Results. A total of 172 patients were enrolled. After a mean of 32 (0.7) months, 165 (96%) were in follow-up, 5 (3%) patients had died (all SSc-related deaths, but none including PH) and 1 patient (1%) was lost to follow-up. During observation, six patients (3.5%) developed PH confirmed by right heart catheterization. Mean DL_{CO} (per cent predicted) ($P < 0.01$), DL_{CO}/VA (%) ($P < 0.05$), calculated RPS (0.05), baseline and stress-induced PASP ($P < 0.05$) or the difference between these values (ΔPASP) ($P < 0.001$) measured at the study enrolment were significantly different in patients who developed PH (Group 1) *vs* those free of this complication at the end of follow-up (Group 2). Univariate PH-free survival was significantly lower in patients with an inappropriate increase in exercise PASP ≥48 mmHg ($P < 0.05$) or in those in the highest quintile of RPS ($P < 0.01$). At the multivariate Cox regression, adjusting for potential confounders, only the value of ΔPASP (HR = 1.2, 1.03–1.4, $P < 0.05$) and being in the highest quintile of RPS (HR = 13.7, 2.06–91, $P < 0.01$) significantly predicted survival.
Discussion. Exercise stress echocardiography identifies SSc patients with an inappropriate response and the difference between PASP values at rest and under stress is predictive of PH-free survival, independently of other known clinical predictors.

S.5.5 FEATURES OF SSc PATIENTS WITH INAPPROPRIATE EXERCISE-INDUCED INCREASE IN PULMONARY ARTERY PRESSURE ESTIMATED BY ECHOCARDIOGRAPHY

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Background. Patients with SSc are at risk of developing pulmonary hypertension. The role of exercise testing in predicting this severe complication is still debated. Our group has recently described an inappropriate response to exercise with particularly high (≥48 mmHg) pulmonary artery systolic pressures (PASP) in a subset of SSc patients.
Aim. To describe baseline characteristics of SSc patients with a stress echocardiographic inappropriate response to exercise.
Methods. Patients with SSc consecutively admitted to two Italian Rheumatology Units were enrolled if in NYHA Class I–II and showing a peak tricuspid regurgitant jet velocity (TRV) <3 m/s at echocardiography. Clinical characterization of patients with SSc was performed according to the European Scleroderma Trial and Research (EUSTAR) recommendations. A risk prediction score (RPS) based on clinical parameters was calculated as recently suggested. Baseline and stress echocardiography were performed at both centres using similar commercial equipments and a standard protocol until patients experienced fatigue or symptoms, or until 85% of the age-predicted maximum heart rate was achieved. Clinical, instrumental and echocardiographic data were collected and analysed with SPSS software for Macintosh (SPSS Inc, Chicago, USA).
Results. A total of 172 patients were enrolled. According to the previously defined cut-off of exercise PASP, SSc patients were divided into those with a value below (Group 1, $n = 151$) or >48 mmHg (Group 2, $n = 21$). Patients in both groups had comparable features concerning sex, SSc subset and autoantibody distribution; likewise there was no statistically significant difference in age, disease duration, mRSS, FVC (% pred), DL_{CO} (%) or DL_{CO}/VA (%). Presence of interstitial lung disease was more frequent in Group 2 than in Group 1 (62 *vs* 40%), but the difference did not reach statistical significance ($P = 0.06$). RPS values also did not discriminate between the two groups [3.42 (0.9) *vs* 3.16 (0.82)].
Discussion. The subset of SSc patients with an inappropriate increase in PASP detected by stress echocardiography cannot be distinguished by any of the disease-specific features in our cohort, including the recently described and validated RPS based on clinical observations. Longitudinal analyses might better clarify whether stress echocardiography results are able to predict development of pulmonary hypertension in SSc, representing an additional screening tool for this severe complication.

