1   Distal Ventricular Pacing for Drug-Refractory Mid-Cavity Obstructive Hypertrophic

2   Cardiomyopathy: A Randomized, Placebo-Controlled Trial of Personalized Pacing.

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4   James W Malcolmson[1,2], Rebecca K Hughes[1,3], Tim Husselbury[1], Kamran Khan[2],

5   Annastazia E Learoyd[2], Martin Lees[1], Eleanor Wicks[4,5], Jamie Smith[6], Alexander

6   Simms[7], James Moon[1,4], Luis Lopes[1,4], Constantinos O'Mahony[1,4], Neha Sekhri[1],

7   Perry Elliott[1,4], Steffen E. Petersen[1,2,8,9], Mehul Dhinoja[1], Saidi A Mohiddin[1,2].

8

9   1. Barts Heart Center, St Bartholomew's Hospital, Barts Health NHS Trust, West

10   Smithfield, EC1A 7BE, London, UK

11 2. William Harvey Research Institute, NIHR Barts Biomedical Research Center,

12   Queen Mary University London, Charterhouse Square, London, EC1M 6BQ,

13   London, UK

14 3. Kings College Hospital, London, SE5 9RS, UK

15 4. Institute of Cardiovascular Science University College London, WC1E 6BT, UK

16 5. Inherited Cardiovascular Diseases Unit, John Radcliffe Hospital, Oxford, OX3

17   9DU, UK

18 6. Raigmore Hospital, NHS Highland, Old Perth Rd, Inverness IV2 3UJ, UK

19 7. Yorkshire Heart Center, Leeds Teaching Hospital NHS Trust, Leeds, LS1 3EX,

20   UK

21 8. Health Data Research UK, Gibbs Building, 215 Euston Road, NW1 2BE, London,

22   UK

23 9. Alan Turing Institute, 96 Euston Road, NW1 2DB, London, UK

24

25 **Short title:** Pacing for mid-cavity hypertrophic cardiomyopathy.

26   **Corresponding author:**

27   Professor Saidi. A. Mohiddin

28   saidi.mohiddin@nhs.net

29   Department of Inherited Cardiovascular

30   Disease Unit SBH

31   St Bartholomew's Hospital

32   West Smithfield

33   London EC1A 7BE

34

35   **Word count** 3572 (exclusive of title, abstract, references, tables, and figure legends)

36

Abstract

Background: Patients with refractory symptomatic left ventricular (LV) mid-cavity obstructive (LVMCO) hypertrophic cardiomyopathy (HCM) have few therapeutic options. Right ventricular (RV) pacing is associated with modest hemodynamic and symptomatic improvement, and LV pacing pilot data suggest therapeutic potential. We hypothesized site-specific-pacing would reduce LVMCO gradients and improve symptoms.

Methods: Patients with symptomatic-drug-refractory LVMCO were recruited for a randomized blinded trial of personalized prescription of pacing (PPoP). Multiple LV and apical RV pacing sites were assessed during invasive hemodynamic study of multisite pacing. Patient-specific pacing-site and atrioventricular (AV) delays, defining PPoP, were selected on basis of LVMCO gradient reduction and acceptable pacing parameters. Patients were randomized to 6 months of active PPoP or back-up pacing in cross-over design. The primary outcome examined invasive gradient change with best-site pacing. Secondary outcomes assessed quality of life and exercise following randomization to PPoP.

Results: A total of 17 patients were recruited; 16 met primary endpoints. Baseline NYHA was 3±0.6 despite medical therapy. Hemodynamic effects were assessed during pacing at RV apex and at a mean of 8 LV sites. The gradients in all 16 patients fell with pacing, with maximum gradient reduction achieved via LV pacing in 14 (88%) patients and RV apex in 2. Mean baseline gradient 80±29 mmHg, fell to 31±21 mmHg with best-site pacing, a 60% reduction (p<0.0001). One cardiac vein perforation occurred in one case, and 15 subjects entered cross-over; 2 withdrawals occurred during cross-over (myocardial infarction, persistent atrial fibrillation). Of the 13 completing cross-over, 9 (69%) chose active pacing in

62   PPoP configuration as preferred setting. PPoP was associated with improved 6-

63   minute walking test performance (328.5±99.9 vs 285.8±105.5 meters, p=0.018);

64   other outcome measures also indicated benefit with PPoP.

65   **Conclusions:** In a randomized placebo-controlled trial, LV pacing reduces

66   obstruction and improves exercise performance in severely symptomatic LVMCO

67   patients.

68   **Registration:** NCT03450252.

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Non-standard Abbreviations and Acronyms

76	AE	Adverse Event
77	ASA	Alcohol septal ablation
78	AF	Atrial fibrillation
79	AV	Atrioventricular
80	CPET	Cardiopulmonary exercise test
81	CIs	Confidence intervals
82	CMR	Cardiac magnetic resonance
83	CVCTU	Cardiovascular Clinical Trials Unit
84	ECG	Electrocardiogram
85	eGFR	Estimated glomerular filtration rate
86	ESC	European Society of Cardiology
87	GA	General anesthesia
88	HCM	Hypertrophic cardiomyopathy
89	HTN	Hypertension
90	ICD	Implantable cardioverter defibrillator
91	IQR	Interquartile range
92	ISRCTN	International Standard Randomized Controlled Trials Number
93	KCCQ	Kansas City Cardiomyopathy Questionnaire
94	LA	Left atrial
95	LGE	Late gadolinium enhancement

96	LV	Left ventricle
97	LVAA	Left ventricular apical aneurysm
98	LVEF	Left ventricular ejection fraction
99	LVMCO	Left ventricular mid cavity obstruction
100	LVOTO	Left ventricular outflow tract obstruction
101	LVWT	Left ventricular wall thickness
102	MCV	Middle cardiac vein
103	MI	Myocardial infarction
104	NIHR	National Institute of Health and Care Research
105	NSVT	Non-sustained ventricular tachycardia
106	NT-proBNP	N-terminal pro B-type natriuretic peptide
107	NYHA	New York Heart Association
108	PPM	Permanent pacemaker
109	PPoP	Personalized prescription of pacing
110	RV	Right ventricular
111	SCD	Sudden cardiac death risk
112	SD	Standard deviation
113	SF-36	Short form 36 questionnaire
114	6MWT	6-minute walk test
115		

116 **Clinical Perspective:**

117 **What is Known?**

118 • Patients with refractory, symptomatic LVMCO present a significant challenge

119   for clinical management, with very few treatment options.

