

Biventricular pacemaker therapy improves exercise capacity in patients with non-obstructive hypertrophic cardiomyopathy via augmented diastolic filling on exercise

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Aims

Treatment options for patients with non-obstructive hypertrophic cardiomyopathy (HCM) are limited. We sought to determine whether biventricular (BiV) pacing improves exercise capacity in HCM patients, and whether this is via augmented diastolic filling.

Methods and results

Thirty-one patients with symptomatic non-obstructive HCM were enrolled. Following device implantation, patients underwent detailed assessment of exercise diastolic filling using radionuclide ventriculography in BiV and sham pacing modes. Patients then entered an 8-month crossover study of BiV and sham pacing in random order, to assess the effect on exercise capacity [peak oxygen consumption (VO_2)]. Patients were grouped on pre-specified analysis according to whether left ventricular end-diastolic volume increased (+LVEDV) or was unchanged/decreased (–LVEDV) with exercise at baseline. Twenty-nine patients (20 male, mean age 55 years) completed the study. There were 14 +LVEDV patients and 15 –LVEDV patients. Baseline peak VO_2 was lower in –LVEDV patients vs. +LVEDV patients (16.2 ± 0.9 vs. 19.9 ± 1.1 mL/kg/min, $P = 0.04$). BiV pacing significantly increased exercise ΔLVEDV ($P = 0.004$) and $\Delta\text{stroke volume}$ ($P = 0.008$) in –LVEDV patients, but not in +LVEDV patients. Left ventricular ejection fraction and end-systolic elastance did not increase with BiV pacing in either group. This translated into significantly greater improvements in exercise capacity (peak $\text{VO}_2 + 1.4$ mL/kg/min, $P = 0.03$) and quality of life scores ($P = 0.02$) in –LVEDV patients during the crossover study. There was no effect on left ventricular mechanical dyssynchrony in either group.

Conclusion

Symptomatic patients with non-obstructive HCM may benefit from BiV pacing via augmentation of diastolic filling on exercise rather than contractile improvement. This may be due to relief of diastolic ventricular interaction. Clinical Trial Registration: ClinicalTrials.gov NCT00504647.

Keywords

Hypertrophic cardiomyopathy • Biventricular pacemaker therapy • Diastolic ventricular interaction

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited disease affecting approximately 1 in 500 of the general population.¹ Patients frequently complain of exertional breathlessness and exercise intolerance. Currently, there are effective therapies for patients in whom symptoms are due to left ventricular (LV) outflow tract obstruction.² However, many symptomatic patients have no LV outflow tract obstruction at rest or on exercise, and exercise impairment appears instead to be a consequence of impaired LV diastolic filling.^{3–5} In these patients, treatment with high-dose calcium channel blockers, beta-blockers and diuretics is often unsuccessful.⁶

Biventricular (BiV) pacing is an effective therapy for patients with severe systolic heart failure who have associated left bundle branch block.⁷ The mechanism of improvement with BiV pacing is thought to relate to an amelioration of intraventricular contractile dyssynchrony.^{8–10} However, we have shown that some of the acute haemodynamic benefit seen with BiV pacing in chronic heart failure is due to a reduction in the external constraint to LV filling by the pericardium (pericardial constraint) and by the right ventricle through the interventricular septum [diastolic ventricular interaction (DVI)].¹¹ Normally, pericardial and right ventricular end-diastolic pressures are close to zero. Pericardial constraint and DVI occur when the pericardium becomes stretched and the pericardial and right ventricular end-diastolic pressures become markedly increased.^{12,13} We previously demonstrated that approximately 40% of patients with systolic heart failure had evidence of marked DVI at rest, and that this was predicted by a LV end-diastolic pressure > 15 mmHg.¹⁴