S.5.6 INTRAVENTRICULAR CONDUCTION DISTURBANCES ON ISOCHRONE MAPS IN PATIENTS WITH SSc

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Background. Presence of cardiac impairments is a harbinger of poor prognosis in the course of systemic scleroderma (SSc). Myocardial fibrosis, considered the hallmark of cardiac involvement in SSc, is patchy and distributed throughout the both ventricles. Fibrosis can affect various portions of the heart conduction system, including intraventricular His bundle. However, in numerous SSc cases, the cardiac abnormalities can remain clinically covert. A goal of the study was to assess diagnostic usefulness of body surface heart potential mapping (BSPM) in detecting conduction disturbances in the patients examined.
Material and methods. Study group consisted of 65 patients (46 females and 19 males) with SSc (36 patients with limited SSc and 29 with diffuse SSc) at the mean age of 51.9 (13.9) years (range 17–65 years). None of the patients presented any intraventricular conduction abnormalities on the standard ECG recordings. BSPM method provides multielectrode ECG recordings collected from entire anterior and posterior thorax. The 87-lead Fukuda Denshi HPM-7100 mapping system was used to obtain isochrone maps, presenting isolines linking the myocardial sites with the same ventricular activation time–so-called VAT maps.
Results. First, the group-mean VAT map for the control population of 50 normal subjects was created. Both quantitative and qualitative features, i.e. VAT maximum and minimum values and their spatial location, of this reference map were established. Then, a precise visual inspection of each patient's VAT map was performed, which rendered the three specific patterns of isochrone distribution in the SSc group. It is worth noting that no patient's VAT map was of normal characteristics. Moreover, the group-mean values of VAT_{max} and VAT_{min} were significantly different ($P = 0.01$), when the control and the patient groups were compared. The three VAT map patterns were classified in the SSc group as non-specific intraventricular conduction disturbances occurring predominantly in the left (32 patients) or right (14 patients) ventricle or in the both ventricles (19 patients). Interestingly, the RV pattern comprised all SSc cases with definite pulmonary hypertension (9/14) but without evident RV hypertrophy.
Conclusion. Isochrone maps obtained using the BSPM method, showing a unique sensitivity as to changes of cardiac electric field owing to high spatial resolution, enable to explore the early-phase intraventricular conduction distortions in patients with systemic sclerosis that are undetectable by the routine 12-lead ECG examination.

SESSION 6

PATHOGENESIS–FIBROSIS

S.6.1 β-CATENIN IS A CENTRAL MEDIATOR IN SSc

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Background. β-catenin is the central integrator of canonical Wnt signalling. Since recent evidence suggests a central role of Wnts in fibrosis, we examined the β-catenin/Wnt pathway in SSc and focused on the role of β-catenin in fibroblast activation.

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Methods. We performed qPCR for several Wnt ligands and axin-2 to examine Wnt expression in SSc skin. We further studied protein levels of Wnt-1, -4, -10b and β-catenin by IHC. To establish the effects of β-catenin/Wnt signalling on collagen release, we created mice with fibroblast-specific stabilization of β-catenin (dEx3 β-catenin (wt/fl) × Col1a2; Cre-ER) as well as mice carrying fibroblast-specific deletion of β-catenin [Ctnnb1(fl/fl) × Col1a2; Cre-ER].
Summary of the results. We could demonstrate mRNA overexpression of Wnt-1, -2, -9a, -9b, -10a, -10b and -16 in SSc skin. Wnt-1, -4 and -10b consistently showed strong expression in SSc skin when compared with healthy skin. On protein level, however, Wnt-4 was indistinguishable between SSc patients and healthy controls, whereas Wnt-1 and Wnt-10b protein levels were increased in SSc skin. The overexpression of Wnt-1 and Wnt-10b resulted in a prominent nuclear accumulation of β-catenin in fibroblasts. Finally, increased mRNA levels of the target gene axin-2 confirmed the activation of canonical Wnt signalling.
In dEx3 β-catenin (wt/ex) mice, we addressed the consequences of enhanced Wnt signalling and increased accumulation of β-catenin in SSc. We selectively targeted β-catenin in fibroblasts. Cre-activated dEx3 β-catenin (wt/fl) × Col1a2; Cre-ER mice showed massive and spontaneous dermal thickening even 2 weeks after Cre activation. Eight weeks after Cre-activation, skin thickening cumulated at 102.6% ($P < 0.001$). In line with the dermal thickening, hydroxyproline content and myofibroblast counts showed strong increases.
To test the therapeutic potential of targeting β-catenin/Wnt signaling, we created Ctnnb1(fl/fl) x Col1a2;Cre-ER mice to specifically delete β-catenin in fibroblasts. After Cre activation and β-catenin deletion in fibroblasts, mice were challenged with bleomycin subcutaneously for 4 weeks. We found that Cre-activated Ctnnb1(fl/fl) × Col1a2; Cre-ER mice were protected from bleomycin-induced dermal with a reduction of skin thickening by 71% ($P < 0.05$).
Conclusions. We demonstrated a prominent activation of canonical Wnt signalling in SSc with nuclear accumulation of β-catenin in fibroblasts and activation of the target gene axin-2. Our results showed that fibroblast-specific stabilization of β-catenin resulted in enhanced collagen release, whereas deletion of β-catenin potently reduced collagen production. Together, our findings highlight a key role of β-catenin in fibroblast activation and fibrosis. Thus, β-catenin may be promising molecular target for anti-fibrotic therapies.