120 • Data on use of right ventricular (RV) pacing in patients with refractory,

121   symptomatic LVMCO indicate suboptimal therapeutic responses whilst pilot

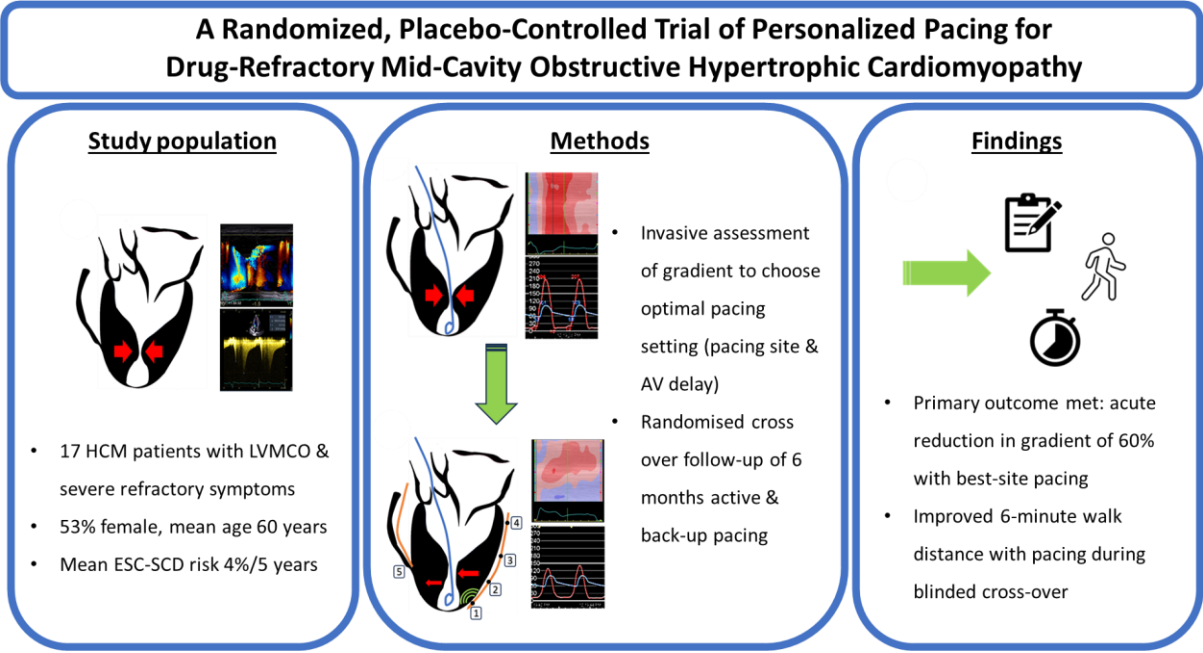122   data indicated a potential therapeutic role for LV pacing.

123 **What the Study Adds?**

124 • Personalized prescription of pacing (PPoP) therapy guided by invasive

125   hemodynamics significantly reduced LVMCO gradients and improved

126   exercise performance in the first randomized, placebo-controlled trial in

127   symptomatic LVMCO.

128 • This study provides the basis for a multicenter trial of PPoP for LVMCO and

129   for the use of site-specific pacing in managing other forms of HCM.

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131 **Graphical Abstract:**

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A Randomized, Placebo-Controlled Trial of Personalized Pacing for Drug-Refractory Mid-Cavity Obstructive Hypertrophic Cardiomyopathy

Study population

- 17 HCM patients with LVMCO & severe refractory symptoms
- 53% female, mean age 60 years
- Mean ESC-SCD risk 4%/5 years

Methods

- Invasive assessment of gradient to choose optimal pacing setting (pacing site & AV delay)
- Randomised cross over follow-up of 6 months active & back-up pacing

Findings

- Primary outcome met: acute reduction in gradient of 60% with best-site pacing
- Improved 6-minute walk distance with pacing during blinded cross-over

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease, affecting around 1 in 500 people.[1] HCM is characterized by abnormal myocardial thickening and hypercontractility, with obstruction to blood flow within the left ventricle (LV) frequently seen at the level of the outflow tract, associated with morbidity and prognosis.[2, 3] LV mid-cavity obstruction (LVMCO) is a less commonly recognized phenotypic form of HCM in which obstruction during LV ejection occurs due to partial or complete obliteration and division of the LV cavity into two distinct areas (basal and apical). Here, hyperdynamic muscular contraction forms a constricting muscular neck at the point of cavity division.[4 5] High pressure gradients form across the point of obstruction, often associated with the development of discrete LV apical aneurysms (LVAA),[6] a risk factor for adverse events.[7]

Patients with LVMCO are often symptomatic,[8] and first-line pharmacologic therapies (including betablockers, calcium channel antagonists, and disopyramide) aim to reduce LV inotropy and/or increase filling time. Those with symptoms refractory to medical therapy have severely limited therapeutic options. A few studies have indicated that pacing may reduce obstructive gradients and improve symptoms in LVMCO.[9, 10] Notably, as we and others have shown,[4, 11, 12] Doppler derived assessments often severely underestimate LVMCO gradient magnitude; invasive methods are needed for accurate measurement.

Our group has pioneered the use of invasive hemodynamic assessments made during a multi-site pacing study to determine optimal pacing configurations. Initial data, obtained in severely symptomatic LVMCO patients with conventional indications for device therapy demonstrated that this personalized prescription of

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158   pacing (PPoP) approach reduced LVMCO gradients, and was associated with

159   symptomatic improvement in an unrandomized cohort of 16 patients.[13] These

160   observational data informed the design of this randomized, placebo controlled cross-

161   over trial of PPoP. Here, we hypothesized that PPoP as guided by invasive

162   hemodynamic measurements of arterial and LV pressures to accurately define

163   obstructive gradients[4] would reliably reduce LVMCO gradient severity (primary aim)

164   and improve functional status (secondary aims).