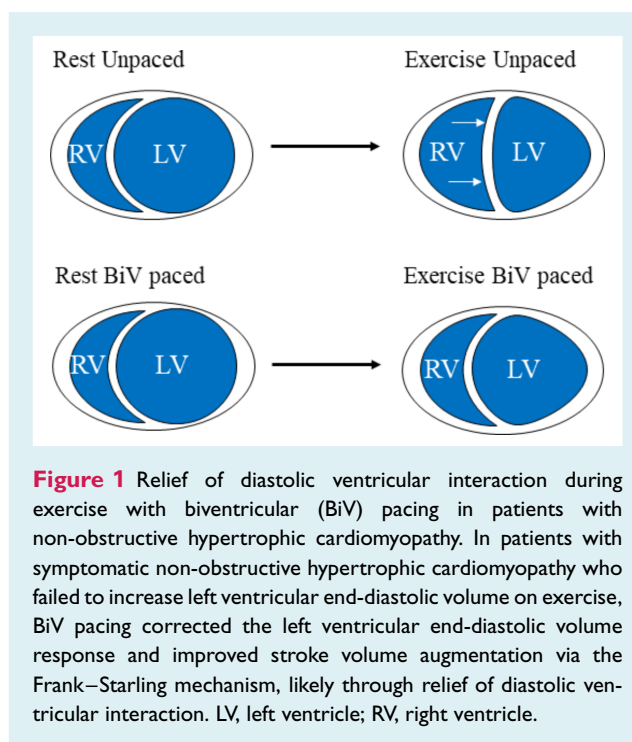
While relatively few patients with HCM have moderate or severe pulmonary hypertension at rest, pulmonary artery pressure often rises markedly on exercise.¹⁵ This might be expected to cause enlargement of the right ventricle on exercise, resulting in pericardial constraint and DVI, thereby attenuating an increase in stroke volume via the Frank–Starling mechanism (Figure 1). In a previous study we showed that both BiV and LV pacing relieved DVI and restored the ability to use the Frank–Starling mechanism to increase stroke volume in patients with systolic heart failure.¹¹ We reasoned that if DVI develops in some patients with HCM on exercise, this might be ameliorated by BiV pacing, restoring the Frank–Starling mechanism.

We therefore hypothesized that BiV pacing could improve exercise capacity in patients with non-obstructive HCM by augmenting the Frank–Starling mechanism on exercise via enhanced diastolic filling rather than via a contractile mechanism.

Methods

Study design

We conducted a double-blind, randomized, crossover proof-of-concept study to compare the effects of BiV pacemaker therapy with sham pacing, comprising acute and chronic phases (ClinicalTrials.gov NCT00504647). Following successful BiV pacemaker implantation, patients underwent an acute crossover study to assess diastolic filling and contractile function at rest and during submaximal exercise using



radionuclide ventriculography (Figure 2). Diastolic filling was also assessed with and without the application of lower body negative pressure to test for DVI at rest. The change in LV end-diastolic volume (LVEDV) on exercise was used to assign patients to groups of those in whom LVEDV increased (+LVEDV), and those in whom it fell (–LVEDV). Following the acute study, patients were randomized into the chronic phase of the study to assess the effects of BiV pacing on exercise capacity, symptom status, and echocardiographic measures of dyssynchrony. The primary endpoint was change in peak oxygen consumption (VO_2) on cardiopulmonary exercise testing during BiV pacing vs. sham pacing.

Patient selection

Patients with exercise limitation due to non-obstructive HCM were recruited from cardiomyopathy clinics at the Heart Hospital, London, UK and the Queen Elizabeth Hospital, Birmingham, UK. All patients provided written informed consent for the study, which was approved by the local research ethics committee and the UK Medicines & Healthcare Products Regulatory Agency, and conformed to the Declaration of Helsinki. Inclusion criteria were: age > 18 years; peak VO_2 < 75% of predicted for age and gender; New York Heart Association (NYHA) class \geq II; sinus rhythm; and the absence of LV outflow tract obstruction (peak gradient < 30 mmHg) either at rest or during exercise. Patients were excluded on the basis of conventional indications for cardiac pacing, presence of epicardial coronary disease, pregnancy or planning to fall pregnant, and LV ejection fraction (LVEF) < 50%.

Pacemaker implantation

Patients who fulfilled the entry criteria underwent implantation of a BiV pacing device, with the right ventricular electrode placed at the apex, and the LV electrode placed via the coronary sinus in a lateral

