No Evidence of Myocardial Oxygen Deprivation in Non-Ischemic Heart Failure

Dass et al: No Evidence of Deoxygenation in DCM

Sairia Dass, MBBS, DPhil1; Cameron J. Holloway, MBBS, DPhil1;
Lowri E. Cochlin, MChem, DPhil2; Oliver J. Rider, MRCP, DPhil1;
Masliza Mahmod, MBChB, DPhil1; Matthew Robson, BA, PhD1; Emily Sever, MBBS1;
Kieran Clarke, PhD2; Hugh Watkins MD, PhD1; Houman Ashrafian, MD, PhD1;
*Theodoros D. Karamitsos, MD, PhD1, *Stefan Neubauer, MD1

1Division of Cardiovascular Medicine, Radcliffe Department of Medicine; 2Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, United Kingdom

*Both senior authors contributed equally

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Correspondence to
Prof. Stefan Neubauer
Director, Oxford Centre for Clinical Magnetic Resonance Research
Division of Cardiovascular Medicine
Radcliffe Department of Medicine
Level 0, John Radcliffe Hospital, Oxford OX3 9DU
Tel: (44) 1865 226829
Fax: (44) 1865 222077
E mail: Stefan.neubauer@cardiov.ox.ac.uk

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Abstract

Background—Whether the myocardium in non-ischemic heart failure experiences oxygen-limitation remains a long-standing controversy. We addressed this question in patients with Dilated Cardiomyopathy (DCM) using a dual approach: First, we tested the changes in myocardial oxygenation between rest and stress states, using oxygenation-sensitive CMR. Secondly, we sought to assess the functional consequences of oxygen limitation at rest by measuring myocardial energetics before and after short-term oxygen supplementation.

Methods and Results—Twenty six subjects (14 DCM; 12 normal) underwent cardiac MRI at 3 Tesla to assess cardiac volumes, function, oxygenation and first-pass perfusion (0.03 mmol/kg Gd-DTPA bolus) at stress and rest (4-6 minutes i.v. adenosine, 140μg/kg/min). Signal intensity change (SIA) and myocardial perfusion reserve index (MPRI) were measured from oxygenation and perfusion images, respectively. Furthermore, the effect of oxygen supplementation on resting myocardial energy metabolism was tested using 31P MR spectroscopy, measuring PCr/ATP ratios in both groups at baseline and after 4 hours of oxygen via facemask in the DCM group.

During stress there were equivalent rises in rate pressure product in both groups (DCM 76±15%, normal 79±9%, P=0.84). MPRI was significantly reduced in DCM (1.51 ± 0.11 vs. normal 1.86±0.10, P=0.03). However, there was no difference in oxygenation between groups: SIA in DCM 17±3% vs. normal 20±2% (P=0.38). Furthermore, at a LV segmental level, there was no correlation between oxygenation-sensitive SIA and MPRI (R=0.06, P=0.43). Resting PCr/ATP was reduced in DCM (1.66±0.07 vs normal 2.12±0.06, P=0.002). With oxygen supplementation, there was no change in PCr/ATP (1.61±0.08, P=0.58, Δ-0.04±0.05). There was also no effect of oxygen on systolic function (EF pre oxygen 34±1%, post oxygen 36±2%, P=0.46; Δ 2±1%).

Conclusions—Our results demonstrate dissociation between microvascular dysfunction and oxygenation in DCM, suggesting that the impairment of perfusion is not sufficient to cause deoxygenation during stress. Cardiac energetics are unaffected by oxygen supplementation, indicating the absence of relevant myocardial hypoxia at rest. Our study suggests that novel treatments for non-ischemic heart failure should focus on efforts to directly target cardiomyocyte function and metabolism rather than oxygen delivery and microvascular function.

Key Words: dilated cardiomyopathy; blood oxygen level dependence; cardiac metabolism
A substantial body of evidence supports the argument that attenuated myocardial blood flow, whether at rest or during physiological/pharmacological stress, is frequently encountered in dilated cardiomyopathy (DCM)\textsuperscript{1-3}. An abnormal coronary flow reserve in DCM appears to independently portend a poorer cardiac prognosis\textsuperscript{4}. In the absence of obstructive epicardial coronary disease, this reduction in flow has been inferred to represent an impaired coronary microcirculation with resultant hypoxia.

