SUPPLEMENTAL MATERIAL

Table S1. Demographic and clinical characteristics, and ongoing therapies of patients with inflammatory diseases.

Patients, n	46
Age,years(range)	73.9±16.8 (18.5)
Females, n	25/46 (54%)
Definite inflammatory diseases, n	46/46 (100%)
Acute infections	31/46 (68%)
Pneumonia	12/31 (41%)
Sepsis	6/31 (19%)
Biliary tract infection	5/31 (16%)
Urinary tract infection	4/31 (12%)
Acute bronchitis	3/31 (9%)
Spondylodiscitis	1/31 (3%)
Skin infection*	1/31 (3%)
Immune-mediated diseases	13/46 (28%)
Rheumatoid arthritis	10/13 (77%)
Inflammatory bowel disease*	1/13 (8%)
Polymyalgia rheumatica	1/13 (8%)
Cryoglobulinemic vasculitis	1/13 (8%)
Other	2/46 (4%)
Acute microcrystalline arthritis	1/2 (50%)
Acute pancreatitis	1/2 (50%)
Therapeutic interventions for inflammatory disease, n	46/46 /100%)
Antibiotics	32/46 (70%)
Piperacillin/Tazobactam	14/32 (42%)
Ceftriaxone	5/32 (15%)
Amoxicillin/Clavulanate	4/32 (12%)
Levofloxacin	4/32 (12%)
Vancomycin	4/32 (12%)
Metronidazole	2/32 (9%)
Clarithromycin	2/32 (6%)
Imipenem	2/32 (6%)
Ceftazidime	1/32 (3%)
Teicoplanin	1/32 (3%)
Meropenem	1/32 (3%)
Oxacillin	1/32 (3%)
Colistin	1/32 (3%)
Fluconazole	1/32 (3%)
Anti-inflammatory drugs	13/46 (28%)
Corticosteroids	10/13 (77%)
Tocilizumab	9/13 (69%)
Methotrexate	2/40 (15%)
Cyclosporine	1/13 (8%)
Leflunomide	1/13 (8%)
Abatacept	1/13 (8%)
Colchicine	1/13 (8%)
Other	1/46 (2%)
Gabexate mesilate	1/1 (100%)

Age is expressed as mean ±standard deviation (interquartile range).

*In one patient, both skin infection and inflammatory bowel disease were concomitantly detected. This patient has been counted in the "Immune-mediated disease" group.

Table S2. Demographic, electrocardiographic and laboratory characteristics of subjects in the control group.

Subjects, n	30
Age, years	73.4±5.2 (7.0)†
Females, n	19 (63%)†
Heart rate, bpm	66.5 (14.2)
PR interval, ms	156.7 (19.2)
Patients with PR interval>200 ms, n	1 (3%)
PRc interval, ms	156.9 (24.2)
Patients with PRc interval>200 ms, n	0 (0%)
PR segment, ms	53.3 (23.3)
PRc segment, ms	55.6 (21.1)
CRP, mg/dl	0.11 (0.17)
IL-6, pg/ml	0.09 (0.33)
IL-1, pg/ml	0.05 (0.32)
TNFα, pg/ml	0.42 (0.22)
IL-10, pg/ml	0.52 (0.19)
Cx43	1.31±0.52

PRc interval: heart rate-corrected PR interval; PRc segment: heart rate-corrected PR segment; CRP: C-reactive protein (reference values <0.5 mg/dl); IL-6: interleukin-6 (reference values 0.49-1.25 pg/ml)*; IL-1: interleukin-1 (reference values 0.08-0.29 pg/ml)*; TNFα: tumor necrosis factor alpha (reference values 0.6-3.24 pg/ml)*; IL-10: interleukin-10 (reference values 0-3.6 pg/ml)*; Cx43: connexin 43 mRNA levels in peripheral blood mononuclear cells.
*Cytokine level range measured in an internal reference group of healthy controls.
†p>0.05 vs patients with systemic inflammation (two tail Mann-Withney test and Fisher exact test, respectively).

Values are expressed as median (interquartile range), or frequency count and percentages. Age is expressed as mean ±standard deviation (interquartile range).

Table S3. Demographic, clinical, laboratory and echocardiography characteristics of patients studied for correlation of connexin43 expression between atrial and/or ventricular tissue and blood.