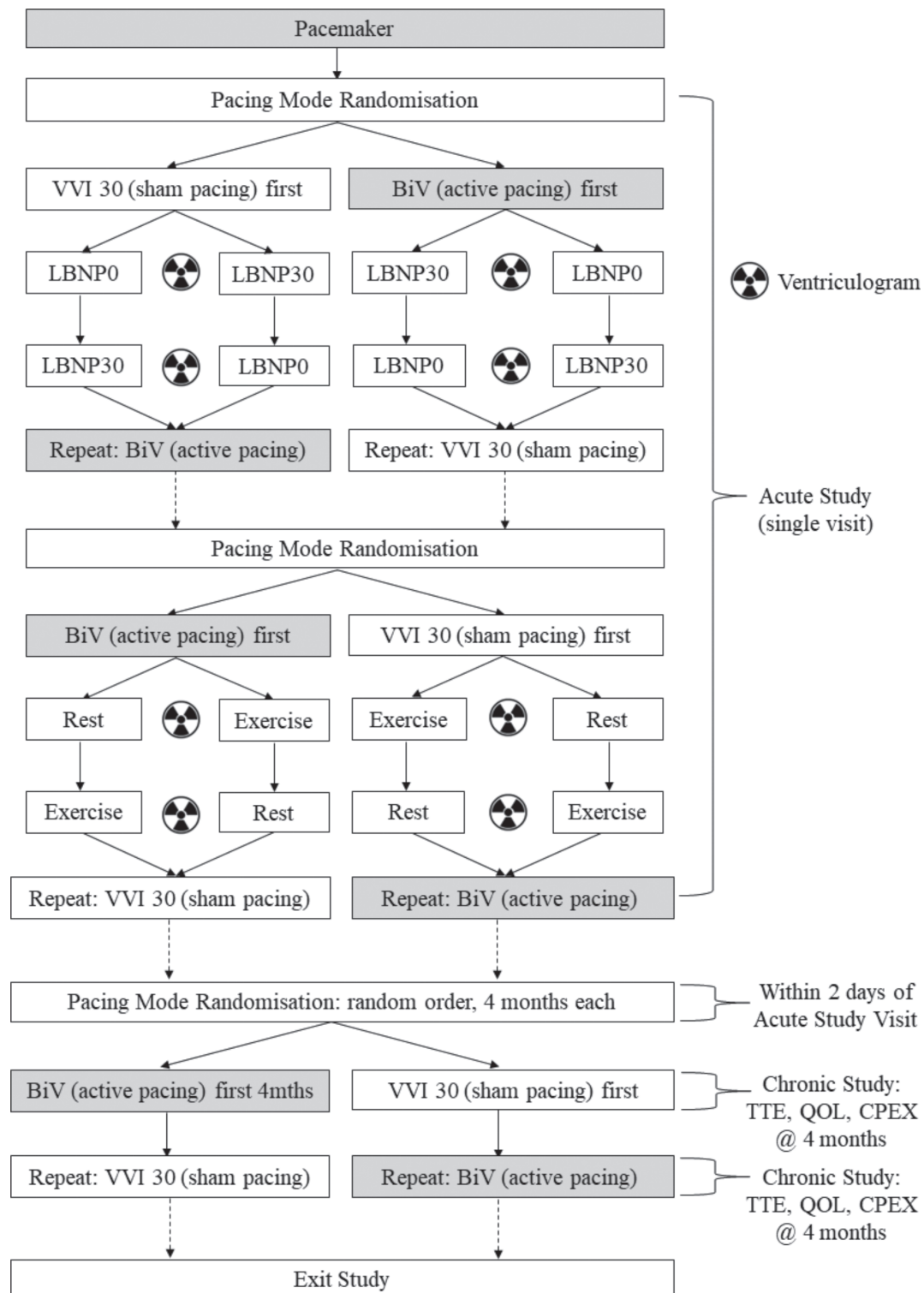


Figure 2 Study protocol. Following pacemaker implantation, patients were invited to attend the acute study visit, which involved radionuclide ventriculography with applied lower body negative pressures of 0 mmHg (LBNP0) and 30 mmHg (LBNP30) in the first pacing mode setting [VVI 30 or biventricular (BiV)]. This was then repeated in the second pacing mode setting. The entire protocol was then repeated at rest and on submaximal exercise to complete the acute study. Patients were then randomized into the subsequent chronic study, following a baseline transthoracic echocardiogram (TTE). CPEX, cardiopulmonary exercise test; QOL, quality of life questionnaire.

position, using a standard technique.^{16–18} Following implantation, the pacemaker was left in VVI 30 mode for approximately 2 weeks until the acute studies were performed.