A number of mechanisms have been proposed to account for this microvasculopathy. Progressive myocardial fibrosis, especially when distributed perivascularly, is a common feature of DCM, and has been proposed to reduce capillary density and increased oxygen diffusion distance\textsuperscript{5}. With progression of disease, ventricular remodelling with increased wall tension conforming to Laplace’s law has been proposed to compress intra-myocardial vessels and contribute to microvascular disease\textsuperscript{6}. Impaired endothelial function (dependent and independent of Nitric Oxide) is known to contribute to microvascular dysfunction. At least in animal models of cardiomyopathy, ACE inhibitors improve myocardial perfusion both in pattern and magnitude\textsuperscript{7}. Finally, structural and functional abnormalities of myocardial resistance vessels (i.e. arterioles) have been proposed to be important determinants of myocardial perfusion in a variety of cardiac conditions (e.g. ischemia) and may contribute to the perfusion patterns in DCM\textsuperscript{6}.

It has been assumed that, in this scenario, impaired myocardial blood flow results in inadequate tissue oxygenation. As a corollary, hypoxia-inducible transcription factor (HIF) pathway is activated in human heart failure, as adduced from the induction of ABCG2, VEGF, and BNIP3\textsuperscript{8}. Chronic HIF-1α stabilization, putatively acting through altered metabolism, deleterious calcium
fluxes and activation of pro-apoptotic pathways, has been proposed to accelerate DCM progression\textsuperscript{9}.

Despite the intuitive logic of this pathological sequence (i.e. inciting aetiology of DCM leading to structural and functional changes resulting in microvasculopathy with rest and stress perfusion defects possibly resulting in adverse molecular consequences of hypoxia and hence progression of disease), tissue oxygenation, especially in the context of physiological/pharmacological stress, has never been directly measured in human DCM. Likewise, at rest, abnormal cardiac energetics is well established as a predictor of mortality in DCM\textsuperscript{10, 11}. However, whether tissue hypoxia contributes to the impaired cardiac high-energy phosphate metabolism and function at rest in patients with DCM is unknown.

In the present study, we asked the question whether the non-ischemic failing human myocardium is oxygen-limited. We addressed this by testing whether, in dilated cardiomyopathy, the oxygenation response to stress is appropriate, and whether resting cardiac function and high-energy phosphate metabolism are improved with inhaled supplemental oxygen (increasing myocardial oxygenation as has been validated in animal models)\textsuperscript{12}. If this were the case, then mechanisms to improve oxygen delivery and utilization would be important targets for therapeutic intervention in treating patients with chronic heart failure due to DCM. To do so, we exploited hemoglobin’s differences in magnetic susceptibility in its diamagnetic oxygenated and paramagnetic deoxygenated state (oxygenation-sensitive CMR imaging).
Methods

Ethics and Study Population

The study was approved by the institutional ethics committee and informed written consent was obtained from all subjects.

Fourteen patients with DCM were recruited from the Heart Failure clinic at the Oxford University Hospitals NHS Trust. DCM was defined as cardiac dilatation greater than 55mm and left ventricular ejection fraction <40% on a clinically indicated transthoracic echocardiography, in the absence of flow limiting coronary artery disease, assessed using invasive coronary angiography. All participants were Class II-III New York Heart Association (NYHA) and stable on optimum tolerated heart failure treatment for at least 6 months, as assessed by their treating physician. Normal controls (12 subjects) were matched for age and gender. Control subjects had no history of cardiac disease, hypertension, family history of cardiomyopathy or sudden death and had a normal 12- lead ECG. No subjects in either group had a history of smoking or contraindications for MR scanning. All participants were instructed to refrain from caffeine-containing drinks in the 24 hours preceding the study.

CMR protocol

All CMR examinations were performed on a Siemens 3T Trio MR system (Siemens Healthcare Erlangen, Germany). In the oxygen supplement arm, subjects were scanned on room air, then fitted with an oxygen face masks (10l/min using a non-rebreathing mask) outside the scan room.
for 4 hours whilst resting comfortably and supplemental oxygen was administered during the follow up scan protocol.