165

2. Methods

Study design and participants

This was a single-center, prospective study of distal ventricular pacing for gradient reduction and symptomatic relief in HCM patients with isolated LVMCO. Ethical approval was granted by the National Research Ethics Service, City Road and Hampstead, London (Reference: 17/LO/1725). The trial was performed in agreement with the Declaration of Helsinki and registered with the following public registries: http://clinicaltrials.gov (NCT03450252) and International Standard Randomized Controlled Trials Number (ISRCTN): ISRCTN82621856. The study was funded by the National Institute for Health and Care Research (NIHR) in the United Kingdom.

Only LVMCO patients with severe drug-refractory symptoms were included. Eligible HCM patients were ≥18 years with LVMCO gradient ≥30 mmHg demonstrated initially by echocardiography, and confirmed by cardiac catheterization at rest or with isoprenaline provocation, referred for pacemaker (PPM) +/- implantable cardioverter defibrillator (ICD) implantation for either primary prevention of sudden cardiac death or other indications such as heart block or obstructive physiology; patients were taking maximum tolerated doses of beta blockers or verapamil +/- disopyramide.

Exclusion criteria included multi-level obstruction (i.e. across the mid-cavity and outflow tract if the latter was determined to be the dominant lesion); moderate or severe primary valvular disease; untreated symptomatic coronary disease; atrial fibrillation at the time of device implantation; pregnancy; eGFR <20mL/min; and patients unable to provide informed consent. Inclusion and exclusion criteria are fully listed in Table 1.

Study design overview

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190   Baseline evaluation of symptom and performance (secondary outcome measures)

191   included NYHA class, Short Form-36 (SF-36) questionnaire scores, Kansas City

192   Cardiomyopathy Questionnaire (KCCQ) scores, 6-minute walk test (6MWT)

193   distance, cardiopulmonary exercise testing (CPET) with stress echocardiography,

194   and serum concentration of N-terminal pro B-type natriuretic peptide (NT-proBNP).

195   Subjects then underwent an invasive hemodynamic assessment of multi-site pacing

196   study to guide LV and RV lead positioning and device implantation. Primary outcome

197   data were collected during the hemodynamic pacing study and comprised of the

198   acute invasively determined changes in LVMCO gradient at the optimal pacing site

199   when compared to sinus rhythm. Quadripolar LV lead position was determined

200   according to a pragmatic synthesis of pacing-site-specific hemodynamic data and

201   appropriate pacing parameters at that site (including thresholds and

202   diaphragmatic/phrenic capture).

203   On the day following device implant, participants were randomized to either active or

204   back up pacing for the first phase of follow-up (6 months), before crossover to the

205   alternate setting for the second 6-month period. Secondary outcome data were again

206   assessed at the end of each follow-up phase. Participant and Principal Investigator

207   were blinded to pacing status, and the subject's stated preference of either 1st or 2nd

208   crossover phase was a prespecified secondary outcome measure.

209   **Hemodynamic pacing study**

210   We have previously described the technique for hemodynamic pacing procedure in

211   detail.[13] Briefly, all hemodynamic pacing studies and device implants were performed

212   in a single procedure under general anesthesia (GA). Arterial access was achieved

213   via the right femoral artery using the Seldinger technique (operator 1) with central

214 venous access similarly achieved via the left sub-clavian or cephalic veins (operator

215 2).

216 Operator 2 advanced the right atrial and RV leads to the heart via the superior vena

217 cava, where they were implanted using standard techniques for active leads

218 (manufacturer dependent). The coronary sinus was intubated using a LV lead

219 delivery guiding catheter and the coronary venous anatomy defined by simultaneous

220 balloon occlusion coronary sinus venography and LV angiography. The coronary

221 vein of interest was intubated with a deflectable quadripolar catheter.

222 During the hemodynamic pacing protocol, pressures were transduced

223 simultaneously from the LV apex using a specially manufactured end-hole pigtail

224 catheter (Cordis^{TM}) and femoral artery via a 7French side arm sheath. Baseline

225 peak-to-peak obstructive gradients were calculated in sinus rhythm; if no resting

226 obstructive gradient was present under GA conditions, steady state isoprenaline

227 infusion was used in provocation: this began at 1 microgram/minute and, if required,

228 was gradually uptitrated to a maximum of 4 micrograms/minute.[14] [15]

229 To select the optimal sensed AV delay, an initial AV delay (60 ms) was lengthened

230 until evidence of QRS fusion was seen on the surface electrocardiogram (ECG)

231 and/or when acute gradient reduction was lost. For each of several pacing

232 configurations (quadripolar LV catheter, RV apex; in unipolar and bi-polar) the best

233 ventricular pacing location (primary outcome) was identified solely according to the

234 greatest acute reduction in obstructive gradient. Each pacing site was systematically

235 tested by turning pacing 'on' for a period of 30 seconds to allow stabilization of

236 hemodynamics, before averaging invasively defined LVMCO gradients over 3

237 consecutive cardiac cycles. When pacing was turned 'off' at an individual site,

238   another 30 second period was initiated to allow for stabilization of intracardiac

239   hemodynamics. When selecting the pragmatic pacing site for PPoP, other pacing

240   related factors (including capture threshold, r-wave sensitivity, diaphragmatic

241   capture, change in surface ECG QRS morphology, lead stability) and hemodynamic

242   responses (the maintenance or improvement in systolic arterial pressure) were also

243   considered by the Principal Investigators (operators 1 and 2).

244   The assessment of obstructive gradients during various pacing configurations was

245   obtained sequentially beginning with single site pacing from the RV apex, followed

246   by multi-site LV pacing from a quadripolar lead in the middle cardiac or other cardiac

247   vein (venous anatomy dependent). Hemodynamic consequences of multi-site LV

248   pacing were assessed sequentially from distal to proximal poles 1-4. Repositioning

249   of the quadripolar lead in the same or alternative cardiac veins was performed when

250   sub-optimal hemodynamic results were obtained, and/or when pacing parameters or

251   lead stability were unsatisfactory. After final pacing parameters were identified,

252   careful pull-back of the pigtail catheter confirmed site and magnitude of resting and

253   pacing obstruction within the LV.

254   **Statistical analysis**

255   **Sample size calculation**

256   Effect size was calculated using our retrospective LVMCO pacing data,[13] where

257   mean acute reduction in mid-cavity gradient with distal ventricular pacing was 60±26

258   mmHg. A conventional significant obstructive gradient is 30 mmHg,[16] and using a

259   conservative approach, we aimed to be able to detect a reduction of 25 mmHg. With

260   two-sided alpha level set at 0.05 a priori, and a power of 90%, the calculated sample

261   size using a paired sample t-test was 15.