S.6.2 JAK2 IS A NOVEL MEDIATOR OF THE STIMULATORY EFFECTS OF TGF-β ON FIBROBLAST ACTIVATION AND TISSUE FIBROSIS

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Background. Uncontrolled activation of fibroblasts releasing large amounts of extracellular matrix proteins is a key feature of SSc. Janus kinase 2 (JAK2) is an important mediator of cytokine signalling and mutations in the *JAK2* gene have been identified in the molecular pathogenesis of myeloproliferative diseases.
Methods. Immunohistochemistry for pJAK2 served as marker for pathway activation. Dermal fibroblasts were stimulated with TGF-β and incubated with the specific JAK2 inhibitor TG 101209. The anti-fibrotic potential of a specific JAK2 inhibition *in vivo* was evaluated in bleomycin-induced dermal fibrosis and tight-skin 1 (Tsk-1) mice.
Results. Increased and prominent accumulation of pJAK2 was observed in fibroblasts in skin of SSc patients and in cultured SSc fibroblasts. Inhibition of JAK2 in SSc fibroblasts by the selective JAK2 inhibitor TG 101209 or by siRNA decreased the formation of stress fibres by 41 (5)%, the expression of αSMA by 41 (6)% and the basal mRNA levels of col 1a1 and col 1a2 by 59 (4)% and 51 (3)% ($P < 0.05$ each). These inhibitory effects in the absence of exogenous stimulation were not observed in healthy dermal fibroblasts. Stimulation of healthy fibroblasts with TGF-β increased time-dependently the levels of pJAK2. Pre-incubation with TG 101209 abrogated the stimulatory effects of TGF-β with decreases in stress fibre formation by 74 (12)%, αSMA expression by 84 (11)% ($P < 0.05$) and reduced col 1a1 and col 1a2 mRNA levels by 90 (21)% and 92 (14)% ($P < 0.05$). Consistently, inhibition of JAK2 exerted potent anti-fibrotic effects in experimental fibrosis. In the model of bleomycin-induced fibrosis, treatment with TG 101209 decreased dermal thickening by 95 (5)% ($P = 0.007$), hydroxyproline content by 76 (7)% ($P < 0.001$) and myofibroblast counts completely back to baseline levels ($P = 0.001$). Application of TG 101209 in Tsk-1 mice reduced hypodermal thickening, hydroxyproline content and myofibroblast counts by 82 (10)% ($P = 0.002$), 75 (25)% ($P = 0.03$) and 99 (13)% ($P = 0.01$).
Conclusion. We demonstrate that JAK2 is activated in SSc in a TGF-β-dependent manner and mediates the stimulatory effects of TGF-β on fibroblasts. As inhibitors of JAK2 are currently evaluated in clinical trials for myeloproliferative disorders and are well tolerated, our findings might stimulate clinical trials with JAK2 inhibitors in SSc patients.