Figure 1 shows the scan protocol.

**Cardiac function**

Cardiac volumes and ejection fraction were calculated based on a short axis stack taken as a series of single breath-hold balanced steady-state free precession (SSFP) cine images as previously described. Each acquisition was prospectively ECG gated, with sequence parameters of flip angle 50°, repetition time 3 ms, echo time 1.5 ms, temporal resolution 60.3 ms and 8 mm thick with 3 mm gap.

**Oxygenation-sensitive CMR**

Oxygenation-sensitive or Blood-Oxygen Level-Dependent (BOLD) CMR was performed acquiring basal, mid ventricular and apical slices at mid-diastole using a T2-prepared ECG-gated SSFP sequence with the following parameters: repetition time/echo time, 2.86/1.43 ms; T2 preparation time, 40 ms; matrix, 168x192; field of view, 340x340 mm; slice thickness, 8 mm; and flip angle, 44°. Each BOLD image was obtained during a single breath-hold over 6 heart beats. Two images of the same slice were acquired at rest and at peak stress (3-4 minutes of adenosine infusion, 140 µg/kg/min).
Myocardial Perfusion Reserve Index (MPRI)

MPRI was measured on the same basal, mid ventricular and apical slices used for oxygenation measurement. Images were acquired during peak stress after commencement of adenosine as previously described. Stress perfusion was measured every heartbeat during the first pass of a bolus of intravenous magnetic resonance contrast agent (0.03mmol/kg body weight of Gadodiamide, Omniscan; GE Healthcare, Amersham, United Kingdom, injection rate, 6 ml/s) followed by a saline flush of 15 mls at the same rate, using a T1 -weighted fast gradient echo sequence. Perfusion pulse sequence parameters were as follows: echo time 0.96 ms, repetition time 2 ms, saturation recovery time 95 ms, voxel size 2.1×2.6×8 mm³, flip angle 17°, slice thickness 8 mm. Rest perfusion imaging was performed after at least 25 minutes and another dose of contrast (0.03mmol/kg body weight) was given. Heart rate and blood pressure were measured before, at two minute intervals during, and after adenosine stress.

31P- Magnetic Resonance Spectroscopy

All 31P MRS were acquired at 3 Tesla using acquisition-weighted chemical shift imaging (AW-CSI), with 10 averages in the centre of k-space. Subjects lay prone, with the left ventricle at magnet iso-centre. Pilot images of vertical-long-axis, horizontal-long-axis and short-axis (3D stack) were acquired. A 16 x 8 x 8 CSI grid with a 240 x 240 x 200 mm field of view was centered in the mid-ventricular septum on the first short axis image showing the papillary muscles. In order to minimize contamination from surrounding tissue, three saturation bands, each 25mm thick, were placed over chest wall muscle and liver. Five 2.5 ms long Nuclear Overhauser enhancement pulses were played out at an inter-pulse delay of 80.5ms, 222.2 Volts
and average flip angle of 150 degrees in between the ECG wave and the 31P excitation to increase the SNR in the acquired spectra.

Non-localised inversion-recovery spectra were acquired and used in conjunction with a field-map to calculate the flip-angle (nominally 35°) achieved in each voxel for each acquisition. MRS data were acquired with 720ms repetition time, using an optimized radio-frequency pulse centered between γ- and α-ATP peaks for uniform excitation of the spectrum, and ultrashort echo time to minimise T2 effects and first order phase artefacts. Each MRS acquisition took 8 minutes to acquire, as previous described.

Image analysis

Evaluation of left ventricular (LV) systolic function

LV short axis epicardial and endocardial borders were manually contoured at end-diastole and end-systole for determining end diastolic volume (EDV); end systolic volume (ESV); and stroke volume (SV). Commercially available software (Argus version VA60C, Siemens Healthcare, Erlangen, Germany) was used. LV mass was calculated based on prior knowledge of myocardial specific density (1.05 g/cm³).

