Evaluation of Nifedipine efficacy upon myocardial perfusion and contractility using cardiac Magnetic Resonance Imaging and Tissue Doppler echocardiography in Systemic Sclerosis

Olivier Vignaux, Yannick Allanore, Christophe Meune, Olivier Pascal, Denis Duboc, Simon Weber, Paul Legmann, and Andre Kahan

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Evaluation of Nifedipine efficacy upon myocardial perfusion and contractility using cardiac Magnetic Resonance Imaging and Tissue Doppler Echocardiography in Systemic Sclerosis

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Abstract

Introduction: Primary myocardial involvement due to microcirculation impairment is common in systemic sclerosis (SSc). Cardiovascular magnetic resonance imaging (MRI) and Tissue Doppler echocardiography (TDE) were recently shown to be more sensitive than conventional methods for the respective assessment of myocardial perfusion and contractility. Previous studies have suggested that dihydropyridine-type calcium channel blockers mitigate both myocardial perfusion and function abnormalities. We therefore investigated the effects of nifedipine on myocardial perfusion by MRI and on contractility by tissue Doppler echocardiography, in patients with SSc.

Patients and Methods: We prospectively evaluated 18 SSc patients without clinical heart failure and with normal pulmonary arterial pressure (14 women, 4 men; mean age 59±9 years; mean disease duration 7±4 years, 10 with diffuse and 8 with limited cutaneous forms). MRI perfusion index, determined from time-intensity curves, and systolic and diastolic Strain Rate determined by TDE were assessed at baseline, after a 72-hour vasodilator washout period, and after 14 days of oral treatment with 60 mg nifedipine per day.

Results: Nifedipine treatment led to a significant increase in MRI perfusion index (0.26±0.07 vs 0.19±0.05 at baseline, p=0.0003) and in systolic and diastolic Strain Rate (2.3±0.6 vs 1.5±0.4 s⁻¹ at baseline, p=0.0002, and 4.2±1.6 vs 3.0±1.2 at baseline, p=0.0003, respectively).

Conclusion: Fourteen days of treatment with nifedipine simultaneously improves myocardial perfusion and function, as evaluated by highly sensitive and quantitative methods.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs. Primary myocardial involvement is common in SSc (1-5) and is recognised as a poor prognosis factor (6-7). SSc vascular lesions display generalised impairment of the microcirculation, including vasospasm. Myocardial fibrosis is thought to follow repeated focal ischaemia, resulting from abnormal vasoreactivity with or without associated structural vascular disease. Indeed, some histological examinations have revealed diffuse patchy fibrosis, with contraction band necrosis unrelated to epicardial coronary artery stenosis (2), whereas other studies have revealed concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries (8).

Single-photon emission computed tomography (SPECT), echocardiography and radionuclide ventriculography have been previously used in order to investigate respectively myocardial perfusion and contractility. The data demonstrated very commonly myocardial perfusion abnormalities together with various degrees of left and right ventricular dysfunction (3-5, 9-10). Moreover, using these methods, vasodilators such as nifedipine, nicardipine and captopril demonstrated that they could acutely mitigate both myocardial perfusion and function (10-13). However, these methods may have some limitations in the assessment of the efficacy of vasodilator treatments. SPECT is a qualitative and semi-quantitative method whereas quantitative method may be preferable for a direct comparison. Moreover, echocardiography and radionuclide ventriculography which are valuable methods to determine global and regional contractility may be influenced by loading conditions and adjacent segment motion.

In contrast, cardiovascular magnetic resonance imaging (MRI) is an accurate quantitative method latterly developed for the non-invasive assessment of myocardial perfusion (14-17). In a recent study, MRI has been able to detect subendocardial perfusion abnormalities in
patients with cardiac syndrome X, suggesting its higher sensitivity than conventional perfusion techniques (18).

Tissue Doppler echocardiography (TDE) is a recently developed ultrasound technique, that allows direct measurements of myocardial velocities and Strain Rate (SR)(19, 20). Previous studies have demonstrated that SR determined by TDE is a powerful indicator of myocardial contraction, more sensitive, not affected by myocardial translational motion and less load-dependent than conventional echocardiography (21-24).

We therefore investigated the effects of nifedipine on myocardial perfusion by MRI and on regional function by TDE in patients with SSc.