Randomization

Patients were randomized to either active or back-up pacing one day after device implantation using a 1:1 ratio. A master randomization list was generated in an appropriate statistical package (STATA, using the ralloc command) to active or back-up pacing with block size varied randomly.

Analysis of primary endpoint

All patients completing the initial hemodynamic pacing study were eligible for primary analysis. Comparison of the gradients during ventricular pacing and sinus rhythm was made using a paired t-test. The effect size is presented as the mean difference (optimum pacing minus sinus rhythm gradients) and 95% confidence interval. In addition, the mean values and standard deviations (SD) for gradients during both sinus rhythm and pacing are presented.

Analysis of secondary endpoints

The proportions completing each assessment and the proportion withdrawing were used to assess feasibility of the study. Secondary outcomes were compared between baseline and pacing settings using repeated measures analyses (ANOVA or Friedman tests depending on normality of distribution using the D'Agostino & Pearson test) with multiple comparisons tests (Tukey's or Dunn's depending on normality) providing a direct comparison between active and back-up pacing settings. Changes between pacing settings during randomized follow-up in each variable were calculated as the value for active pacing minus the value for back-up pacing for each patient. Data are presented as mean±SD or median and interquartile range (IQR) as appropriate.

285   Data was examined for the presence of carry-over period effects. No carry-over

286   effect was found. There was minor evidence of a period effect influencing the KCCQ

287   results which was not deemed to substantially affect the results presented.

288   All analyses were performed in R™ version 2022.27.1, and figures created in

289   Graphpad Prism™ version 9.5.1.

290

291   **Study Overview and Data Monitoring**

292   Study overview was provided by the Cardiovascular Clinical Trials Unit (CVCTU) at

293   the William Harvey Research Institute, London. Trial safety data was reviewed

294   routinely by an independent Data Safety Monitoring Committee, and oversight

295   provided by independent Trial Steering Committee. All trial data was held in a secure

296   database (REDCAP™), source data verification undertaken by CVCTU monitors,

297   and statistical analyses performed by CVCTU statistician.

298

299   **3. Results**

300   **General characteristics of population**

301   Between February 2018 and March 2022, 17 patients were recruited to the trial. 29

302   patients were pre-screened for eligibility during work-up for potential invasive therapy

303   for LVMCO and refractory symptoms in a specialist heart muscle / electrophysiology

304   clinic after referral from their primary clinician (Figure 1). Of these 29, 12 patients

305   were excluded after not meeting symptomatic inclusion criteria (n=11), and 1 clinical

306   event prior to trial recruitment taking place (symptomatic ventricular arrhythmia and

307   urgent dual chamber ICD implant).

308   **Baseline characteristics**

309   The study population consisted of 17 patients on maximal tolerated medical therapy

310   with LVMCO. Of these, 53% were female, and mean age at recruitment 55.9±10.3

311   years (Table 2). One patient was withdrawn before the implant procedure due to

312   comorbidities. Of the 16 who underwent hemodynamic pacing study and had devices

313   implanted, 15 (94%) patients received an ICD and one patient received a pacemaker

314   device. At baseline assessment, 17 (100%) patients reported exertional dyspnea, 15

315   (88%) reported exertional chest pain, 16 (94%) reported palpitations, and 14 (82%)

316   reported presyncope. Seven patients (41%) reported prior unexplained complete

317   loss of consciousness.

318   **Primary end point: acute change in invasive gradient**

319   Primary end point assessment was completed in 16 patients. Hemodynamic effects

320   of distal ventricular pacing were assessed from the RV apex in all patients, and

321   additionally in a mean of 8 LV sites (range 4-16). LV pacing was achieved via the

322   middle cardiac vein in 10, and another cardiac vein in four. All LVMCO gradients fell

323   with pacing.

324   Mean LVMCO gradient at baseline was 80±29 mmHg (range 40-139), falling to

325   31±21 mmHg (range 0-80) when paced from the optimal ventricular site. This

326   represents a mean fall in LVMCO gradient of -49 mmHg (95% CI -62 to -36 mmHg,

327    $p<0.0001$) (Figure 2). Alternatively, this can be expressed as a mean 60% reduction

328   (range 14-100%). The greatest reductions in LVMCO were from a pacing site in the

329   LV in 14 (87.5%) patients, and from the RV apex in 2.

330   **Secondary endpoints**

331   Pre-implant assessment and both pacing settings during follow-up were completed

332   by 13 patients (with the order of active or back-up pacing randomized) who were

333   eligible for comparison of secondary endpoints between the three time points.

334   Reasons for drop-out are discussed under adverse events below.

335   **Participant choice of favored pacing setting:** At the end of the final study visit,

336   whilst still masked to treatment allocation, subjects were asked in which phase, if

337   any, they felt better. Nine of 13 (69%) subjects chose the active pacing phase as

338   their preferred setting. The remaining 4 (31%) patients reported no difference in

339   symptoms between the two phases.

340   **NYHA class:** Subjects self-reported NYHA class on 'good' and 'bad' days (Figure 3

341   panels A and B). Median NYHA class on a good day was 3 pre implant, 2 in the

342   active pacing arm, and 3 in the back-up pacing arm (IQRs all 2 to 3, p=0.26). The

343   median difference in NYHA class on a good day between active and back-up pacing

344   was zero (p>0.99). Median NYHA class on a bad day was 3 (IQRs 3 to 4) in pre

345   implant, 3 (IQRs 3 to 3) during active and 3 (IQRs 3 to 4) during back-up pacing

346   (p=0.013). The median difference in NYHA class on a bad day between active and

347   back-up pacing was zero (p=0.42). Subjects were also asked to report the ratio of

348   good to bad days throughout the week as: more good days than bad, more bad days

349   than good, or equal good and bad days. More good than bad days were reported

350   with active pacing, and more bad than good days were reported during backup

351   pacing (supplementary Figure S1).