S.6.3 TGF-β ACTIVATES CANONICAL WNT SIGNALLING TO DRIVE FIBROSIS IN SSc

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Background. Aberrant activation of the canonical Wnt pathway has been implicated in a variety of different diseases. To avoid uncontrolled activation, Wnt signalling is tightly controlled by endogenous inhibitors such as dickkopf-1 (Dkk-1). Here, we investigated the interaction between TGF-β-dependent pathways and canonical Wnt signalling in SSc.
Results. Canonical Wnt signalling is activated in SSc with nuclear accumulation of β-catenin, the central mediator of canonical Wnt signalling, and increased expression of the target gene axin-2. The activation of canonical Wnt signalling in SSc is mediated at least in part by TGF-β. TGF-β decreases the levels of the endogenous inhibitor Dkk-1 in a p38-dependent manner by >80%. The expression of Dkk-1 is almost undetectable in the skin of SSc patients and in different models of experimental models of fibrosis. TGF-β potently activated canonical Wnt signalling *in vitro* and *in vivo* with nuclear accumulation of β-catenin, increased TOP-reporter activity and induction of axin-2 mRNA. In contrast, inhibition of TGF-β-signaling in experimental models of fibrosis by SD-208, a selective inhibitor of TGF-β receptor kinase activity, strongly decreased the activation of canonical Wnt-signalling, thereby highlighting the key-role of TGF-β for the activation of Wnt signalling in fibrosis. The activation of Wnt signalling directly contributes to the pro-fibrotic effects of TGF-β. Canonical Wnt signalling stimulates the release of collagen *in vitro* and induces massive fibrosis *in vivo*. Recombinant Dkk-1 strongly reduced the stimulatory effects of TGF-β and decreased the TGF-β-induced up-regulation of collagen, αSMA and stress fibres by up to 75%. Moreover, transgenic overexpression of Dkk-1 ameliorates fibrosis in mice induced by adenoviral transfection of constitutively active TGF receptor type I with reduction of dermal thickening, myofibroblast counts and hydroxyproline content by up to 85 (5)%. Overexpression of Dkk-1 also exerted potent anti-fibrotic effects in bleomycin-induced dermal fibrosis and in Tsk-1 mice.
Conclusions. TGF-β activates canonical Wnt signalling in SSc by decreasing the expression of the Wnt inhibitor Dkk-1. The activation of canonical Wnt signalling directly contributes to the profibrotic effects of TGF-β and potently induces fibroblast activation and tissue fibrosis. Overexpression of Dkk-1 significantly decreases the pro-fibrotic effects of TGF-β and prevents fibrosis in different experimental models, demonstrating that the interaction of the canonical Wnt pathway and TGF-β plays a key role in the pathogenesis of fibrotic diseases.

S.6.4 INHIBITION OF FOCAL ADHESION KINASE PREVENTS EXPERIMENTAL LUNG FIBROSIS AND MYOFIBROBLAST FORMATION

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Tissue fibrosis caused by pathological activation of fibroblasts with increased synthesis of extracellular matrix components is a major hallmark of SSc. Focal adhesion kinase (FAK), an essential component in the extracellular matrix-mediated adhesive signalling, was found to be hyperactivated in lesional scleroderma fibroblasts, and therefore this kinase has been hypothesized to be a key mediator of this disease. The present study was undertaken to investigate the role of FAK signalling in SSc and to evaluate the therapeutic potential of FAK inhibition for the treatment of lung fibrosis. FAK activity and expression is up-regulated in lungs of mice subjected to non-infectious injury and in human idiopathic pulmonary fibrosis (IPF) or scleroderma (SSc) patients as investigated by immunohistochemistry (IHC). Genetic or pharmacological targeting of FAK abrogates fibrogenesis in the bleomycin-induced lung fibrosis model as quantitated by IHC and collagen content. *In vitro*, FAK activation is required for endothelin-1-induced myofibroblast differentiation, extracellular matrix (ECM) production and contractility as tested by western blot, real-time PCR and gel contraction assay. These results implicate FAK as a central mediator of fibrogenesis, and highlight this kinase as a potential therapeutic target in fibrotic diseases. These findings might have direct translational implications because different inhibitors of FAK are available and have yielded promising results in cancer trials.

SESSION 7

MUSCULOSKELETAL

S.7.1 ULTRASONOGRAPHIC HAND FEATURES IN SYSTEMIC SCLEROSIS AND CORRELATES WITH CLINICAL, BIOLOGICAL AND RADIOGRAPHIC FINDINGS

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Background. Articular involvement is a common feature of SSc with major impact on quality of life. However, assessment is frequently difficult, as clinical assessment is limited by concomitant skin involvement and X-ray cannot capture tendon damages. Therefore, the prevalence and characteristics of joint involvement are imperfectly known. Ultrasonography (US) has demonstrated its major input in other rheumatic conditions but only scarce data are available in SSc. Therefore, we set out to investigate ultrasonographic hand and wrist features in consecutive SSc patients and their relationships with clinical examination, biological and radiographic data.
Materials and methods. A total of 52 consecutive SSc were included in a cross-sectional observational study and in addition 24 patients with RA were enrolled as controls. All the patients underwent clinical examination. Global disability was assessed using the HAQ and the Duruoz Hand Index. US was performed on joints of both hands, both wrists and fingers. The following predefined features were searched for: synovitis, tenosynovitis, acro-osteolysis, calcinosis, power Doppler in the nail bed and in the pulp. Radiographies of the hands and wrists were also performed. Data were statistically analysed using chi-square tests and the Student's *t*-test. A multivariate, step-wise logistic regression analysis was also performed for all variables identified with $P < 0.10$. $P < 0.05$ was considered statistically significant.
Results. The characteristics of SSc patients were: mean age: 56.3 (14.1) years, 75% were women, mean disease duration: 8.6 (8.6) years, 40% fulfilled diffuse cutaneous subtype. Prevalences of US abnormalities in SSc patients were as follows: synovitis in 46%, tenosynovitis in 27%, calcifications in 40%, acro-osteolysis in 19% and impairment in the distal microvascularization in 44%. Synovitis were in 57% of cases mildly inflammatory (Doppler Grade 1), whereas tenosynovitis showed a mixed pattern associating both inflammatory and fibrotic changes. As compared with RA patients, US hand features specific to SSc were 'sclerosing' tenosynovitis ($P < 0.01$), soft-tissue calcifications ($P = 0.01$) and impairment in the distal microvascularization ($P < 0.01$). US detected 31 and 21% more patients with synovitis and tenosynovitis, respectively, than clinical examination. In multivariate analysis, a CRP level superior to 10 mg/l was associated with inflammatory activity at power Doppler assessment ($P = 0.03$).
Conclusion. Our study confirms that articular involvement in SSc is frequent and under-estimated by clinical examination. It is characterized by mild inflammatory damages associated with biological inflammatory syndrome and with US sclerosing findings for tenosynovitis. Further prospective studies are warranted to evaluate the predictive value of these findings.