Oxygenation analysis

For oxygenation analysis, QMass software (version 6.2.3, Medis, Leiden, The Netherlands) was used. Myocardial signal intensity (SI) was measured after manually tracing the endocardial and epicardial contours. Mean signal intensities were calculated for resting and stress conditions by averaging signal measurements from images during rest and adenosine stress, respectively.
BOLD SI measurements were corrected for variations in heart rate between resting and stress as previously described.\textsuperscript{19}

**Perfusion analysis**

QMass software (version 6.2.3, Medis, Leiden, The Netherlands) was used. Signal intensity over time curves were generated by tracing endocardial and epicardial contours after manual correction for displacement during breathing. A region of interest was drawn in the LV blood pool, avoiding any papillary muscles therein, to permit the derivation of an arterial input function. Rest and stress myocardial perfusion upslopes were calculated using 5 point linear fit model of SI vs. time and normalized to the LV blood pool upslope. Myocardial perfusion reserve index (MPRI) was then calculated by dividing the results at vasodilation through the results at rest. MPRI is a semi-quantitative method and has been widely adapted for perfusion analysis\textsuperscript{14}.

\textsuperscript{31}P- Magnetic Resonance Spectroscopy analysis

Spectra were direct current corrected and baseline corrected based on the last half of acquired data points. Spectral peaks were imported into jMRUI (Java Magnetic Resonance User Interface\textsuperscript{20}) and fitted using the AMARES algorithm (Advanced Method of Accurate, Robust and Efficient Spectroscopic fitting \textsuperscript{21}) making use of prior knowledge relating to the relative peak frequencies, amplitudes, phases and j-coupling patterns.

Spectral peak areas were corrected for nuclear overhauser effect (NOE) using correction factors determined by prior experiment\textsuperscript{16}: NOE correction factors used were PCr 0.80, $\beta$-ATP 0.88, $\alpha$-
ATP 0.88, γ-ATP 0.79, 2, 3-DPG 0.70. Correction for radiofrequency (RF) saturation was calculated for each subject using the repetition time (TR) and experimentally determined excitation flip angle at the chosen voxel and T1 values from the literature: PCr 3.8 s, γ-ATP 2.4 s, α-ATP 2.5 s, β-ATP 2.7 s, 2,3-DPG 1.39 s, and PDE 1.1 s. The resulting peak areas of the three ATP signals were averaged and corrected for blood contamination by subtracting 11% of the 2, 3-DPG peak area.

**Statistical analysis**

All data are expressed as mean±SE and checked for normality using Kolmogorov–Smirnov test. Additionally all data were plotted to confirm that they are normally distributed. Comparisons between the groups were performed using independent t-tests whereas comparisons within groups were performed using paired t-tests. Fisher exact test was used to compare discrete data. Statistical tests were two tailed, and a P value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analysis was performed with commercially available software packages (IBM SPSS Statistics, version 19.0 and MedCalc version 12).

Power calculations using G* Power 3.2.1. software based on the use of independent T test and pilot data (DCM PCr/ATP 1.65 ± 0.4 vs Normal 2.1 ± 0.2) suggested 9 subjects would be needed in each group to detect a difference in PCr/ATP ratio (α= 0.05, power= 80%).

**Results**

**Study groups and functional measurements**

Subject characteristics are described in Table 1. There were no differences in age and gender between the DCM and normal groups. As expected, the DCM group had significantly lower
ejection fraction compared to normal (33±1% vs 69±1%, P<0.0001) as well as significantly higher end-diastolic volumes (200±20mls vs 142±12mls, P=0.02).

During adenosine stress there was an equivalent rise in RPP in both groups (DCM 76±15%, normal 79±9%, P=0.84), Table 2.

**Perfusion and Oxygenation response to Stress**

During adenosine infusion, stress perfusion was blunted in DCM compared to normal (DCM: 1.51 ± 0.11; normal 1.86±0.10; P=0.03; Figure 2), in keeping with previous reports of abnormal perfusion in DCM\(^1\)-\(^3\). However, in spite of this, in DCM, the oxygenation response to vasodilator stress was not significantly different from normal (BOLD SIA DCM: 17±3%, normal: 20±2%; P=0.56; Figure 2). To put these numbers in context, using similar methods, we have previously published significantly lower BOLD SIA in patients with coronary artery disease (3±1%)\(^19\), hypertrophic cardiomyopathy (7±1%)\(^14\) and aortic stenosis (5±9%)\(^24\).

