

Supplementary Table 1: Effects of Ventricular Dyssynchrony on Cardiac Metabolism: evidence from clinical studies

| Study models (N) | Dyssynchrony models (N) | Major findings | | | | | Interpretation | Ref |
|---|--|---|---|---|---------------------------|--------------------|---|-------------------------------------|
| | | Glucose uptake | Fatty acid uptake | MVO ₂ /Myocardial efficiency | Oxidative phosphorylation | Others | | |
| Human (25) | DCM with LBBB (25) | ↑ Glucose uptake heterogeneity (↓ septal FDG uptake, ↑ lateral FDG uptake) | N/A | N/A | N/A | ↔ MBF distribution | LBBB decreased septal wall glucose uptake compared to lateral wall, independent of MBF. | Degtiarova et al. 2021 ¹ |
| Human (22) | DCM with LBBB (9) vs DCM without LBBB (13) | ↑ Glucose uptake heterogeneity, related with QRSd (↓ septal FDG uptake, ↑ lateral FDG uptake) | N/A | N/A | N/A | N/A | LBBB decreased septal wall glucose uptake compared to lateral wall, correlated with electrical dyssynchrony. | Castro et al. 2012 ² |
| Human with SSS or AVB (8) | RVP, 69±9 bpm, 4 months (8) vs Baseline, 51±16 bpm (8) | ↓FDG uptake surrounding pacing site and septal area | N/A | N/A | N/A | ↔ MBF distribution | Dyssynchrony induced by RVP reduced glucose uptake in septal wall and surrounding pacing area, independent of MBF. | Preumont et al. 2005 ³ |
| Human with SSS or AVB, with dual chamber PPM (55) | Atrial synchronous RVP, 68±9 bpm, 1733±1433 days (28) vs RAP only, 62±4 bpm, 1733±1433 days (27) | N/A | ↓Septal, inferior, apical fatty acid (BMIPP) uptake | N/A | N/A | N/A | Dyssynchrony induced by RVP reduced fatty acid uptake in the septal, inferior, and apical walls, in contrast to the lateral wall, indicating heterogeneity in fat uptake. | Yoshida et al. 1999 ⁴ |

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| Human (31) | DCM with LBBB (31) vs DCM without LBBB (14) | N/A | N/A | ↑ MVO ₂ (↑ ¹¹ C-acetate clearance) at lateral wall | N/A | ↑ MBF (↑ ¹¹ C-acetate uptake) at lateral wall | LBBB increased lateral wall myocardial blood flow and O ₂ consumption, possibly due to increased mechanical stress. | Lindner et al. 2005 ⁵ |
| Human with SSS and intact AV conduction with dual chamber PPM (10) | RVP on, AVD 129±30 ms, 1hr (10) vs RVP off, AVD 262±79 ms, 1hr (10) RVP with mechanical dyssynchrony* (6) vs RVP without mechanical dyssynchrony* (4) | N/A | N/A | ↔Efficiency | ↑ Oxidative phosphorylation heterogeneity (¹¹ C-acetate clearance at lateral >septal wall) | ↔ MBF | Dyssynchrony induced by RVP decreased cardiac efficiency and enhanced oxidative phosphorylation and MBF in lateral wall compared to septal wall, especially in individuals with significant mechanical dyssynchrony. | Ukkonen et al. 2009 ⁶ |
| | | N/A | N/A | ↓Efficiency | ↑↑ Oxidative phosphorylation heterogeneity (¹¹ C-acetate clearance at lateral >>septal wall) | ↑ MBF at lateral >septal wall | | |
| Human (11) | RVP at rate 70 bpm in patients with bradycardia (5), 120 bpm in healthy (6) vs Healthy before pacing (6) | N/A | N/A | -MVO ₂ : ↑ at 70 bpm, ↑↑ at 120 bpm -Efficiency: ↓ at 70 bpm, ↓↓ at 120 bpm | N/A | N/A | Dyssynchrony induced by RVP decreased cardiac efficiency with increased O ₂ consumption particularly at higher pacing rate. | Nawa et al. 1992 ⁷ |

AV indicates Atrioventricular; AVB, Atrioventricular block; AVD, Atrioventricular delay; DCM, Dilated cardiomyopathy; FDG, 18-Fluorodeoxy glucose; hr, hour(s); k_{mono}, Oxidative phosphorylation; LBBB, Left bundle branch block; MBF, Myocardial blood flow; MI, Myocardial infarction; MVO₂, Myocardial oxygen consumption; ms, millisecond(s); PPM, Permanent pacemaker; QRSD, QRS complex duration; RAP, Right atrial pacing; RVP, Right ventricular pacing; SSS, Sick sinus syndrome

*Time to peak radial strain difference between the septal and lateral wall >130 ms.

