SUPPLEMENTAL MATERIAL

Supplemental Methods

Study population.

-Torsades de pointes cohort (TdP cohort)

The TdP cohort consisted of 40 consecutive patients who presented with TdP from January 2008 to April 2016. All patients who came to our attention in that period of time were enrolled, independent of ongoing therapies and concomitant diseases. No patients were excluded. Detailed information regarding the TdP cohort is provided in Table 1 and Supplementary-Table 1.

-Rheumatoid arthritis patients (RA)

Ten RA patients with active disease were selected (among the 17 screened). Inclusion criteria were: (i) disease activity score in 28 joints (DAS28) > 3.2 [1], and (ii) C-reactive protein (CRP) levels >0.5 mg/dl. Notably, 60% of patients showed severe active disease, i.e. DAS28>5.1. Ongoing treatments in RA patients included steroids (n=6, mean prednisone-equivalent dose 10.8 mg daily), methotrexate (n=2, mean dose 12.5 mg weekly), cyclosporine (n=1, mean dose 50 mg daily), and leflunomide (n=1, mean dose 20 mg daily). Detailed information regarding age, sex, disease duration, disease activity, CRP and cytokine levels of the RA group is provided in the Supplementary-Table 2.

-Co-morbidity controls (CC)

A group of 10 patients comparable with the TdP-cohort in terms of age, sex and co-morbidity burden, but without TdP, was enrolled. Clinically-evident acute or chronic inflammatory diseases represented exclusion criteria (two out of 12 patients screened were excluded for the presence of fever and productive cough, respectively). Co-morbidities in the selected patients included: cardiac diseases (n=9, 90%, i.e. dilated cardiomyopathy/heart failure [n=5, 50%], coronary artery disease [n=4, 40%], left ventricular hypertrophy [n=3, 30%], atrio-ventricular blocks [n=2, 20%], Tako-

Tsubo cardiomyopathy [n=1, 10%]), extra-cardiac diseases (n=7, 70%, i.e. chronic kidney disease [n=4, 40%], diabetes mellitus type II [n=3, 30%], anorexia nervosa [n=1, 10%]), and electrolyte imbalances (i.e. hypocalcemia [n=2, 20%], hypomagnesemia [n=1, 10%]). Five patients (50%) were also under treatment with QTc prolonging-medications, including amiodarone (n=3, 30%), sertraline (n=1, 10%), and amitriptyline (n=1, 10%). Detailed information regarding age, sex, CRP and cytokine levels of the CC group is provided in the Supplementary-Table 2.

-Healthy controls (HC)

Healthy control group consisted of healthy volunteers, age- and sex-matched with patients, and without clinical signs of ongoing acute infections. Among a total of eleven consecutive subjects screened, 10 were selected (one woman, who complained for mild dysuria, was excluded). Detailed information regarding age, sex, CRP and cytokine levels of the HC group is provided in the Supplementary-Table 2.

ECG recordings.

In patients with TdP, the QTc interval was manually measured on a standard 12-lead ECG, from the onset of the Q wave or the onset of the QRS complex to the end of the T wave, defined as the return to the T-P baseline. When prominent U waves (>1 mm) merging into T waves were present, they were included in QT measurement [2]. QT interval, determined as the longest hand-measured QT interval in any lead [3] was corrected for heart rate by the Bazett formula (dividing the QT interval by the square root of the R-R interval) to yield the QTc value. QTc was measured from 3 non-consecutive beats (mean value) by a single investigator .

In patients without TdP, measurement of the heart rate (HR), RR, QRS, QT, and QTc intervals (Bazett formula) was automated. These parameters were obtained from three ECGs consecutively recorded and the mean values were used. Intra-observer coefficients of variation for QTc were 0.6% (PRE) and 0.7 % (POST), respectively. A single investigator blinded to the clinical and laboratory findings of the patients reviewed all ECGs to validate the measured intervals. All patients showed

sinus rhythm and an RR interval longer than 521 ms and shorter than 1,111 ms (Bazett's formula considers values outside this range to be unreliable). Since the Bazett formula may over- or underestimate QTc at higher and lower HRs [4], respectively, we additionally evaluated QTc using alternative correction formulas, i.e. Fridericia, Framingham and Hodges, the latter being recognized as the correction formula showing the least heart-rate dependence [4].

According to the American Heart Association/American College of Cardiology (AHA/ACC) suggestions, QTc was considered prolonged if >470 ms in males, or >480 ms in females [5].

Laboratory analysis.

Blood samples were centrifuged at 1000 rpm and serum samples were stored at -80°C.

CRP was assayed by a particle-enhanced turbidimetric method (COBAS-6000 platform, Roche Diagnostics GmbH; Mannheim, Germany) and the values were expressed as mg/dl (normal values <0.5).Circulating levels of IL-6, TNFα and IL-1 were evaluated by multiplex assay for cytokine quantification (Bioplex, Bio-Rad, Hercules, CA). Cytokine concentrations were calculated using a standard curve established from serial dilutions of each cytokine standard as described in the manufacturer's protocol and expressed as pg/ml.

References:

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