Furthermore, in DCM on a segmental level, there was no significant correlation between BOLD SIA and MPRI (R=0.06, P=0.43).

**Cardiac energetics during short-term Oxygen supplementation**

BOLD imaging can detect oxygenation difference between rest and stress states, but does not measure absolute oxygenation levels. The myocardial oxygenation findings therefore did not rule out the possibility of an oxygen deficit during resting conditions. To test whether oxygen was limiting in the non-ischemic failing myocardium at rest, we measured cardiac energetics before
and after 4 hours of oxygen supplementation. At baseline, the PCr/ATP ratio was significantly reduced in DCM (1.66±0.07, normal 2.12±0.06, P=0.002, Figure 3). In DCM, four hours of oxygen supplementation did not result in any change in the cardiac PCr/ATP ratio (1.61±0.08, P=0.58, Δ-0.04±0.05, Figure 3). Moreover, there was no effect of oxygen supplementation on systolic function (EF pre oxygen 34±1%, post oxygen 36±2%, P=0.46; Δ 2±1%, Figure 3). These findings suggest that in DCM neither cardiac function nor cardiac energetics were acutely limited by oxygen availability. Figure 4 shows an example of spectra obtained pre and post oxygen supplementation.

**Discussion**

Whether myocardial oxygenation is a limiting factor in human non-ischemic heart failure is an important question. On one hand, experimental studies using $^{31}$P- and $^1$H- MRS in large animals led by Zhang’s group have not found evidence for such deoxygenation.$^{25}$ On the other hand, this question has so far not been examined in human myocardium, and a body of literature is accumulating describing both microvascular dysfunction in DCM and maladaptive ensuing sequelae of hypoxia including HIF-1alpha stabilization.$^{8,9}$ Consequently, the non-invasive detection of hypoxia in cardiac tissue has the potential to be an important prognostic biomarker. The presence of hypoxia has been inferred as a consequence of microvascular dysfunction. The observation that even healthy subjects experience deterioration in cardiac function and energy metabolism in the context of sustained hypoxia represents a rationale for this pathological sequence.$^{13}$
Set against this background, we now measured the myocardial oxygen response to stress in DCM with a direct comparison to perfusion reserve on a per segment basis. The principal finding of our study is that, whilst we confirm that patients with DCM have impaired myocardial perfusion reserve, our oxygenation-sensitive CMR studies, reflecting tissue hemoglobin saturation, suggest that there is no disturbance of the oxygen supply/demand balance in these patients during stress. Additionally in DCM, although there are alterations in cardiac volumes, function and energy metabolism, short-term oxygen supplementation does not improve these changes. In aggregate, these data suggest that hypoxia does not contribute significantly to the pathogenesis of DCM.

**Oxygenation response to vasodilator stress**

The lack of a correlation between BOLD SIA and MPRI (R=0.06, P=0.43) suggests that despite the confirmation of microvascular dysfunction as indicated by reduced myocardial perfusion reserve in DCM, this appears not to be severe enough to affect the oxygen supply/demand balance. This contrasts with observations in coronary artery disease, reporting that BOLD SIA was significantly lower in segments supplied by coronary arteries with fractional flow reserve less than 0.8. Nevertheless, Karamitsos et al validated BOLD against myocardial perfusion assessed by positron emission tomography in patients with coronary artery disease and concluded that in this population, reduced perfusion does not always lead to deoxygenation. Moreover, Arnold et al, in comparing BOLD with first pass perfusion in patients with CAD on a segment based analysis, provided further evidence that a dissociation between oxygenation and perfusion can exist even in coronary artery disease.
This study confirms the finding of reduced resting PCr/ATP ratio in non ischemic heart failure (see 28 for review). However, our data now provide further mechanistic insight and suggest that abnormal resting PCr/ATP ratio in DCM is not explained by the acute consequences of tissue hypoxia. Therefore, the more likely mechanisms responsible are the chronic consequences of molecular remodeling including changes in substrate utilisation 29,30, mitochondrial structure and function 31 and high energy transfer and utilization 32.