S.7.2 ELF SCORE: A VALIDATED SERUM TEST STRONGLY PREDICTIVE OF FIBROSIS IN SSc

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Background. The absence of a serum test predictive of activity or severity in Scleroderma (SSc) is a major burden both for clinical intervention studies and for clinical management. Recently, a large multicentre study has identified an algorithm of three serum biomarkers as predictive of severity and clinical outcome in chronic liver disease. The algorithm, known as Enhanced Liver Fibrosis (ELF), includes the measurement of serum concentrations of hyaluronic acid, TIMP-1 and aminoterminal propeptide of procollagen Type III.
Objective. To evaluate the predictive value of ELF test as surrogate outcome measure of fibrosis in SSc.
Methods. A total of 210 SSc patients were enrolled in the study. All patients were investigated for clinical and serological subset, disease duration (d.d.), vascular, skin, joint, tendon, muscle, oesophago-gastrointestinal, lung, heart and kidney involvement, disease severity, disease activity and HAQ-DI. ELF score was determined blindly by an independent commercial service (iQur, London, UK). Correlations were calculated using Spearman's correlation test. Mann–Whitney test was used to perform comparison between groups. All the variables found to be correlated in univariate analysis were subsequently assessed by step-wise regression analysis. Data were analysed using SPSS18 software.
Results. The mean ELF score in SSc patients sera was 8.71 (1). ELF score significantly correlated with: mRSS ($r = 0.28$; $P < 0.0001$), FVC ($r = -0.16$; $P = 0.0287$), DLCO ($r = -0.32$; $P < 0.0001$), EScSG-Activity Index ($r = 0.23$; $P = 0.02$), total Medsger's disease severity score ($r = 0.3$; $P < 0.0001$) and severity score of skin ($r = 0.31$; $P < 0.0001$), joint/tendon ($r = 0.23$; $P = 0.0007$), muscle ($r = 0.27$; $P < 0.0001$), GI tract ($r = 0.17$; $P = 0.0144$), heart ($r = 0.22$; $P = 0.0011$), HAQ-DI ($r = 0.32$; $P < 0.00001$), ESR ($r = 0.25$; $P = 0.0003$), age ($r = 0.41$; $P < 0.0001$). Step-wise regression analysis identified mRSS (standardized $\beta = 0.299$, $P < 0.0001$), age (standardized $\beta = 0.289$, $P = 0.001$), DL_{CO} (standardized $\beta = -0.245$, $P = 0.004$) and gender (standardized $\beta = 0.235$, $P = 0.005$) as independently associated with ELF score. The median ELF score was significantly higher in patients with dcSSc enrolled within the first year of the disease than in age-/gender-matched lcSSc patients with >5 years d.d. ($P = 0.0152$) and not significantly higher when compared with matched dcSSc with >3 years d.d. The median ELF score was higher in SSc patients with chest HRCT fibrosis and $DL_{CO} \pm FVC$ <80% predicted value, than in SSc controls matched for age, gender, subset, mRSS and d.d. ($P = 0.0079$).
Conclusion. The ELF test is a simple serum test that significantly correlates with several measures of fibrosis in SSc. It has a clear face validity for measuring the concentration of molecules involved in extracellular matrix turnover and correlates with fibrotic severity and activity in SSc. ELF test should be considered as outcome measure in clinical trials.

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