**Patients and Methods**

**Patients**

Consecutive patients fulfilling the LeRoy's classification criteria for SSc (25) were included. The clinical features of their disease were assessed as recommended (26). The exclusion criteria were pregnancy, symptoms of heart failure, venous distension and/or recent major lower limb oedema, pulmonary arterial hypertension (systolic arterial pressure > 40 mmHg and/or mean artery pressure > 25 mmHg determined by echocardiography), severe pulmonary involvement (forced vital capacity or carbon monoxide diffusing capacity < 50% of the predicted value), renal involvement (creatinine concentration > 106 µmol/l), or severe disease complications such as cancer or gangrene. Three months of stable current treatment was necessary for inclusion, and prednisone at a dose less than 10 mg/day was authorised. Vasodilator treatments had to be withdrawn at least 3 days before inclusion, a time-interval superior to 5 drug half-lives. All patients gave informed consent for all procedures and the study was approved by the local ethics committee (Paris, Cochin).

The following investigations were carried out for all patients: laboratory tests including blood cell counts, Westergren erythrocyte sedimentation rate, C-reactive protein levels, serum creatinine concentration, anti-centromere and anti-topoisomerase I antibody assays. Pulmonary involvement was assessed by computed tomography (CT) scan, forced vital capacity (FVC) and the ratio of carbon monoxide diffusion capacity to haemoglobin concentration (DLCOc/Hb). Pulmonary arterial systolic pressure (PAPs) was determined by Doppler echocardiography at rest, based on the tricuspid and or pulmonary regurgitation, adding 10 millimetres of mercury, as an estimation of right atrial pressure.

Myocardial evaluations were performed over a 30-minute period, in patients at rest, at room temperature, at baseline and after 2 weeks of nifedipine treatment (20 mg 3 times/day). All measurements were performed in similar conditions, with MRI performed first, followed by TDE one hour later.

**Magnetic Resonance Imaging**

All patients were examined in the supine position (1.5 T Echospeed GEMS, Milwaukee, USA) using a phased-array cardiac dedicated coil. After determination of the axis and length of the left ventricular (LV) cavity, 3 short-axis planes were imaged. The distance between each plane was individually set as one third of the end-systolic length of the LV cavity. A interleaved notched saturation segmented k-space turbo-gradient-echo/echo-planar-imaging (EPI)-hybrid technique with notched saturation prepulse and T1 preparation (echo time [TE] = min full, R-R interval = 2, flip = 25; inversion time = 160 msec; matrix, 128 x 128; slice thickness, 8 mm) was used. Multislice acquisitions were performed during the first pass of 0.025 mmol gadolinium-diethylenetriamine pentaacetic acid (DOTA)/kg body weight.
(Guerbet) flushed with 10 mL 0.9% NaCl (flow rate, 5 mL/s; Medrad, Spectris). Images were acquired during breath-holding for 10 heartbeats before and 60 heartbeats during the injection.

**Visual Image Analysis.** Hard copy images without any information (including name and date) were developed and the enhancement of axial images retrospectively analysed side by side by two radiologists. If a segment showed a reduced signal intensity (SI) or delayed wash-in, it was regarded as pathological (perfusion defect). The two readers who were blinded as regards to treatment, independently evaluated the sets of images with a three-point rating scale: (0) homogenous enhancement considered as normal myocardial perfusion, (1) one segmental perfusion defect, (2) two or more perfusion defects. Consensus reading was used for discordant grades. Examples are provided in figure 1.

**Parametric Image Analysis.** The endocardial and epicardial contours were traced by an examiner blinded to angiography thanks to a dedicated software (MASS, Medical Imaging Solutions, Leiden, Netherlands) and corrected manually for displacements (e.g., breathing). The outer 50% of the myocardium were excluded to get stronger weighting of the subendocardium. LV signal intensity (SI) of the cavity and myocardial SI were determined for all time points. This software allows the determination of a time-intensity curve for the whole myocardium. The signal intensities before injection of the agent at the time zero are averaged and used as offset. The peak SI, time to peak and maximum upslope of the SI time curves were thus determined. If the whole myocardium showed a diffuse reduced peak SI or reduced time to peak on parametric image (bull’s eyes view from apex to base), it was graded as (2) two or more perfusion defects. Segmental perfusion defect initially assessed with visual analysis was also analysed on parametric images and regarded as pathological only if reduced peak SI or reduced time to peak was found on the same segment. The example of one patient representative of the whole group is provided in figure 2. A myocardial perfusion index was determined by dividing the myocardial upslope through the LV upslope. This allows the correction for differences of the speed and compactness of the contrast agent bolus and avoids thereby to take into account the interstudy variation of extrinsic parameters such as the heart rate and the arterial pressure.