Limitations

Although the current study was relatively small with 14 patients, it was powered adequately for the novel endpoint of oxygenation sensitive CMR in DCM. Nevertheless, it remains an important caveat that the lack of myocardial hypoxia may not be germane to all categories of DCM. Furthermore, in the present study, oxygen supplementation was given for 4 hours. Whether the adaptive consequences of chronic hypoxia are sustained (e.g. hibernation) and require prolonged tissue oxygenation to ameliorate gene expression and lead to an improvement in cardiac function and energy metabolism remains unclear, and further studies would be needed to investigate this possibility.

Conclusion and Clinical Implications

Our results demonstrate dissociation between microvascular dysfunction and oxygenation in DCM, suggesting that the impairment of perfusion is inadequate to cause myocardial deoxygenation during stress. We also demonstrate that cardiac function and energetics are unaffected by short-term oxygen supplementation, suggesting that there is no significant disturbance of the oxygen supply/demand balance at rest. Our findings therefore suggest that
novel treatments for non-ischemic heart failure should focus on efforts to directly target cardiomyocyte function and metabolism, rather than oxygen delivery and microvascular function.

Sources of Funding

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Disclosures

None.

References

Table 1. Baseline characteristics of study groups

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<th>DCM (n=14)</th>
<th>Normal (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±2</td>
<td>57±3</td>
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<tr>
<td>Male, n (%)</td>
<td>10(71)</td>
<td>9(75)</td>
<td>0.84</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>33±1</td>
<td>69±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-diastolic volume(ml)</td>
<td>200±20</td>
<td>142±12</td>
<td>0.02</td>
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<tr>
<td>End-systolic volume(ml)</td>
<td>125±17</td>
<td>47±4</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV Mass index</td>
<td>74±4</td>
<td>57±4</td>
<td>0.02</td>
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<td>NYHA Class 1/2/3/4 (n)</td>
<td>0/10/4/0</td>
<td>NA</td>
<td>-</td>
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<tr>
<td>ACE/ARB, n (%)</td>
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<td>0</td>
<td>-</td>
</tr>
<tr>
<td>B-Blockers, n (%)</td>
<td>14(100)</td>
<td>0</td>
<td>-</td>
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<tr>
<td>‘Spironolactone, n (%)</td>
<td>1(7)</td>
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<td>-</td>
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<tr>
<td>Digoxin, n (%)</td>
<td>2(14)</td>
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<td>-</td>
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<tr>
<td>Loop diuretic, n (%)</td>
<td>8(57)</td>
<td>0</td>
<td>-</td>
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<tr>
<td>Haemoglobin</td>
<td>14±0.3</td>
<td>14±0.2</td>
<td>0.10</td>
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Table 2. Haemodynamic Data at Rest and during Adenosine Infusion for the Study Population

<table>
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<th>DCM</th>
<th>Normal Controls</th>
<th>Between group comparison P values</th>
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<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
<td>P value</td>
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<tr>
<td>Heart Rate, beats/min</td>
<td>61±3</td>
<td>85±3</td>
<td>&lt;0.0001</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>117±3</td>
<td>133±7</td>
<td>0.005</td>
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<tr>
<td>RPP, beats/min x mm Hg</td>
<td>7249±687</td>
<td>11502±998</td>
<td>0.0004</td>
</tr>
<tr>
<td>Rise in RPP with stress, %</td>
<td>76±15</td>
<td></td>
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</table>

Data are presented as mean±SE,
**Figure Legends**

Figure 1. Scan Protocol, Gadolinium: 0.03mmol/kg was given with stress and rest perfusion.

Figure 2. Oxygenation and stress perfusion measurements. Error bars are ±SE. BOLD SIA indicates blood-oxygen level-dependent signal intensity change; MPRI, myocardial perfusion reserve index.

Figure 3. The effect of oxygen supplementation on PCr/ATP and ejection fraction in DCM. Error bars are ±SE.

Figure 4. Example of voxel location for measurement of PCr/ATP (red rectangle) and examples of typical $^{31}$P-spectra obtained.
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