study and in the study by Baeten et al (11), the number of RA patients with both mixed and tortuous patterns is even higher than that with straight pattern. These differences could point to difficulties in evaluating synovium with both straight and tortuous vessels in similar proportions.

As previously was shown for PsA and ReA patients, our study shows that AS and uSpA patients also share predominantly the same, tortuous, bushy, vascular pattern. The diagnostic specificity of the tortuous pattern for PsA and SpA is remarkable (95%), although 18% of patients with a tortuous pattern had RA, and 20% had UA. However, only 25% of patients with RA and 22% of patients with UA with tortuous patterns were RF+. These findings



confirm earlier studies in patients with early and longstanding psoriatic arthritis and suggest that the tortuous pattern is highly specific for the group of spondyloarthropathies (PsA and SpA) (8-11). When such a pattern appears in patients with RA or UA, these patients are predominantly seronegative. A recent study describes synovial capillary changes such as "meandering with tight terminal convolutions" in 65% of patients with PsA and 5.5% of patients with RA (10). Although this vessel morphology has been proposed by some authors as specific of psoriasis (14), in our study, it is included as a variety of the tortuous pattern, because it had a similar prevalence in SpA patients without psoriasis. Compared with the straight and mixed pattern, there was a better correlation in the prevalence of tortuous pattern in PsA among all these studies.

To our knowledge, this is the first prospective study of vascular synovial patterns that included patients with UA. As expected, the group was heterogeneous, with the tortuous pattern being the most prevalent. Monarthritides and mixed pattern were more frequent in patients that remained unclassified. Because only 6 of 17 of our patients with UA developed a definite diagnosis after 2 years of follow-up, our results are not conclusive. However, it seems that patients with RF+ UA and a straight vascular pattern are at higher risk of developing RA, as compared with UA patients with a tortuous pattern who will probably develop SpA/PsA.

In the OA and CPPD disease group, the tortuous-like pattern predominated. There are no previous studies on vascular changes in OA or CPPD disease available for comparison. Although the number of patients is small, these noninflammatory arthropathies have been examined only for comparative purposes; their vessel morphology was some similar to the SpA/PsA group. OA and CPPD disease frequently coexist, and there are clinical and laboratory studies supporting an important role for calcium crystal in causing or worsening OA (15). Thus, these chronic arthropathies could develop a reactive synovitis that could share some traits of vessel morphology with seronegative synovitis.

The higher RF positivity in the RA patients with a straight or mixed pattern compared with RA patients with a tortuous pattern, and the close association between the tortuous pattern and PsA/SpA, suggests a pathogenic association between these vascular patterns and the type of arthritis. The molecular basis of this association remains

unclear, although there are some interesting preliminary data (9,16).

Angiopoietins and ephrins control vascular growth and development. Angiopoietin-1 participates in the maturation of blood vessels whereas angiopoietin-2 (ang-2) is their natural antagonist. The ephrins are ligands of the Eph family of receptor tyrosine-kinase and play key roles in development, axon guidance, and vasculogenesis. The ephrin gene expression patterns suggest functional roles for these molecules in vascular patterning in many different adult tissues (17). Vascular endothelial growth factor (VEGF) is a specific growth factor for endothelial cells. A simple VEGF gene gives rise, by alternative splicing, to multiple isoforms that display distinct roles in vascular patterning and arterial development in animal models (18). VEGF and ang-2 are overexpressed in the synovial tissue of PsA compared with RA, and it has been suggested that this coexpression determines synovial vascular morphology (16,19). The same authors found that high levels of synovial fluid metalloproteinase (MMP)-9 and VEGF, and low levels of endothelial cell apoptosis, are closely related to tortuous, bushy pattern in PsA. It was shown previously that differences among vascular patterns were not a reflection of differences in intensity of inflammation (9). On the other hand, VEGF165, the most angiogenic isoform, is selectively up-regulated in the synovial tissue of RA patients and its expression correlates significantly with vascular density (20). Thus, it seems that differential production of angiogenic factors in the synovial membrane may result in different angiogenic phenotypes in RA and PsA, with important implications for pathogenesis.

Our study has some limitations, such as the small number of patients in some disease groups and the small number of joints other than the knee. Further studies will be required to clarify the diagnostic usefulness and to understand the pathogenic significance of distinct synovial vessel morphology in chronic inflammatory synovitis.

In conclusion, this study suggests that arthroscopic assessment of synovial vascular changes in chronic arthritis may be of diagnostic and pathogenic interest, although a consensus on some aspects of vascular pattern definition seems necessary in order to optimize this technique. The diagnostic and/or prognostic application of this tech-

nique to UA patients may be a complementary tool for their treatment, but larger, prospective studies are needed to confirm this hypothesis. Additional

trials are also needed to determine whether specific vascular patterns within RA are associated with disease outcome.

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