ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2026) **27**, 74–77
https://doi.org/10.1093/ehjci/jeaf310

RESEARCH LETTER

A double-blind, randomized placebo-controlled trial examining the effect of MitoQ on myocardial energetics in patients with dilated cardiomyopathy

Brian P. Halliday [1,2]*, Ruth Owen[3,4,5], Aaraby Ragavan[1,2], Katherine L. Smith[1,2], Ben Statton[6], Alaine Berry[6], Alex Kasiakogias[2], Zoi Tsoumani[2], Mayooran Shanmuganathan[2,7], Jason N. Dungu[8,9], Antonio de Marvao[10,11], Upasana Tayal[1,2], James S. Ware[1,2,6], Declan P. O'Regan[6], Dudley J. Pennell[1,2], John GF Cleland [12], Sanjay K. Prasad[1,2], John Gregson [3], Michael P. Murphy[13,14], Oliver J Rider [7], and Ladislav Valkovič[7,15]

[1]National Heart and Lung Institute, Imperial College London, Sydney Street, London SW3 6NP, UK; [2]Royal Brompton and Harefield Hospitals, Part of Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; [4]Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain; [5]Oxon Epidemiology, Madrid, Spain; [6]Medical Research Council Laboratory of Medical Sciences, Imperial College London, London, UK; [7]Oxford Centre for Clinical MR Research (OCMR), Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [8]Department of Cardiology, Basildon and Thurrock Hospitals NHS Foundation Trust, Basildon, Essex, UK; [9]Anglia Ruskin University, Essex, UK; [10]Department of Cardiology, Guy's and St Thomas" NHS Foundation Trust, London, UK; [11]School of Cardiovascular Science, King's College London, London, UK; [12]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [13]MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, UK; [14]Department of Medicine, University of Cambridge, Cambridge, UK; and [15]Department of Imaging Methods, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovakia

Received 29 October 2025; accepted 31 October 2025; online publish-ahead-of-print 10 November 2025

Keywords dilated cardiomyopathy • mitochondrial dysfunction • oxidative stress • heart failure

Oxidative stress may be an important driver of dilated cardiomyopathy (DCM) causing mitochondrial dysfunction and reduced ATP production, which mitochondria-targeted antioxidants, such as MitoQ may improve.[1] We investigated whether MitoQ had an effect on myocardial energetics in patients with DCM using ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS) in a phase-2 randomized, double-blind, placebo-controlled trial.

Participants provided written informed consent. The trial was approved by the National Research Ethics Committee (21/LO/0035) and registered on ClinicalTrials.gov (NCT05410873). Inclusion criteria were 1) patients with DCM, 2) LVEF ≤45% on two studies ≥3 months apart, 3) on guideline therapy for ≥3 months, 4) in sinus rhythm, 5) elevated NT-pro-BNP (>250 ng/L if >65 years, > 100 ng/L if ≤65 years). Exclusion criteria were 1) atrial fibrillation, 2) contraindication to CMR or gadolinium, 3) environmental trigger for DCM, 4) late gadolinium enhancement (LGE) > 25% 5) current cancer, 6) CoQ10 use and 7) cardiac device.

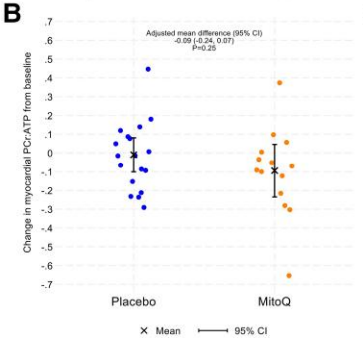
Participants underwent CMR and ^{31}P-MRS on a 3-Tesla scanner (Prisma, Siemens, Germany). Cardiac ^{31}P-MRS was performed using a 20 cm loop transmit-receive coil (Pulse Teq, UK) and a 3-dimensional chemical shift imaging sequence.[2] For skeletal muscle energetics, dynamic ^{31}P-MRS was performed with a 15 cm loop transmit-receive coil (Pulse Teq, UK) over the vastus lateralis. With weights on the ankle, participants performed leg raises during two periods of 1 min exercise. This was followed by cine imaging, LGE imaging and extracellular volume (ECV) mapping. NT-pro-BNP was measured (Roche, Switzerland). Patients completed the Kansas City Cardiomyopathy Questionnaire (KCCQ) and a 6-minute walk test.[3]