**Tissue Doppler Echocardiography**

TDE was performed with an ATL HDI5000 system (ATL ultrasound, Bothell, Washington, DC) equipped with tissue Doppler, second harmonic imaging technologies and a 2-3.5Mhz phased array transducer. Myocardial velocities were measured by an experienced practitioner, in the posterior wall, from a parasternal short axis view at the level of the papillary muscle on M-mode TDE recordings. Special attention was paid to the proper alignment of the beam perpendicular to the left ventricular wall and gains were adjusted to optimise the images. Off-line TDE measurements were made by two cardiologists, according to a blind protocol, with the HDI Lab software package installed on a standard PC workstation.

We first manually drew lines in the sub-endocardium and in the sub-epicardium, in order to determine endocardial and epicardial velocity patterns over time. Peak systolic velocity and peak early diastolic velocities, defined as maximal velocity during LV ejection time and early diastole respectively, were then determined from endocardial (EndoV\textsubscript{SYS}, EndoV\textsubscript{DIA}) and epicardial (EpiV\textsubscript{SYS}, EpiV\textsubscript{DIA}) velocity patterns. Peak systolic and early diastolic strain rate (SR) was defined as the maximal transmural velocity gradient during systolic (SR\textsubscript{SYS}) and early diastolic (SR\textsubscript{DIA}) times and was calculated as: \( \text{SR (s}^{-1}) = (\text{EndoV-EpiV/d (where } d \text{ is the distance between endocardium and epicardium). SR determination is provided in one patient at baseline on figure 3.} \)}
The mean value between the 2 cardiologists results was taken into account for statistical analysis.

**Statistical analysis**

In order to detect a $\Delta/SD = 1$ increase in perfusion index (3), with a unilateral $\alpha$ value of 0.05 and a $\beta$ value of 0.1, 18 patients have been enrolled. Data, expressed as means $\pm$ SD, were analysed using Mann-Whitney (unpaired data) and Wilcoxon (paired data) tests for the comparison of groups. Spearman’s rank correlation test for assessment of the relationship between quantitative variables. McNemar’s test, a chi² test for paired analysis, was used to compare the number of ischaemic segments on MRI. P values less than 0.05 were considered significant (Statview Software, Abacus Concept, Berkeley, CA, 1998).

**Results**

**Clinical findings**

Eighteen patients were included (14 women, 4 men, 10 patients with diffuse cutaneous disease and 8 with limited cutaneous disease); their clinical and biological characteristics are presented in table 1. Blood pressure was not affected by 14 days nifedipine and although heart rate increased, the systolic pressure-heart rate product remained unchanged (table 2).

**Magnetic resonance imaging**

Thirteen patients had at least one segmental perfusion defect at baseline; 6 with one and 7 with more than one. Myocardial perfusion index was significantly reduced in patients with more than 1 segmental defect (n=7) as compared to the others patients (n=11; 0.154$\pm$0.01 vs 0.213$\pm$0.04, p=0.01), and there was a trend for reduced perfusion when patients with 1 segmental defect (n=6) were compared to patients without defect (n=5; 0.183$\pm$0.05 vs 0.208$\pm$0.03, p=0.09).

Nifedipine treatment resulted in an increase in myocardial perfusion index (from 0.19$\pm$0.05 to 0.26$\pm$0.07, p=0.0003) (figure 4) and significantly decreased the number of patients with at least one segmental perfusion defect which decreased from 13/18 (72%) to 6/18 (33%; p=0.02) (table 2). The number of patients with more than one segmental perfusion defect decreased from 7/18 (39%) to 0/18 (p<0.05). Figure 2 shows MRI images with baseline aspect (2A) and changes after nifedipine treatment (2B) for one patient representative of the whole group. Age, disease duration, cutaneous form of the disease, pulmonary artery pressure, pulmonary fibrosis, carbon monoxide diffusion, autoantibody status and treatment were not associated with baseline MRI results or changes in perfusion index values after treatment.

**Tissue Doppler imaging**

The inter-observer variability was 0.13 for systolic strain rates and 0.17 for diastolic strain rates, which are consistent with previous studies (24). Nifedipine significantly increased systolic SR from 1.5$\pm$0.4 s⁻¹ at baseline to 2.3$\pm$0.6 (p=0.0002) and diastolic strain rates from 3.0$\pm$1.2 s⁻¹ at baseline to 4.2$\pm$1.6 (p=0.0003). Figure 3 shows systolic SR results. The characteristics of the SSc patients were not associated with significant differences in TDE baseline values or changes.