352   **SF36 score:** Detailed SF36 results are in Supplementary Figure S2. The mean

353   General Health Score was 26±18 pre-implant, 33±30 during active pacing, and

354   25±21 during back-up pacing (p=0.18). Mean increase in General Health Score with

355   active compared to back-up pacing was 3 (95% CIs -3 to 9, p=0.42) (Figure 3 panel

356   C).

357 **KCCQ score:** Mean overall KCCQ score was 33±22 pre-implant, 42±22 during

358 active pacing, and 34±16 during back-up pacing (p=0.22). Mean clinical KCCQ score

359 was 36±18 pre-implant, 42±22 during active pacing, and 36±18 during back-up

360 pacing (p=0.34). Mean increase in overall KCCQ score with active compared to

361 back-up pacing was 7±20 (95% CIs 19 to -5, p=0.44) (Figure 3 panel D). Mean

362 increase in clinical KCCQ score with active compared to back-up pacing was 6±19

363 (95% CIs 18 to -5, p=0.50) (Figure 3 panel E).

364 **Doppler defined LVMCO gradient:** Mean Doppler defined gradient was 42±32

365 mmHg pre-implant, 24±17 mmHg during active pacing, and 46±28 mmHg during

366 back-up pacing (p=0.004). The mean reduction in gradient with active compared to

367 back-up pacing was 21±14 mmHg (95% CIs 11.5 to 29.9, p=0.002) (Figure 3 panel

368 F).

369 **6MWT:** Mean 6MWT distance was 296±88 meters pre-implant, 329±100 meters

370 during active pacing, and 286±106 meters during back-up pacing (p=0.038). The

371 mean increase in 6MWT distance with active compared to back-up pacing was

372 43±47 meters (95% CIs 71 to 14, p=0.018) (Figure 3 panel G).

373 **NT-proBNP:** Median NT-proBNP concentration was 483 (IQR 243 to 928) ng/L/L

374 pre-implant, 549 (IQR 286 to 1014) ng/L during active pacing, and 422 (IQR 301 to

375 818) ng/L during back-up pacing (p=0.039). Median increase in NT-proBNP

376 concentration during active compared to back-up pacing was 63 ng/L (IQR 136 ng/L,

377 p=0.12) (Figure 3 panel H).

378 **VO2 max:** Mean VO2 max was 13.3±2.4 mL/min/kg pre-implant, 14.4±4.4 mL/min/kg

379 during active pacing, and 12.4±3.4 mL/min/kg during back-up pacing (p=0.24). Mean

380 increase in VO2 max during active compared to back-up pacing was 1.9±4.4

381 mL/min/kg (95% CIs 1.0 to 4.9, p=0.34) (Figure 3 panel I).

382

Safety

Hemodynamic pacing study and device implant: 16 subjects underwent

successful device implantation, of whom 15 (94%) had uncomplicated procedures.

Cardiac vein perforation and subsequent pericardial effusion treated with

pericardiocentesis occurred in 1 case. In this subject the LV lead was not implanted,

and they received a dual chamber ICD without further complication. This subject was

withdrawn from the study after the implant procedure.

Adverse events during follow-up: There were two patient withdrawals during

follow-up due to adverse events unrelated to the study. One patient suffered an

acute myocardial infarction, and another went into persistent fast atrial fibrillation in

the first follow-up period.

394

4. Discussion

Patients with drug-refractory symptomatic LVMCO have very few therapeutic options.[9, 16] For the first time, we demonstrate that ventricular pacing tailored to individual patient characteristics is safe, technically feasible, and improves LV intracavity hemodynamics. Furthermore, we present data indicating improved patient functional status, and provide the context and justification for a larger multicenter trial powered for symptom and functional measures.

Other therapeutic options for symptomatic LVMCO include surgical myectomy,[17] alcohol septal ablation (ASA),[18] and cardiac transplant.[19] The novel pharmacological class of myosin inhibitors are not currently licensed for this indication. Prevalence of LVMCO has been reported to be as high as 9-13% of HCM patients.[20, 21] Notably, as many patients with LVMCO have primary or secondary indications for transvenous ICDs, a trial of PPoC therapy may have a key role earlier in the management of these patients, with progression to other therapies if this fails.

Surgical Myectomy: Much of the published data on surgery for LVMCO comes from a single center of surgical excellence.[17, 22, 23] Results indicate similar levels of absolute gradient reduction compared to PPoP. Symptoms were significantly improved with myectomy in a cohort of patients with a less severe phenotype than included in our trial (lower baseline functional limitation and prevalence of LVAA).[17] Notably, high levels of early complications were reported,[23] and the surgical expertise required for such specialist procedures is not widely available. By contrast, most centers that implant devices for heart failure already have the experience, expertise and resources required for PPoP. Additionally, as at least half of the published surgical cohorts had pacemaker / ICDs prior to surgery,[17] a trial of PPoP

419   can be considered before surgery. Finally, unlike for PPoP, no randomized

420   prospective trails of myectomy has been completed.

421   *Alcohol septal ablation (ASA)*: Data on the use of ASA in the treatment of LVMCO

422   is even more limited. ASA reduced obstructive gradients and improved symptoms in

423   a cohort 22 patients.[18] However, severely elevated residual LVMCO gradients were

424   twice as common when compared to our PPoP cohort (23% vs 12.5%). Furthermore,

425   ASA was associated with intra-procedural complete heart block in a third, and one

426   patient developed ventricular fibrillation.[18] Once again, there have been no

427   prospective trials of ASA for this indication, and a trial of PPoP prior to ASA may be

428   warranted in the context of baseline ICD indications and the high risk of ASA-related

429   conduction disease.[24]

430   *Cardiac Myosin Inhibitors*: Recent trials of myosin inhibitors, a novel class of

431   agents, report reductions in LV outflow tract obstruction (LVOTO) gradients and

432   improved functional outcomes in patients with 'classic' obstructive HCM.[25] However,

433   perhaps as many as two thirds of HCM patients in EXPLORER-HCM did not achieve

434   primary outcomes, and patients with LVMCO were excluded from the trial. A trial of

435   myosin-inhibitors in symptomatic LVMCO patients is warranted; PPoP may continue

436   to have a role in the management of patients refractory to that treatment, and in

437   those that have indications for transvenous ICDs.

438   **Future work**

439   Our trial provides the basis for a larger multicenter trial of PPoP for refractory

440   LVMCO by providing positive signals of safety and clinical benefit, and data required

441   for a study powered to detect clinically meaningful improvements in symptoms and

442   functional status.