* Corresponding author. E-mail: b.halliday@imperial.ac.uk

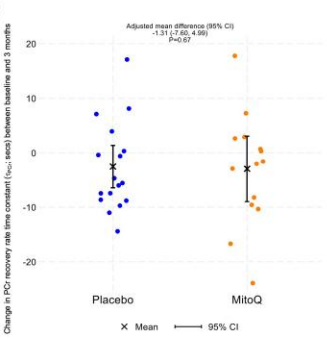
A

		MitoQ (n=16)	Placebo (n=18)
Age (years)		63 (54 - 72)	50 (45 - 61)
Male n (%)		13 (81)	13 (72)
BMI (kg/m2)		28 (22-30)	27 (24-28)
NYHA class n (%)	I	10 (63)	7 (39)
	II	6 (38)	11 (61)
NT-pro-BNP (ng/L)		557 (215-700)	340 (224-817)
Previous AF n (%)		2 (13)	1 (6)
Hypertension		5 (31)	1 (6)
Diabetes mellitus		5 (31)	1 (6)
Medications			
ACEi/ARB/ARNI n (%)		15 (93)	18 (100)
Beta-blocker n (%)		14 (88)	16 (89)
MRA n (%)		13 (81)	17 (94)
SGLT2i n (%)		7 (44)	15 (83)
Loop diuretic n (%)		3 (19)	4 (22)

B



C



D

End-points	MitoQ Mean (SD)	n	Placebo Mean (SD)	n	Adjusted mean difference (95% CI)*	P value
Myocardial PCr/ATP (primary)						
Baseline	1.33 (0.32)	14	1.36 (0.20)	18		
3 months	1.24 (0.31)	14	1.35 (0.30)	18	-0.09 (-0.24, 0.07)	0.25
Skeletal Muscle PCr recovery rate time constant (τ_{PCr})						
Baseline	31.3 (10.2)	14	34.4 (12.9)	17		
3 months	28.3 (7.8)	14	31.8 (14.2)	17	-1.31 (-7.60, 4.99)	0.67
LVESVi (ml/m2)						
Baseline	55 (16)	15	64 (29)	18		
3 months	55 (21)	15	60 (32)	18	3.8 (-3.7, 11.3)	0.31
12 months	56 (22)	15	63 (35)	17	3.2 (-8.1, 14.6)	0.57
LVEF (%)						
Baseline	45 (7)	15	42 (8)	18		
3 months	44 (7)	15	46 (10)	18	-4.1 (-8.3, 0.1)	0.055
12 months	44 (9)	15	45 (12)	17	-3.2 (-9.5, 3.1)	0.3
ECV (%)						
Baseline	31 (5)	12	31 (3)	17		
12 months	32 (3)	12	32 (3)	17	-0.3 (-2.0, 1.4)	0.7
logNT-pro-BNP						
Baseline	6.1 (0.7)	15	5.9 (0.8)	18		
3 months	5.8 (0.9)	15	5.8 (1.0)	18	-0.2 (-0.7, 0.3)	0.4
12 months	5.8 (1.7)	13	5.9 (1.2)	15	-0.5 (-1.4, 0.3)	0.18
6-minute walk test distance (m)						
Baseline	438 (340-517)	15	409 (373-479)	18		
3 months	495 (378-539)	15	446 (375-479)	17	3 (-23, 27)	0.8
12 months	564 (402-595)	15	468 (450-542)	17	23 (-12, 59)	0.19
KCCQ score						
Baseline	87 (18)	15	81 (21)	18		
3 months	92 (14)	15	88 (16)	18	0.2 (-6.9, 7.3)	0.95
12 months	92 (21)	17	88 (18)	17	1.4 (-9.5, 12.3)	0.79

Figure 1 (*A*) Baseline characteristics by randomized treatment allocation; (*B&C*) Change in myocardial and skeletal muscle energetics by treatment allocation; (*D*) Change in primary and secondary end-points by treatment allocation. *Adjusted for baseline value and estimated using analysis of covariance. All differences are summarized as mean (95% CI) except for 6MWT which is summarized as median (95% CI). **6MWT is summarized as median (interquartile range) and *P*-values calculated using the non-parametric Mann-Whitney U test.

Patients were randomized 1:1 stratified by left ventricular end-systolic volume (LVESV). Identical MitoQ or placebo were dispensed according to randomization code. Trial staff remained blind to allocation. Participants took two 20 mg capsules of MitoQ or placebo daily and had repeat testing at 3 and 12 months (^{31}P-MRS only at 3 months).