**Discussion**

Our main finding was that 14 days of treatment with nifedipine improved both myocardial perfusion and function, as evaluated by two modern, highly sensitive and quantitative methods, MRI and TDE. Single-photon emission computed tomography perfusion abnormalities have frequently been described in SSc patients and improvements in perfusion following treatment with nifedipine,
nicardipine and captopril have been reported before, suggesting that at least some of the defects observed were not fixed fibrotic defects (3, 9). However, SPECT is limited by the occurrence of attenuation artefacts and the use of radioactive tracers precludes regular follow-up examinations. MRI may constitute an ideal alternative as it is a non-invasive, quantitative, highly sensitive method for the assessment of myocardial perfusion. Indeed, parameters analysed for myocardial perfusion evaluation are usually determined by analysing the first pass of a contrast agent bolus through the myocardium. Visual assessment may facilitate rapid diagnosis without the need for quantification, and high-resolution perfusion MRI techniques can be used to identify small subendocardial defects. These defects do not correspond to any epicardial coronary artery distribution, and therefore are highly suggestive of microvascular alteration. In our study, perfusion MRI revealed segmental perfusion defects at rest in systemic sclerosis patients and showed that most of these segmental perfusion defects improved after 14 days of treatment with nifedipine.

Moreover, the myocardial gradient (the rate of increase of the myocardial signal) significantly increased after 14 days of treatment with nifedipine. Despite the use of an extravascular contrast agent (gadolinium-DOTA) that rapidly diffuses into the extracellular space, the rate of early myocardial signal enhancement during the first pass (gradient) is related to myocardial blood flow and vascular resistance. Therefore, the increase in the rate of myocardial signal enhancement after treatment with nifedipine may result from the lowering of myocardial vascular resistance. Intravascular contrast agents, which are currently under development, may constitute a step towards more accurate quantitative analysis in the future.

Left ventricular function in patients with suspected cardiomyopathy is commonly assessed by echocardiography or radionuclide ventriculography. Some measurements, such as end-diastolic diameter, fractional shortening, and left ventricular ejection fraction, are made in routine clinical practice. However, these indices are load-dependent and do not systematically reflect the contractile state of the myocardium. In this issue, TDE has been introduced as a quantitative, more objective and sensitive method for the assessment of myocardial function. TDE is a novel approach that allows direct and valid measurement of myocardial velocities and strain-rate (19, 20). Myocardial strain-rate is related to the difference in velocities that exists between endocardium and epicardium (subendocardial velocities are higher than subepicardial resulting in the existence of an intramyocardial velocity gradient or strain rate), and has shown to be a strong index of contractility independent of myocardial translation (21, 22, 23), less dependent on loading conditions (27, 28). Furthermore, SR determined by TDE is a more sensitive method than conventional echocardiography or radionuclide ventriculography in order to detect changes in myocardium contractility (22, 29, 30). As peak systolic and early diastolic SR are respective markers of regional contractility and diastolic function (23, 24, 31), our study strongly suggest that nifedipine improves myocardial intrinsic properties, possibly due to increase of myocardial perfusion. On the other hand, calcium channel blockers are antihypertensive agents and nifedipine has also been reported to result in an increase in sympathetic tone. Therefore, our result could be partially consecutive to these changes in loading conditions. However, SR determined by TDE is less load-dependent than other methods (23, 24, 27, 28), and afterload estimated by the systolic blood pressure-heart rate product did not change significantly after nifedipine (table 2). Taking together with MRI demonstrated increased perfusion, we assume that increase in myocardial perfusion may be the main determinant of observed increased contractility. Contrast echocardiography is a recent and accurate method to determine global and regional perfusion as well as global and regional contractility (32-34). MRI is also pertinent to determine local and global myocardial perfusion and is able to provide a “one-stop-shop” examination with fine analysis of the segmental contractility at the same time. These methods may be considered in future studies aimed at evaluating the cardiac impact of vasodilators in patients with SSC.
The limited number of patients included in this series, the global nature of MRI evaluation in contrast to the segmental evaluation by TDE may account for the absence of correlation between perfusion and function improvement. Moreover, myocardial perfusion may increase in segments with various degrees of fibrotic lesions, resulting in different impact on function parameters.