22

443   While technology developed for resynchronization pacing has enabled this study,

444   there is a need for equipment and techniques developed specifically for this

445   indication. Broadly, these will address challenges that include: predicting optimal

446   lead positioning prior to the invasive procedure; selective intubation of, and

447   attainment of lead stability in the cardiac vein of choice; mitigating effects of

448   myocardial fibrosis on pacing thresholds; and avoiding phrenic nerve capture. Most

449   notably, even small differences in pacing site location can result in strikingly different

450   hemodynamic effects (Figure 4); pre-implant techniques that predict where pacing is

451   likely to have greatest beneficial hemodynamic effects, and an ability to pace beyond

452   anatomical restrictions imposed by cardiac venous anatomy will be key

453   developments.

454   **Limitations**

455   This study was not powered to detect functional or symptomatic benefit and included

456   only the most severely symptomatic patients. Despite this, we demonstrate

457   significant improvements in the 6-minute walking test, and the overwhelming majority

458   of other functional parameters indicate trends for symptom benefit. Further, to avoid

459   exposing participants to the risks of repeat invasive procedure during follow-up, we

460   relied on Doppler echocardiography to report relative changes in LVMCO gradient,

461   with known shortcomings in this population.[4] Nonetheless, the significantly lower

462   Doppler-derived gradients during active pacing indicate that the beneficial

463   hemodynamic effect is sustained. Although not significant, mean NT-proBNP was

464   greater following pacing, and was the only secondary outcome not to show a trend

465   towards benefit. Altered atrio-ventricular coupling and/or contractile desynchrony

466   may affect the production of NT-proBNP independently to the magnitude of mid-

467   cavity obstruction; further investigation is warranted.

23

468   **5. Conclusions**

469   In the first randomized placebo-controlled trial of therapy for symptomatic mid-cavity

470   obstructive HCM, we demonstrate that PPoP is a safe and effective therapeutic

471   option. Personalized approaches to pacing most commonly identifies pacing from a

472   site in the LV as the most effective place from which to obtain gradient reduction.

473   Future work will include trials designed to detect symptom and physical performance

474   benefit and attempt to determine how pacing contributes to LVMCO management

475   algorithms that include myosin inhibitors and other invasive therapeutic options.

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490   **Disclosures**

491   SEP provides Consultancy to Circle Cardiovascular Imaging Inc., Calgary, Alberta,

492   Canada.

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584   **Tables**

585   **Table 1: Inclusion and exclusion criteria**

Inclusion Criteria

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a) Male or female, >18 years.

b) Referred for PPM +/- ICD implantation for either primary prevention of sudden cardiac death or other indications such as heart block or obstructive physiology.

c) HCM patients with evidence of mid-cavity gradient demonstrated by echocardiography and gradient ≥30 mmHg confirmed by cardiac catheterization at rest or with isoprenaline provocation.

d) All patients should be taking maximum tolerated doses of beta blockers or verapamil with or without disopyramide.

e) Symptoms refractory to optimum medical therapy as above, for example breathlessness, chest pain, dizziness, or syncope.

Exclusion Criteria

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a) Patients with multi-level obstruction, i.e. across the mid-cavity and outflow tract.

b) Patients with moderate or severe valvular stenosis or regurgitation due to primary valvular disease.

c) Patients with untreated symptomatic coronary disease.

d) Patients in atrial fibrillation at the time of implantation.

e) Pregnancy.

f) Renal failure with eGFR <20mL/min.

g) Any patient not suitable in the clinician's opinion.

h) Any patient who is for whatever reason is not expected to survive for more than one year.

i) Patients unable to provide informed consent.

587 **Table 2: Baseline characteristics**

Demographics and symptoms	n=17
Age at recruitment (years)	55.9 ± 10.3
Male, n (%)	9 (53)
Family history inherited heart disease, n (%)	10 (59)
HTN, n (%)	11 (65)
Chest pain, n (%)	15 (88)
Dyspnea, n (%)	17 (100)
Palpitations, n (%)	16 (94)
Presyncope, n (%)	14 (82)
SCD risk profile	n=17
Family history of SCD, n (%)	1 (6)
Unexplained syncope, n (%)	7 (41)
Prior NSVT on Holter / ICD (out of 16), n (%)	09/16 (56)
Maximum LV wall thickness ≥30 mm, n (%)	0 (0)
LVAA, n (%)	14 (82)
LVOTO gradient ≥30 mmHg, n (%)	0 (0)
ESC SCD risk score (% 5-year mortality)	3.7 ± 2.1
≥ intermediate risk score, n (%)	6 (35)
SCD risk factors (0/1/2/3 risk factors), n (%)	2 (12) / 9 (53) / 5 (29) / 1 (6)
Medications	n=17
β-Blockers, n (%)	9 (53)
Calcium channel blockers, n (%)	13 (76)

|	
Disopyramide, n (%)	6 (35)
Anticoagulation, n (%)	7 (41)
Number on 1/2/3 medical therapies, n (%)	9/7/1 (53/41/6)
Echocardiography	n=17
Max LVWT (mm)	20 ± 4
Resting Doppler LVMCO gradient (mmHg)	32 ± 21
Post exercise Doppler LVMCO gradient (mmHg)	50 ± 35
LA diameter (mm)	40 ± 5
LVAA, n (%)	14 (82)
Paradoxical apical diastolic flow, n (%)	13 (76)
CMR	n=12
LVEF (%)	69 ± 9
Max LVWT (mm)	20 ± 3
LV mass (g)	167 ± 37
LVAA, n (%)	9 (75)
Presence of LGE, n (%)	12 (100)
Apical LGE, n (%)	12 (100)
Circumferential perfusion defect (out of 9), n (%)	8/9 (89)
Apical thrombus, n (%)	0 (0)