Patient	Heart chamber	Age, years	Sex	Diagnosis	EF, %	proBNP, pg/ml	CRP, mg/dl
1	Left atrium Left ventricle Right ventricle	63	Male	Ischemic cardiomyopathy	<20	842	0.15
2	Right atrium	59	Male	Aortic valve prosthetic endocarditis	60	3149	5.68
3	Left atrium	79	Female	Aortic valulopathy	60	131	0.08
4	Right atrium	79	Male	Mitral and aortic valulopathy	55	58	0.57
5	Right atrium	81	Male	Mitral and aortic valulopathy	55	821	1.15
6	Right atrium	60	Male	Mitral and aortic valulopathy	60	132	0.03
7	Left atrium	60	Female	Mitral valulopathy	70	77	0.46
8	Right atrium	73	Female	Aortic valulopathy	50	346	0.01
9	Left atrium Left ventricle Right ventricle	55	Male	Ischemic cardiomyopathy	<20	813	4.06
10	Right atrium	56	Male	Interatrial communication with partial anomalous pulmonary venous drainage	55	1697	0.35
11	Right atrium	75	Female	Mitral and aortic valulopathy	55	155	0.53
12	Left atrium	57	Male	Mitral valulopathy	60	131	0.03
13	Left ventricle Right ventricle	47	Female	Hypertrophic cardiomyopathy	35	5066	0.34
14	Left ventricle	59	Female	Hypertrophic cardiomyopathy	40	524	0.08

EF: ejection fraction; proBNP: pro-brain natruiretic peptide; CRP: C-reactive protein.

Table S4. Demographic, clinical, electrocardiographic and laboratory findings in inflammatory disease patients with PRc>200 ms *vs* those with PRc<200 ms during active disease (PRE).

	PRc>200 ms	PRc<200 ms	*p*
Patients, n	11/46 (24%)	35/46 (76%)	-
Age, years	84.8±9.0 (16.5)	70.1±17.3 (23.0)	**0.0052**
Females, n	6/11 (55%)	19/35 (54%)	1.0
IL-6 (PRE), pg/ml	22.0 (38.5)	11.2 (12.3)	**0.048**
PRc-interval (POST), ms	195.4 (42.6)	156.9 (23.9)	**<0.0001**
PRc-segment (POST), ms	80.2 (36.9)	57.7 (12.3)	**<0.0001**
CVD, n	5/11 (45%)	18/35 (51%)	1.0
Heart disease*, n	1/11 (9%)	9/35 (26%)	0.24
Hypertension, n	4/11 (36%)	8/35 (23%)	0.44
Diabetes, n	2/11 (18%)	5/35 (14%)	1.0

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CVD: patients with heart disease and/or hypertension and/or diabetes; PRc-interval: heart rate-corrected PR interval; PRc-segment: heart rate-corrected PR segment; IL-6: interleukin-6 (reference values 0.49-1.25 pg/ml); PRE: active disease; POST: after therapeutic interventions resulting in a CRP decrease >75% when compared to the baseline. Cytokine level range measured in an internal reference group of healthy controls.

*Including: chronic heart failure, coronary artery disease, hypertensive heart disease, valvular heart disease.

Values are expressed as median (interquartile range), or mean±standard deviation, or frequency count and percentages.

Differences were evaluated by the two-tail Mann-Whitney test or unpaired T-test.
Difference in categorical variables were evaluated by the two-sided Fisher's exact test.
P values <0.05 are presented in bold.

Table S5. Changes in laboratory and electrocardiographic parameters in a sub-cohort of patients with inflammatory diseases (n=13) underwent expression analysis of circulating connexin43, during active disease (PRE) and after therapeutic interventions resulting in a CRP decrease >75% when compared to the baseline (POST).

	PRE	POST	*p*
CRP,mg/dl	16.8 (12.8)	1.8 (1.5)	**<0.0001**
IL-6, pg/ml	22.3 (57.4)	3.7 (4.7)	**0.004**
IL-1, pg/ml	0.39 (0.47)	0.32 (0.41)	0.32
TNFα, pg/ml	0.80 (0.31)	0.80 (0.32)	0.73
IL-10, pg/ml	0.60 (0.22)	0.49 (0.16)	0.96
PRc-interval, ms	179.1 (68.1)	167.5 (29.6)	**0.024**
PRc-segment, ms	84.6 (65.1)	69.3 (36.7)	**0.012**
Cx43	1.01±0.44	1.24±0.87	0.15