The number of patients limited the assessment of potential relationship between cardiac results and SSc characteristics; however, it should be noted that no difference in cardiac baseline data or nifedipine-induced changes were observed for the two cutaneous subsets of SSc. This is consistent with myocardial involvement in both cutaneous subtypes of SSc (5). We assessed the effects of nifedipine treatment on myocardial perfusion and segmental function only after 14 days; thus, no formal conclusion can be drawn from this study about the possible sustained therapeutic benefits of this drug. Moreover, as this study was not conducted according to a randomised, controlled, double-blind protocol, our results may be considered as preliminary and require confirmation. However, these results emphasise previous data and highlight the beneficial microvascular and cardiac effects of nifedipine which should be regarded as a crucial treatment in systemic sclerosis.

Conclusion
Fourteen days of treatment with nifedipine simultaneously improves myocardial perfusion and regional function, respectively determined by quantitative, accurate and highly sensitive methods, MRI and TDE. Our data demonstrate the strikingly beneficial short-term myocardial effects of this drug in systemic sclerosis patients.
Legends of the figures:

Figure 1: Mid-ventricular short-axis view after bolus of Gadolinium-DOTA exhibiting different patterns of subendocardial perfusion defect (visual analysis) before treatment with nifedipine. Notice that these defects do not correspond to any epicardial coronary artery distribution.

A- small inferoseptal defect (scored as grade 1)
B- larger defect anterior and septal defect (scored as grade 2)
C- diffuse subendocardial defect (scored as grade 2)

Figure 2. Parametric analysis by MRI in one patient.

A- Parametric analysis (peak SI on bull’s eye) confirming diffuse hypoperfusion (scale from yellow for high peak SI to dark red for low peak SI) before treatment with nifedipine.
B- Parametric bull’s eye analysis (peak SI) showing global improvement of myocardial perfusion with almost diffuse increased peak SI after treatment with nifedipine.

Figure 3: Strain rate (SR) measurement by TDE at baseline in one patient.

A- Color M-mode TDE acquisition in the inferior wall from a short axis parasternal view-subendocardium and subepicardium delimitation.
B- Extraction of myocardial velocities in the subendocardium (black) and subepicardium (grey line).
C- SR determination.

Figure 4:

Individual data (25th to 75th percentile) of significant increase in myocardial perfusion index, as measured by magnetic resonance imaging (A) and increase in systolic strain rate as measured by tissue Doppler echocardiography (B), after 14 days of treatment with nifedipine (60 mg/d).

References


Table 1: Clinical and biological characteristics of patients with systemic sclerosis (SSc)

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<tr>
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<th>SSc patients (n = 18)</th>
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<tr>
<td>Age: mean±SD years (range)</td>
<td>59±8.9 (42-79)</td>
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<tr>
<td>Disease duration: mean±SD years (range)</td>
<td>7.2±4.3 (1-17)</td>
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<td>Raynaud’s phenomenon; n patients (%)</td>
<td>18 (100)</td>
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<td>Lung fibrosis (CT scan): n patients (%)</td>
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<td>Forced vital capacity; mean±SD % of predicted value n patients &lt; 75%</td>
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<td>DLCOc/Haemoglobin; mean±SD % of predicted value n patients &lt; 75%</td>
<td>76±16</td>
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<td>Systolic pulmonary arterial pressure; mean±SD mmHg (range)</td>
<td>32±4 (21-38)</td>
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<td>Positive for anti-topoisomerase I antibodies: n patients (%)</td>
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<td>Positive for anti-centromere antibodies: n patients (%)</td>
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<td>Mean creatinine±SD (µmol/l; range)</td>
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<td>Erythrocyte sedimentation rate (mm/h; mean±SD, range)</td>
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<td>C-reactive protein concentration (mg/l; mean±SD, range)</td>
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<td>Whole SSc population (n=18)</td>
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<tr>
<td>MRI perfusion index</td>
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<td>0.20±0.05</td>
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<td>0.17±0.03</td>
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<td>TDE systolic strain rates (s⁻¹)</td>
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<td>TDE diastolic strain rates (s⁻¹)</td>
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Figure 2
A

MR perfusion index

Baseline | Nifedipine

p = 0.0003

B

Systolic strain rates

Baseline | Nifedipine

p = 0.0002
Evaluation of nifedipine efficacy on myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue Doppler echocardiography in systemic sclerosis

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