Acute studies – gated blood pool radionuclide ventriculography

Diastolic filling studies were performed using equilibrium R-wave gated blood pool scintigraphy (camera Olivetti Modulo-M-200ESL). Red blood cells were labelled by a modified *in vivo* technique.¹⁹ In brief, 10 min after intravenous injection of stannous pyrophosphate, 5 mL of blood was drawn into a heparinized syringe and incubated for 20 min with 750 MBq of technetium-99m pertechnetate before reinjection. Lower body negative pressure was applied by asking patients to lie in a specially constructed lower body suction bed as previously described by us.²⁰ Internal device pressure was measured via a transducer to achieve suction at 30 mmHg. Suction was turned off during the 0 mmHg negative pressure studies. The protocol was performed with the pacemaker programmed to VVI 30 for the sham pacing arm of the study. For BiV pacing, DDD mode was used, with an atrioventricular (AV) delay of 90 ms to ensure capture of the ventricles, with the left ventricle paced slightly earlier than the right ventricle [interventricular (VV) delay 40 ms]. AV and VV delays were not altered. The order of pacing modes (sham or BiV) was randomized. DVI at rest was inferred if LVEDV paradoxically increased with the application of lower body negative pressure, due to relief of the constraint on the left ventricle caused by the RV diastolic volume, as we have previously described.²¹

Volumetric data were analysed with Link Medical MAPS software (Sun Microsystems, Hampshire, UK). A count-based ratio method was used to calculate accurate LV volumes,²² and end-systolic volumes were calculated from end-diastolic volume and ejection fraction. Intra-observer variability for LV volumes was 2%, and inter-observer variability was 4%. Intra-observer variability for LVEF was 3% of the measured LVEF, with an inter-observer variability of 5%.

For the acute exercise studies, patients exerted themselves at a workload that achieved 50% of estimated heart rate reserve. Three minutes of volumetric data were acquired at rest and during exercise after a 30 s period for stabilization of heart rate at the commencement of each stage. A 5 min 'run-in' interval was given after each pacemaker mode selection. Again, this was performed during sham and BiV pacing modes, in random order. LV end-systolic elastance was calculated from the ratio of end-systolic pressure/end-systolic volume indexed to body surface area.²³ End-systolic pressure was estimated as 90% of the brachial arterial systolic blood pressure, obtained non-invasively via sphygmomanometer. A time-activity curve for the left ventricle was used to derive filling fractions by splitting the diastolic filling phase (minimum volume to maximum volume) into equal tertiles. The proportion of filling occurring during each tertile of diastole was then expressed as a percentage of total diastolic filling.

Chronic study

On completion of the acute studies, the device was returned to VVI 30 mode, and all patients underwent baseline assessments within 2 days (symptom status, cardiopulmonary exercise testing, and echocardiography). Patients were then randomized by an independent technician (to ensure clinician and patient blinding) to either sham or BiV pacing modes. After 4 months, patients underwent repeat assessment (blinded to results from the acute studies) then crossed over to the other arm of the study for a further 4 months.

Cardiopulmonary exercise testing

Participants underwent symptom-limited erect treadmill exercise testing (Schiller CS-200 Ergo-Spiro exercise machine) using a standard ramp protocol with simultaneous respiratory gas analysis.^{24,25} Peak VO_2 was defined as the highest VO_2 achieved during exercise (with respiratory exchange ratio > 1.0) expressed in mL/kg/min. The minute ventilation/carbon dioxide production (VE/VCO_2) slope was measured up to the anaerobic threshold.

Quality of life/symptom severity assessment

Quality of life was assessed by completion of the Minnesota Living with Heart Failure Questionnaire²⁶ at baseline, crossover, and completion of the study. In addition, symptom status (NYHA class) was determined by a single investigator (I.A.).

Transthoracic echocardiography

Transthoracic echocardiography was performed with participants in the left lateral decubitus position using a Vivid 7 (GE Healthcare) echocardiographic machine with a 2.5 MHz transducer. Mean wall thickness was recorded, and LVEF was derived from the modified Simpson's formula.²⁷ Conventional color-coded tissue Doppler imaging (TDI) was performed to quantify LV dyssynchrony (EchoPac GE Medical systems). The extent of LV systolic dyssynchrony was calculated as the maximum time delay on TDI between peak systolic velocities of basal septal, lateral, anterior and inferior LV segments⁹ to derive the Yu index.²⁸ For speckle tracking analysis, standard greyscale two-dimensional images were acquired in the parasternal short axis view at the papillary muscle level. The standard deviation of the time to peak systolic radial strain for all six segments (SDt_{6s})²⁹ was derived as a further index of global LV synchrony, which has the advantage over TDI of being direction-independent. Diastolic dyssynchrony was quantified using the standard deviation of time to early peak diastolic velocities (Te-SD) on TDI as previously described.³⁰