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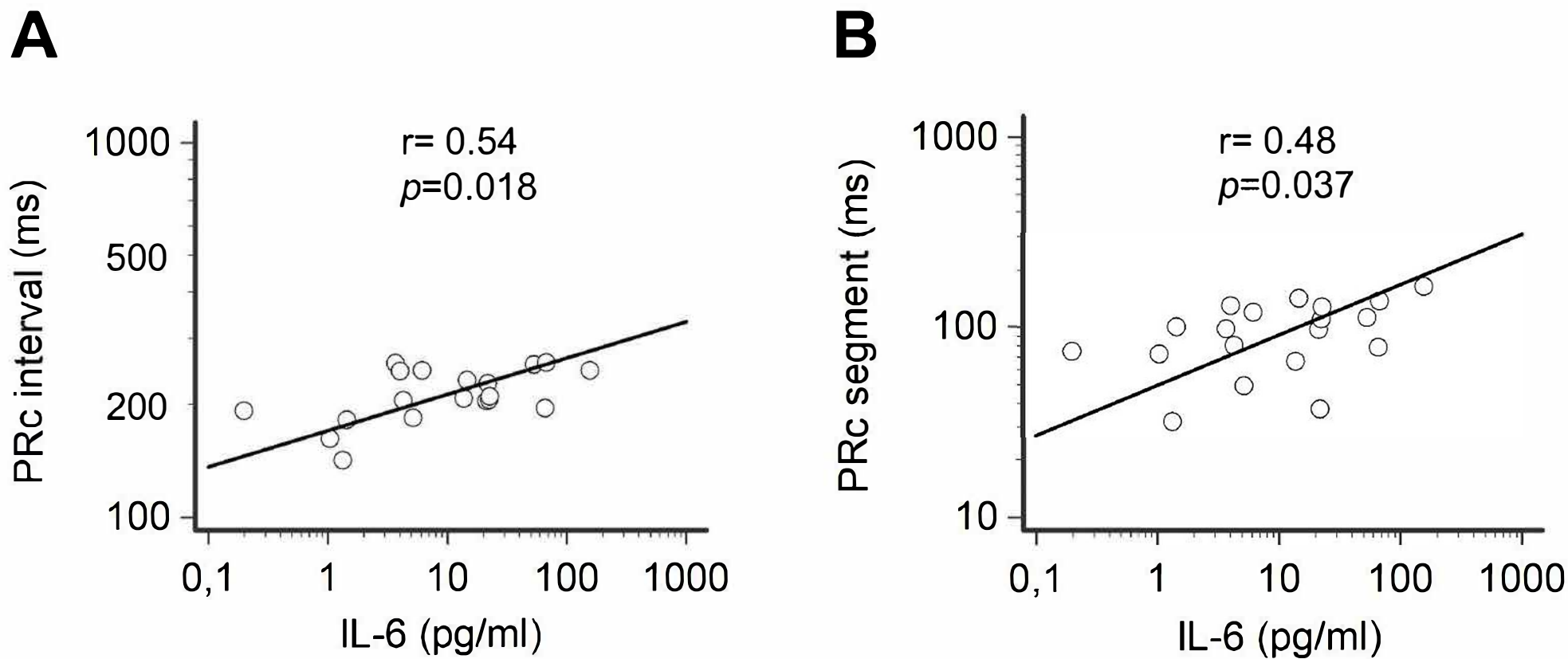
PRc-interval: heart rate-corrected PR interval; PRc-segment: heart rate-corrected PR segment; CRP: C-reactive protein (reference values <0.5 mg/dl); IL-6: interleukin-6 (reference values 0.49-1.25 pg/ml); TNFα: tumor necrosis factor alpha (reference values 0.6-3.24 pg/ml); IL-1: interleukin-1 (reference values 0.08-0.29 pg/ml). Cytokine level range measured in an internal reference group of healthy controls.

Values are expressed as mean±standard deviation or median (range).

Differences were evaluated by the two-tail Student's paired "t" test, or the two-tail Wilcoxon matched pairs test.

Figure S1. Relationship over time between PRc-interval and PRc-segment with IL-6 levels in inflammatory disease patients presenting with PRc-interval>200 ms during active disease.

Spearman test. Patients, n=11. PRc-interval: heart rate-corrected PR interval; PRc-segment: heart rate-corrected PR segment; IL-6: interleukin-6.