Data are represented as mean ± SD or n (%). HTN, hypertension; SCD, Sudden Cardiac Death Risk; NSVT, non-sustained ventricular tachycardia; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVAA, left ventricular apical aneurysm; LVOTO, left ventricular outflow tract obstruction; ESC, European Society of Cardiology; LVWT, LV wall thickness; LVMCO, left ventricular mid-cavity obstruction; LA, left atrial; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement.
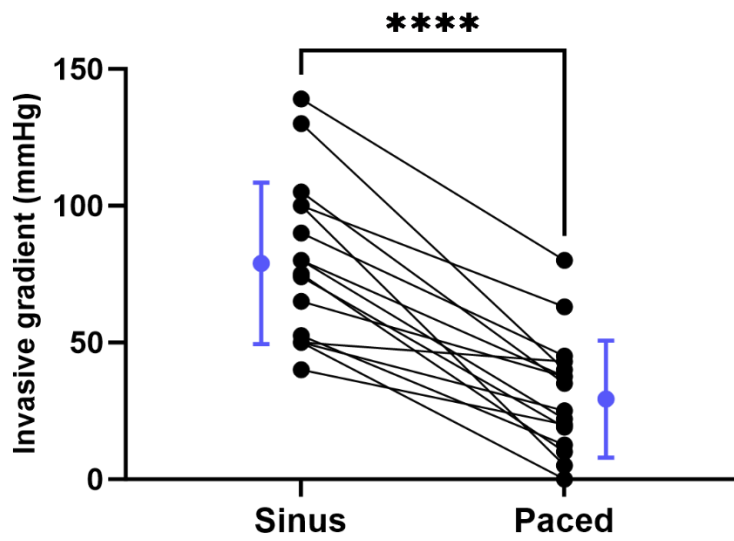
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589 **Figures with Figure Legends**
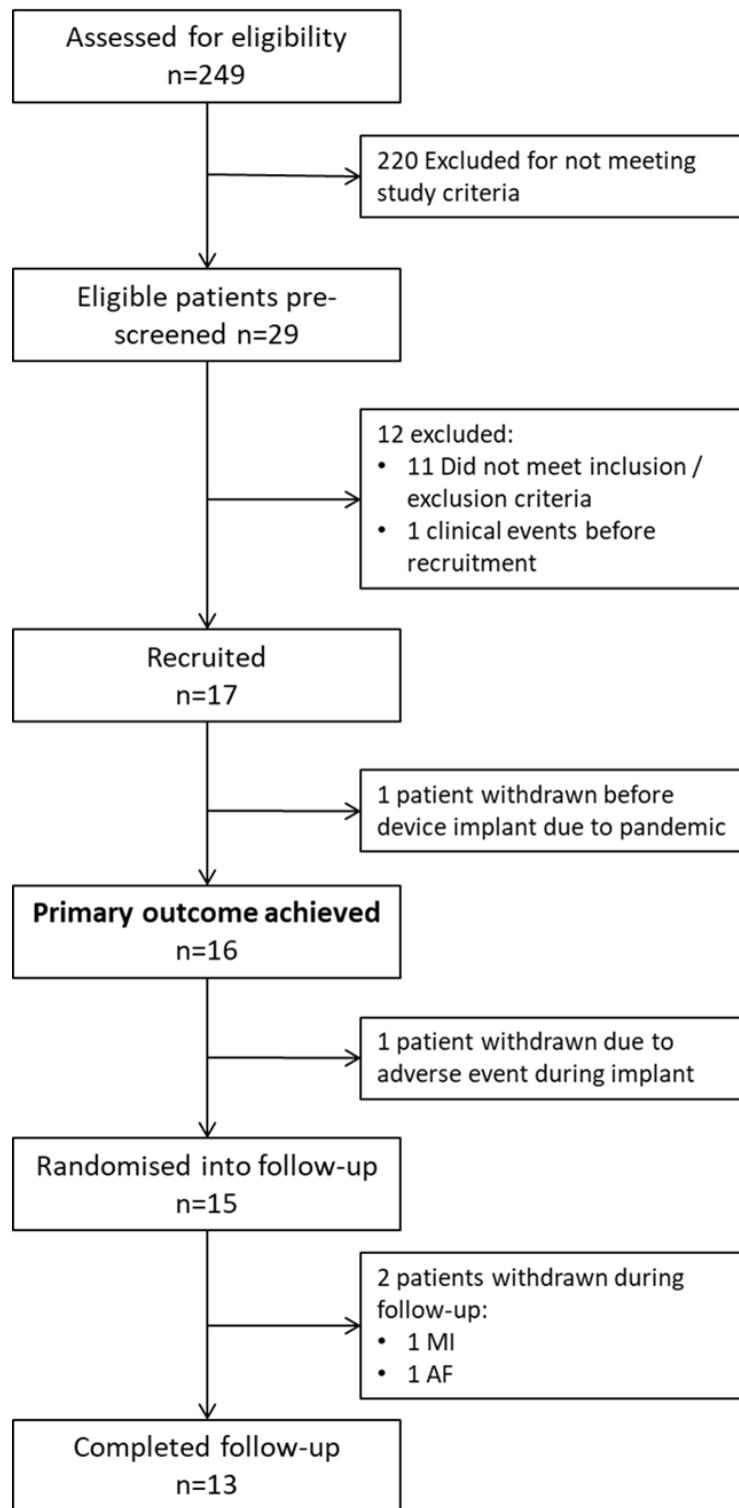
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591 **Figure 1:** Trial consort diagram. (n, number; MI, myocardial infarction; AF, atrial

592 fibrillation)

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Figure 2: Acute change in LVMCO gradient. Sinus, sinus rhythm; Paced, optimal