Supplementary Table 2: Effects of Cardiac Resynchronisation on Cardiac Metabolism: evidence from clinical studies

| Study models (N) | Synchronization models (N) | Major findings | | | | | Interpretation | Ref |
|---|---|---|-------------------------------------|--|---|--|---|-----------------------------------|
| | | Glucose metabolism | Fatty acid metabolism | TCA cycle | MVO ₂ /Myocardial efficiency | Others | | |
| <i>Ventricular synchronization</i> | | | | | | | | |
| Human with DCM, LBBB with CRT, BiVP (15) | BiVP 2 weeks (15) vs baseline (15) | Restored glucose uptake homogenisation (↑ septal, ↓ lateral FDG uptake) | N/A | N/A | N/A | ↔ CBF distribution | Ventricular resynchronisation with BiVP restored homogenous myocardial glucose uptake with minimal impact on perfusion. | Nowak et al. 2003 ⁸ |
| Human with DCM, LBBB with CRT, BiVP (45) | BiVP 6 months (45) vs baseline (45) | N/A | ↑ β-oxidation (↓ C14:1/C12:1 ratio) | ↑ | N/A | ↓ Ketone bodies oxidation (↓ β-hydroxybutyrate) ↓ Anaerobic respiration (↓ Lactate) | Ventricular resynchronisation with BiVP enhanced energy production from mitochondrial metabolism, with a reduction in ketone body oxidation and anaerobic respiration. | Martens et al. 2021 ⁹ |
| Human with DCM and LBBB with CRT, BiVP (24) | BiVP 3 months (24) vs baseline (24) | ↑ Glucose metabolism relative to fatty acid (↑ glucose-palmitate ratio) | | ↑ TCA cycle intermediates (↑ succinate-glutamate ratio, ↑ citrate-glutamate ratio) | N/A | Reverse remodelling (↑ LVEF, ↓ PASP, ↓ MR) improved symptom (↓ FC) | Ventricular resynchronisation with BiVP balanced substrate utilisation and increased TCA flux. CRT responder had higher residual substrates from energy production for protein synthesis. | Nemutlu et al. 2015 ¹⁰ |
| | Responder [†] (10) vs non-responder (14) | N/A | N/A | N/A | N/A | ↑ Protein synthesis (↑ isoleucine, phenylalanine, leucine, and valine) | | |

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| Human with DCM, with CRT, BiVP (21) | Responder† (17) vs non-responder (4) | ↔ Glucose utilisation (↔ Glucose-ExtFx, ↔ Glucose/MVO2) | ↓FFA utilisation (↓ FFA-ExtFx, ↓ FFA/MVO2) | N/A | ↔ O2 extraction (↔ O2-ExtFx) | ↓ Maximal ATP synthesis (↓ ATP/MVO2) correlated with FC improvement | The CRT responder reduced fatty acid utilisation and required a lower ATP production relative to O2 intake to maintain function at the baseline. | Obrzut et al. 2010 ¹¹ |
| Human with DCM, with CRT, BiVP (14) | BiVp on vs Intrinsic | N/A | ↑ FFA utilisation (with Insulin + Glucose infusion) | N/A | ↔ O2 extraction ↑ Efficiency | ↑ Cardiac work ↓ LVEDV at 6 months (correlated with FFA utilisation) | If the heart can retain metabolic flexibility and utilises fatty acids more effectively as a primary energy source, this would correlate with reverse remodelling following CRT implementation. | Green et al. 2025 ¹² |