The primary endpoint was change in myocardial PCr/ATP at 3 months. Secondary endpoints included change in (i) PCr recovery rate time constant in skeletal muscle, (ii) LVESVi, (iii) LVEF, (iv) ECV, (v) NT-pro-BNP, (vi) 6MWT distance and (vii) KCCQ score. ^{31}P-MRS and CMR data were analysed in a standardized fashion by expert operators blind to allocation (OXSA, Oxford, UK[4]; CMR42 V6.0.3, Circle Cardiovascular Imaging, Canada). 34 patients had 90% power to detect a difference of 0.28 in change of PCr/ATP, assuming a standard deviation of 0.25, a 2-sided alpha of 0.05 and a 10% drop-out. The effect of MitoQ was assessed using analysis of covariance on Stata V18.0 (StataCorp, TX, USA). Analyses were by modified intention to treat. $P < 0.05$ was taken as significant.

Of 34 eligible patients, 16 were randomized to MitoQ and 18 to placebo (*Figure 1A*). One withdrew; another had incomplete primary endpoint data; 32 participants were included in the primary analysis. Patients randomized to MitoQ were older with higher NT-pro-BNP but less symptomatic (*Figure 1A*). Rates of heart failure therapy were high.

After three months, there was no evidence that MitoQ had an effect on myocardial energetics [adjusted mean difference PCr/ATP −0.09 (95% CI −0.24, 0.07); $P = 0.27$] or skeletal muscle energetics (adjusted mean difference PCr recovery rate time constant (τ_{PCr}) −1.3 [95% CI −7.6 to 4.9] seconds; $P = 0.67$) (*Figure 1B/1c*). In addition, MitoQ did not affect LVESV, LVEF, ECV, NT-pro-BNP, 6MWT or KCCQ at 3 or 12 months (*Figure 1D*).

Treatment was well tolerated and self-reported compliance was excellent [mean number of missed doses of 0.5 (1.3)]. Fewer adverse events were reported in the MitoQ arm compared to the placebo arm (26 vs. 49); 3 in the MitoQ and 2 in the placebo arm were at least possibly related to treatment; all graded as mild. There were 3 serious adverse events unrelated to treatment, including a heart failure hospitalization in the MitoQ arm and hospitalizations for pulmonary embolism and kidney injury in the placebo arm.

This trial provides the first randomized data examining the effect of MitoQ on energetics in DCM. We determine that it is unlikely that MitoQ has an effect on myocardial energetics. Our analysis achieved >90% power to detect an improvement in PCr/ATP of at least 0.25; an effect observed with perhexilene.[5] The upper limit of the 95% confidence interval suggests the chance of a clinically significant effect on energetics is very small. The results may therefore reflect that: (i) mitochondrial oxidative stress is not an important mediator of energetic impairment in DCM or (ii) an effect is only present in a sub-group of patients (such as those with severe heart failure). Altered substrate utilization is an alternative mediator of energetic impairment.[5]

In conclusion, our trial in patients with DCM found that it is unlikely that MitoQ has a clinically significant effect on myocardial energetics. Further work is required to understand energetic dysfunction across the spectrum of DCM, discover the most appropriate therapies and define sub-groups in which they may be most effective.

Acknowledgements

We thank the steering committee chaired by Dr Lisa Anderson. We thank Dr Ana Boshof, Operations Manager, the team at Imperial Clinical Trials Unit and the team at the Cardiovascular Research Centre, Royal Brompton Hospital. We thank Antipodean Pharmaceuticals for providing MitoQ and placebo free-of-charge for the duration of the trial.