Statistical analysis

Data were analysed using SPSS version 22.0 for Windows and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria), and are expressed as mean \pm standard error of the mean. The acute effect of BiV pacing on the Frank–Starling mechanism with exercise and lower body negative pressure, was evaluated by analysis of covariance (ANCOVA) using baseline resting values as covariates. Analysis of the effect of BiV pacing on peak VO_2 was performed by repeated measures analysis of variance. Statistical significance was set at $P < 0.05$. The study had 80% power to detect a 1.5 mL/kg/min difference in peak VO_2 between the interventions at a significance of 5%.

Results

Overall, 31 patients were enrolled onto the study. Two patients discontinued at the crossover phase of the study. One of these patients became extremely symptomatic after crossing to the sham pacing arm of the study, and declined further participation. The second patient developed intractable diaphragmatic twitching and was unable to continue. Data are therefore presented for

the 29 patients who completed the study. There were no deaths or other serious adverse device events during the study period. Baseline clinical characteristics and cardiopulmonary exercise test results of +LVEDV ($n = 14$) and -LVEDV ($n = 15$) patients are summarized in Table 1. A mix of devices including Guidant (13), Medtronic (10), and St Jude (6), were implanted.

Acute haemodynamic studies

Lower body negative pressure

Baseline LVEDV for the whole patient group was 120 ± 6.1 mL, and fell to 114 ± 6.0 mL with BiV pacing, but this was not statistically significant ($P = 0.18$; online supplementary Table S1). Application of 30 mmHg lower body negative pressure during sham pacing resulted in a fall in LVEDV (Δ LVEDV $-16.6 \pm 3.8\%$, $P < 0.001$). However, in four patients there was a paradoxical increase in LVEDV with the application of lower body negative pressure, implying the presence of substantial DVI at rest. This was reversed in three of these patients with the application of BiV pacing. Compared to sham pacing, BiV pacing did not change the LVEDV response to 30 mmHg lower body negative pressure (Δ LVEDV $-21.1 \pm 3.4\%$, $P = 0.39$). Stroke volume fell by a mean of $18.3 \pm 3.8\%$ with 30 mmHg lower body negative pressure during sham pacing ($P < 0.001$) and by $21.6 \pm 4.1\%$ during BiV pacing ($P = 0.36$ vs. sham pacing).

Exercise

Patients were separated into the pre-specified patient subgroups. +LVEDV patients ($n = 14$) had a mean increase in LVEDV on exercise of $20.2 \pm 3.8\%$ (to 141 ± 14.0 mL) during sham pacing, and -LVEDV patients ($n = 15$) experienced a mean fall of $22.3 \pm 4.3\%$ (to 106 ± 8.5 mL) (Figure 3A). Stroke volume increased with exercise during sham pacing in +LVEDV patients by $24.4 \pm 5.0\%$ (to 111 ± 11.6 mL), and fell in -LVEDV patients by $21.0 \pm 5.3\%$ (to 71 ± 6.9 mL). With BiV pacing, -LVEDV patients demonstrated a normalization of the volume response to exercise, increasing LVEDV by $3.4 \pm 7.0\%$ (to 124 ± 8.9 mL) and stroke volume by $5.8 \pm 7.6\%$ (to 80 ± 5.2 mL), and this was significant compared to sham pacing (Δ LVEDV $P = 0.004$; Δ SV $P = 0.008$) (Figure 3A). In contrast, in +LVEDV patients there were no significant differences in LVEDV ($P = 0.43$) or stroke volume ($P = 0.28$) responses to exercise during BiV vs. sham pacing (Figure 3A). A significant negative correlation was seen between Δ LVEDV% on acute exercise during sham pacing, and the effect of BiV pacing on the LVEDV response to exercise ($r = -0.77$, $P < 0.001$) (Figure 3B).