pacing setting. Error bars: mean±SD. ****=$p < 0.0001$ in pairwise comparisons.
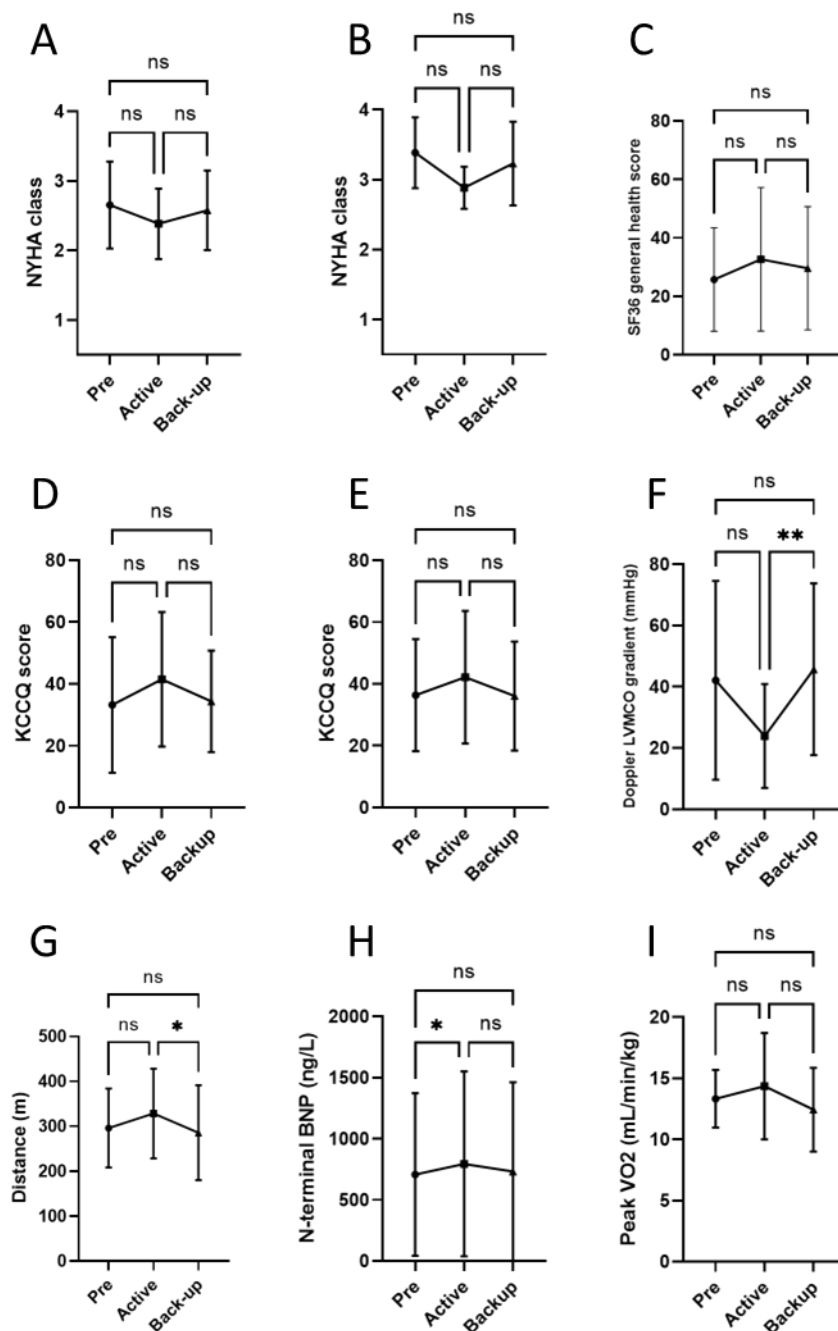
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Figure 3: Secondary outcome data across 3 time points: pre-implant, active pacing, and back-up pacing (A-I) (order of active and back-up pacing was randomized). NYHA class on a good and bad day (A & B); SF36 General Health Score (C), KCCQ overall and clinical scores (D & E); Doppler LVMCO gradient (F); 6MWT distance (G); NT-BNP level (H); and VO2 max (I). Error bars: mean±SD. Results of multiple comparisons: ns= $p > 0.05$, *=$p < 0.05$, **=$p < 0.01$ in multiple comparisons.

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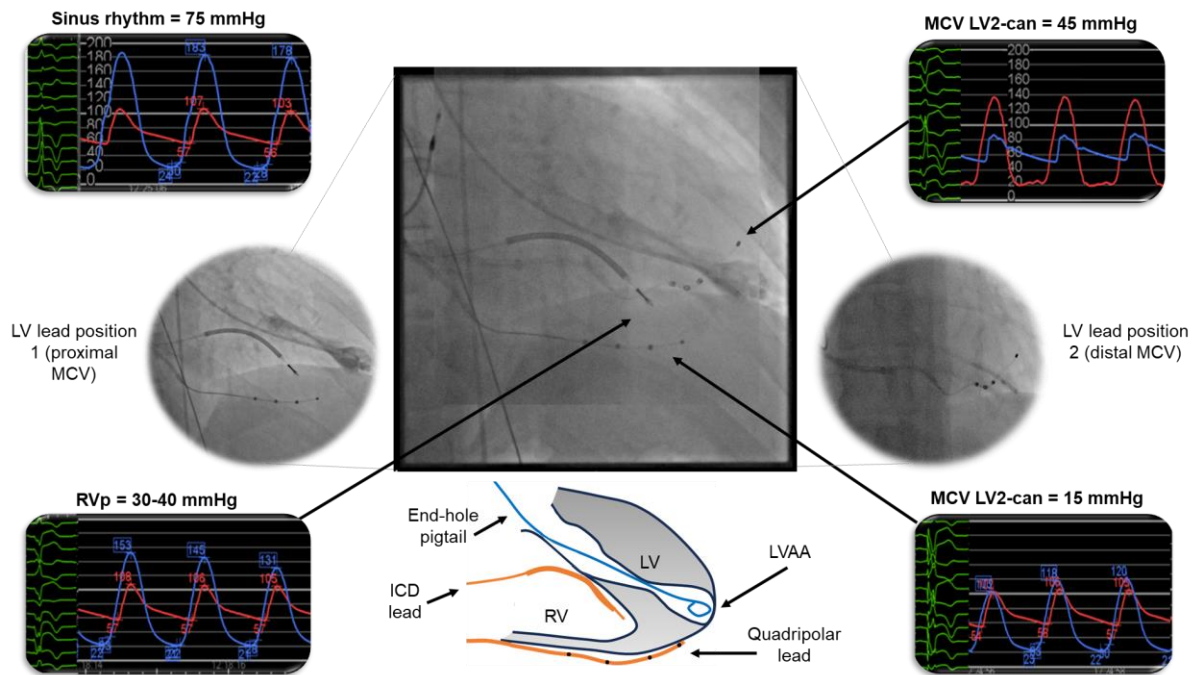
Figure 4: Example pressure traces from hemodynamic pacing study, with overlaid fluoroscopy of the LV quadripolar lead in two different loci within the MCV. Pacing from the more distal position in the MCV produced an unsatisfactory reduction in LVMCO gradient, whereas in this case, pacing from a more proximal location in the same vein almost entirely abolished the obstructive gradient. A schematic representation of pacing leads and catheter orientation relative to ventricular chambers can be seen at the bottom of the figure. ICD, implantable cardioverter defibrillator; LV, left ventricular; LVAA, left ventricular apical aneurysm; LV2, quadripolar lead pole 2; MCV, middle cardiac vein; RA, right atrial; RVp, right ventricular pacing.

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