Author contributions

Brian Halliday (Data curation [lead]; Formal analysis [lead]; Funding acquisition [lead]; Investigation [lead]; Methodology [lead]; Project administration [lead]; Resources [lead]; Supervision [lead]; Writing—original draft [lead]), Michael P Murphy (Conceptualization [supporting]; Funding acquisition [supporting]; Methodology [supporting]; Resources [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), John Gregson (Formal analysis [supporting]; Funding acquisition [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), Sanjay K Prasad (Conceptualization [supporting]; Funding acquisition [supporting]; Methodology [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), John G F Cleland (Conceptualization [supporting]; Funding acquisition [supporting]; Methodology [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), Dudley J Pennell (Funding acquisition [supporting]; Methodology [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), Declan P OE28099Regan (Methodology [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), James S Ware (Project administration [supporting]; Resources [supporting]; Writing—review & editing [supporting]), Upasana Tayal (Project administration [supporting]; Resources [supporting]; Writing—review & editing [supporting]), Oliver Rider (Investigation [supporting]; Methodology [supporting]; Software [supporting]; Supervision [supporting]; Writing—review & editing [supporting]), Antonio de Marvao (Investigation [supporting]; Methodology [supporting]; Project administration [supporting]; Resources [supporting]; Writing—review & editing [supporting]), Mayooran Shanmuganathan (Data curation [supporting]; Project administration [equal]; Resources [equal]; Writing—review & editing [supporting]), Zoi Tsoumani (Data curation [equal]; Formal analysis [equal]; Investigation [supporting]; Methodology [supporting]; Project administration [supporting]; Writing—review & editing [supporting]), Alex Kasiakogias (Data curation [equal]; Formal analysis [equal]; Investigation [equal]; Methodology [supporting]; Project administration [supporting]), Alaine Berry (Data curation [equal]; Formal analysis [equal]; Investigation [equal]; Methodology [equal]), Ben Statton (Data curation [equal]; Formal analysis [equal]; Investigation [equal]; Methodology [equal]; Project administration [equal]; Resources [equal]), Katherine L Smith (Data curation [equal]; Project administration [equal]; Validation [equal]; Writing—review & editing [equal]), Aaraby Ragavan (Data curation [equal]; Formal analysis [equal]; Project administration [equal]; Writing—review & editing [equal]), Ruth Owen (Formal analysis [lead]; Investigation [supporting]; Methodology [supporting]; Visualization [lead]), Jason N Dungu (Investigation [supporting]; Methodology [supporting]; Project administration [equal]; Resources [supporting]; Writing—review & editing [supporting]), and Ladislav Valkovič (Formal analysis [supporting]; Investigation [supporting]; Methodology [supporting]; Software [supporting]; Supervision [supporting]; Writing—review & editing [supporting])

Funding

The study was funded by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/ICRF/21/26019) awarded to BPH and Rosetrees Trust. Funding was also provided by the NIHR Imperial Biomedical Research Centre. DPO'R is supported by the Medical Research Council (MC_UP_1605/13) and the British Heart Foundation (RG/19/6/34387, RE/24/130023, CH/P/23/80008). L. Valkovic is funded by a Sir Henry Dale Fellowship supported jointly by the Wellcome Trust and The Royal Society (grant 221805/Z/20/Z) and acknowledges the support of Slovak Grant Agencies VEGA (Vedecka grantova agentura MSVVaM SR a SAV; grant 2/0004/23) and APVV (Agentura na Podporu Vyskumu a Vyvoja; grant 21-0299). Antipodean Pharmaceuticals provided MitoQ and placebo

free-of-charge for the duration of the trial. None of the funders had any role in data acquisition, analysis or interpretation nor preparation of the manuscript.
Conflict of interest: BPH has been an advisor to Astra Zeneca, Novo Nordisk, Eli Lily and Zoll. DPO'R holds grants from Bayer AG and Calico Labs, and honoraria from BMS and Circle Cardiovascular Imaging. DJP has received research funding from Siemens and speaker fees from Chiesi. MPM holds stock in MitoQ Inc and is chair of their SAB. Remaining authors have nothing to disclose.

Data availability

Anonymized participant data, the study protocol, including the statistical analysis plan, and a data dictionary are available from the time of publication. Appropriate institutional data transfer agreements will be required. Requests should be made via email to the corresponding author along with an analysis proposal.

References

1. Goh KY, He L, Song J, Jinno M, Rogers AJ, Sethu P *et al.* Mitoquinone ameliorates pressure overload-induced cardiac fibrosis and left ventricular dysfunction in mice. *Redox Biol* 2019; **21**:101100.
2. Rayner JJ, Peterzan MA, Clarke WT, Rodgers CT, Neubauer S, Rider OJ. Obesity modifies the energetic phenotype of dilated cardiomyopathy. *Eur Heart J* 2021;**43**: 868–77.
3. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D *et al.* An official European respiratory society/American thoracic society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;**44**:1428–46.
4. Purvis LAB, Clarke WT, Biasiolli L, Valkovic L, Robson MD, Rodgers CT. OXSA: an open-source magnetic resonance spectroscopy analysis toolbox in MATLAB. *PLoS One* 2017; **12**:e0185356.
5. Beadle RM, Williams LK, Kuehl M, Bowater S, Abozguia K, Leyva F *et al.* Improvement in cardiac energetics by perhexiline in heart failure due to dilated cardiomyopathy. *JACC Heart Fail* 2015;**3**:202–11.