Left ventricular end-systolic elastance at rest did not differ between sham pacing vs. BiV pacing in either +LVEDV patients (2.96 ± 0.5 vs. 2.59 ± 0.4 mmHg/mL, $P = 0.57$) or -LVEDV patients (2.44 ± 0.3 vs. 2.84 ± 0.4 mmHg/mL, $P = 0.43$) (Table 2). Similarly, left ventricular end-systolic elastance did not differ in either group with sham vs. BiV pacing during exercise (+LVEDV: 3.15 ± 0.5 vs. 3.10 ± 0.5 mmHg/mL, $P = 0.93$; -LVEDV: 3.62 ± 0.5 vs. 3.54 ± 0.5 mmHg/mL, $P = 0.91$). LVEF did not differ between BiV pacing and sham pacing at rest ($72.4 \pm 2.3\%$ vs. $73.8 \pm 7.7\%$, $P = 0.62$), or during exercise ($73.7 \pm 2.4\%$ vs.

Table 1 Baseline data

	+LVEDV	-LVEDV	P-value
No. of patients	14	15	0.18
Male sex	11	9	
Age (years)	54 ± 2.6	55 ± 3.3	0.96
Resting heart rate (bpm)	63 ± 2.6	59 ± 2.1	0.29
Resting systolic BP (mmHg)	128 ± 4.2	131 ± 5.5	0.63
Resting diastolic BP (mmHg)	79 ± 1.9	75 ± 2.7	0.21
MLWHF Questionnaire score	49 ± 5.5	48 ± 6.8	0.91
QRS duration (ms)	108 ± 7.0	90 ± 3.1	0.02*
Echocardiography			
Mean wall thickness (mm)	17.7 ± 1.4	19.8 ± 1.1	0.28
LA volume index (mL/m ²)	33.0 ± 2.8	37.6 ± 2.4	0.23
LV ejection fraction (%)	60.6 ± 1.8	62.6 ± 1.6	0.82
Mitral E velocity (m/s)	0.71 ± 0.02	0.75 ± 0.06	0.63
Mitral A velocity (m/s)	0.80 ± 0.03	0.63 ± 0.07	0.07
Mitral E/A ratio	0.9 ± 0.1	1.4 ± 0.2	0.03*
TDI S velocity (m/s) (ant-lat)	0.05 ± 0.005	0.05 ± 0.006	0.85
TDI E' velocity (m/s) (ant-lat)	0.05 ± 0.005	0.05 ± 0.006	0.87
TDI A' velocity (m/s) (ant-lat)	0.05 ± 0.007	0.04 ± 0.005	0.55
E/E' (antlat)	15.7 ± 3.2	15.2 ± 2.1	0.89
SD _{t6s} (s)	0.07 ± 0.012	0.05 ± 0.008	0.55
Yu index by TDI (s)	0.07 ± 0.01	0.07 ± 0.01	1.00
Te-SD (s)	0.054 ± 0.011	0.044 ± 0.005	0.95
Medications (%)			
Beta-blocker	7 (50)	8 (53)	0.80
ACE inhibitor	4 (29)	3 (20)	0.43
Calcium channel blocker	6 (43)	9 (60)	0.21
Diuretic	5 (36)	1 (7)	0.001*
Warfarin	0 (0)	3 (20)	0.08

Values are mean \pm standard error of the mean.

A, late diastolic atrial filling wave; A', late diastolic mitral annular tissue velocity in atrial filling; BP, blood pressure; E, early diastolic mitral inflow wave; E', early diastolic mitral annular tissue velocity; LA, left atrial; LVEDV, left ventricular end-diastolic volume; MLWHF, Minnesota Living with Heart Failure; SD_{t6s}, standard deviation of the time to peak systolic radial strain for the six segments; Te-SD, standard deviation of time to early peak diastolic velocities; TDI, tissue Doppler imaging.

* $P < 0.05$.

$74.1 \pm 2.1\%$, $P = 0.90$), and there were no differences between -LVEDV and +LVEDV patients (Table 2). However, BiV pacing was associated with a significant shortening of the duration of systole compared to sham pacing, both at rest (0.38 ± 0.02 s vs. 0.33 ± 0.02 s, $P = 0.03$) and during exercise (0.32 ± 0.01 s vs. 0.27 ± 0.01 s, $P = 0.002$).