AV synchronisation in CRT

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|--|--|-----|-----|-----|----------------------------------|-----|--|------------------------------------|
| Human with DCM and LBBB undergoing CRT implantation (11) | BiVp with AVD 40 ms (11) vs Intrinsic LBBB (11) | N/A | N/A | N/A | ↔ MVO ₂ ↔ Efficiency | N/A | AV delay optimisation to maximise BP in CRT resulted in an adequate ventricular filling and increased cardiac efficiency beyond the increased MVO ₂ . | Kyriacou et al. 2014 ¹³ |
| | BiVp with AVD 120 ms (11) vs Intrinsic LBBB (11) | N/A | N/A | N/A | ↑ MVO ₂ ↑ Efficiency | N/A | | |
| | BiVp with AV Opt*, mean AVD 181 ms (11) vs BiVp with AVD 120 ms (11) | N/A | N/A | N/A | ↑ MVO ₂ ↑↑ Efficiency | N/A | | |

AV indicates Atrioventricular, AVD, Atrioventricular delay interval; AV Opt, Non-invasive haemodynamic optimal atrioventricular delay time; ATP, Adenosine triphosphate; BiVp, Biventricular pacing; bpm, beats per minute; C14:1/C12:1 ratio, Myristoleic to lauroleic acid ratio; CBF, Coronary blood flow; CO, Cardiac output; CRT, Cardiac resynchronisation therapy device; DCM, Dilated cardiomyopathy; ExtFx, Extraction fraction; FC, Functional class; FDG, 18-Fluorodeoxy

glucose; FFA, Free fatty acid; LBBB, Left bundle branch block; LVEDV, Left ventricular end diastolic volume; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; MVO_2 , Myocardial oxygen consumption; PASP, Pulmonary artery systolic pressure; PCWP, Pulmonary capillary wedge pressure; RAP, Right atrial pacing; RVP, Right ventricular pacing; SBP, Systolic blood pressure; TCA, tricarboxylic acid

* Series of AV delay were evaluated against a reference AV delay of 120 ms over numerous forward and backward transitions, facilitating the maximal augmentation of systolic blood pressure.

† Patients exhibiting an enhancement in LVEF by $> 5\%$ and a decrease in NYHA functional class by ≥ 1 .

Supplementary Table 3: Effects of Cardiac Synchronisation on Cardiac Mitochondria: evidence from clinical studies

| Study models (N) | Dyssynchrony models (N) | Major findings | | | Interpretation | Ref |
|-----------------------------------|---|--|------------------------------|--|--|------------------------------------|
| | | Mitochondrial inner membrane potential | AnxA5 | Others | | |
| Human with DCM, on CRT, BiVP (45) | BiVP 6 months (45) vs before BiVP (45) | ↓ Mitochondrial depolarisation (↓ 99mTc-MIBI washout rate) | N/A | ↑ LV function (↓ LVESV, ↑ LVEF) | Ventricular resynchronisation by BiVP attenuated mitochondrial depolarisation and enhanced oxidative phosphorylation, resulting in improved LV function. | Martens et al. 2021 ⁹ |
| Human with DCM, on CRT, BiVP (30) | Responders* (12) vs non-responders (18) | ↓ Mitochondrial depolarisation (↑ 99mTc-MIBI uptake at septal, inferior, anterolateral area) | N/A | ↓ Electrical dyssynchrony (↓ QRSD) ↓ Mechanical dyssynchrony (↓ dyssynchrony indices) ↑ LV function (↑ LVEF, ↓ LVESV, ↓ LVEDV) | CRT responders showed decreased electrical and mechanical dyssynchrony and greater LV function, due to the attenuation of mitochondrial depolarisation. | Brandão et al. 2009 ¹⁴ |
| Human with DCM, on CRT, BiVP (57) | Responders [†] (31) vs non-responders (26) | N/A | ↔ At baseline ↓ At 1 year | ↑ LV function (↓ LVESV, ↑ LVEF) correlated with AnxA5 level | The AnxA5 level, associated with mitochondrial dysfunction, was reduced in CRT responders after one year, suggesting an amelioration of LV remodelling. | Ravassa S et al 2010 ¹⁵ |

99mTc-MIBI indicates (99m)Tc-methoxyisobutylisonitrile; AnxA5, Annexin A5; BiVP, Biventricular pacing; CRT, Cardiac resynchronisation therapy device; DCM, Dilated cardiomyopathy; LV, Left ventricle; LVEF, Left ventricular ejection fraction; LVEDV, Left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume; QRSD, QRS complex duration

* Patients with increase in LVEF more than 5% or decrease in LVESV more than 15%.

† Patients with increase in LVEF more than 5% and decrease in NYHA functional class by ≥ 1 .

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