Myocardial fibrosis in systemic sclerosis assessed by cardiac magnetic resonance is associated with vascular endothelial growth factor expression

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The hallmarks of systemic sclerosis (SSc) are endothelial dysfunction and fibrosis of the skin and the internal organs, including the heart. Primary cardiac involvement related to SSc is more related to fibrosis and its complications (1). Recurrent episodes of vasospasm with ischaemia and reperfusion cause abnormal myocardial perfusion with subsequent fibrosis (2). In SSc vascular damage and chronic tissue hypoxia promote angiogenesis with production of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) (3). Endomyocardial biopsy is an invasive procedure used to diagnose myocardial fibrosis. To date, cardiac magnetic resonance (CMR) is employed in SSc to detect myocardial fibrosis showing patchy fibrosis distributed in both ventricules (4). As confirmed by a histopathological study, myocardial fibrosis can be detected through late gadolinium enhancement (LGE) on CRM with the same degree of reliability provided by myocardial biopsy (5).

In this pilot study we aimed to evaluate myocardial fibrosis in SSc using CMR with LGE and VEGF expression.

The protocol, according to Declaration of Helsinki, was approved by local Ethics Committee. Twenty-eight SSc patients [20 women, aged 40 (36-48) years] were enrolled. Exclusion criteria were coronary artery disease, congestive heart failure, left ventricular dysfunction, pulmonary hypertension, valvular abnormalities. Serum VEGF levels were determined in SSc patients by commercial ELISA kit (Human VEGF, Quantikine ELISA, R&D Systems, Minneapolis MN), with a sensitivity of 9 pg/ml and an assay range of 31.2– 2000 pg/ml.

CMR imaging was performed with a 1.5-T unit (Magnetom Avanto; Siemens Healthcare GmbH, Erlangen, Germany) using an 8-channel phased-array coil and vectocardiogram triggering. LGE imaging was performed between 10 and 15 min after the second bolus injection of contrast agent using a segmented T1-weighted phase-sensitive inversion-recovery pulse.

Table I shows clinical and CMR features. Serum median value of VEGF was 187 pg/ml (128-251).

In 17 (60.7 %) SSc patients focal areas of LGE were found predominantly with patchy mesocardial distribution. Evidence of ischaemic LGE was not identified in any patient. Focal myocardial oedema was observed in 4 (14.3%) SSc patients. Extracellular Volume Fraction (ECV) was 26.5 (25.4-29) between patients with and without LGE. The median value of VEGF was higher (p<0.01) in SSc patients with LGE than in SSc patients without LGE [233 (183-270) *vs*. 100 (67-191)]. No significant differences of VEGF was observed in SSc patients with or without digital ulcers or ECV. Serum level of VEGF did not show differences in SSc subset and capillaroscopic patterns.

Table I. Anthropometric, clinical and cardiac magnetic resonance features in systemic sclerosis patients.

Disease features	
Age, years	40 (36-48)
Female, n and %	20 (71.5%)
Disease duration, years	8 (6-11)
lcSSc/dcSSc	10/18
mRSS	14 (12-20)
DAI	2 (1.5-3.75)
Digital ulcers history, n and %	18 (64.3%)
Capillaroscopic pattern (early/active/late), n	8/9/11
VEGF (pg/ml)	187 (128-251)
Ventricular Function	
LV-end diastolic volume (mL/m^2; mean ± SD)	72 (59-83)
LV-end systolic volume (mL/m^2; mean ± SD)	27 (22-34)
LV-ejection fraction (%; mean ± SD)	61 (56-66)
LV-Mass (g/m^2; mean ± SD)	46 (38-54)
RV-end diastolic volume (mL/m^2; mean ± SD)	70 (53-78)
RV-end systolic volume (mL/m^2; mean ± SD)	31 (25-40)
RV-ejection fraction (%; mean ± SD)	57 (50-64)
Tissue characterisation	
LGE (n, %)	17 (60.7)
Focal myocardial oedema (n, %)	4 (14.3)
Pericardial effusion (n, %)	5 (17.8)
ECV (%; mean ± SD)	26.5 (25.4-29)

lcSSc: limited cutaneous SS; dc: diffuse cutaneous SSc; mRSS: modified Rodnan skin score; DAI: disease activity index; VEGF: vascular endothelial growth factor; LV: left ventricle; RV: right ventricle; LGE: late gadolinium enhancement; ECV: extracellular volume fraction.

Late gadolinium enhancement is the gold standard to evaluate myocardial fibrosis and it is associated with ejection fraction reduction, left ventricular dysfunction and arrhythmia (6). Several studies report the role of CRM in SSc related cardiac involvement. Rodrıguez-Reyna *et al*. found the prevalence of myocardial fibrosis in 45% of patients and its correlation with microvascular damage (7). The angiogenesis in SSc is impaired and is linked to the progression of microvascular damage (8). Avouac *et al*. found higher VEGF levels in late scleroderma pattern characterised by severe loss of capillaries with extensive avascular area with progression toward fibrosis. In this study, the authors suggest that when microvascular damage occurs, it leads to VEGF up-regulation (9). In SSc patients, coronary vasoconstriction or cardiac Raynaud's phenomenon causes recurrent ischaemia promoting myocardial fibrosis over time (5).

In SSc regulators of angiogenesis are abnormal. Several studies reported that angiogenic factors such as VEGF are activated in response to vascular damage. Tissue fibrosis is the result of this impaired angiogenesis (10). LGE shows a positive correlation with VEGF. We can suppose that in primary cardiac involvement related to SSc, microvascular damage stimulates impaired angiogenesis. The defect in the vascular repair and new blood vessels formation favours myocardial fibrosis.

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