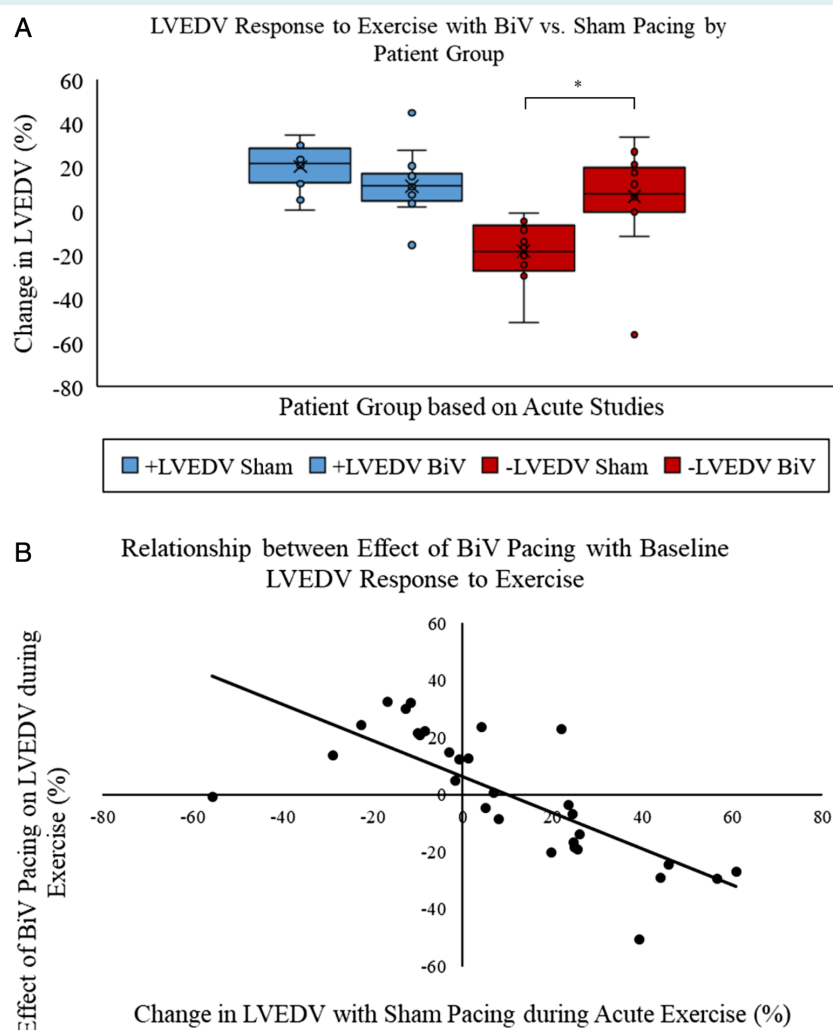


Figure 3 Change in left ventricular end-diastolic volume (LVEDV) during exercise with sham and biventricular (BiV) pacing in acute exercise studies. (A) Patients were divided into groups based on whether LVEDV increased (+LVEDV, $n = 14$; $+20.2 \pm 3.8\%$) or fell (–LVEDV, $n = 15$; $-22.3 \pm 4.3\%$) during acute exercise testing with sham pacing (VVI 30). BiV pacing normalized the LVEDV response on exercise in –LVEDV patients ($P = 0.004$), with no effect seen in +LVEDV patients ($P = 0.43$). (B) There was a negative correlation in the whole patient group suggesting a relationship between Δ LVEDV% with sham pacing during acute exercise, and the effect of BiV pacing on the LVEDV response to exercise ($r = -0.77$, $P < 0.001$).

Diastolic filling time increased on exercise with BiV vs. sham pacing in –LVEDV patients (0.34 ± 0.02 s vs. 0.44 ± 0.03 s, $P = 0.002$), but not in +LVEDV patients (0.35 ± 0.04 s vs. 0.38 ± 0.04 s, $P = 0.47$). In –LVEDV patients, the contribution of the final two thirds of diastole to LV filling during exercise increased with BiV pacing compared to sham pacing ($62 \pm 4.3\%$ vs. $80 \pm 3.2\%$, $P = 0.003$), and this was also true for +LVEDV patients ($66 \pm 3.7\%$ vs. $76 \pm 3.0\%$, $P = 0.04$) (Table 2).

Chronic study

Exercise

Baseline peak VO_2 was significantly lower in –LVEDV patients compared to +LVEDV (16.4 ± 0.9 vs. 19.5 ± 1.1 mL/kg/min, $P = 0.04$

vs. –LVEDV). BiV pacing increased peak VO_2 in the whole patient group compared to sham pacing ($+1.17$ mL/kg/min, $P = 0.02$; online supplementary Table S2). By pre-specified patient subgroup, peak VO_2 increased significantly during BiV pacing vs. sham in –LVEDV patients (16.2 ± 0.9 vs. 17.6 ± 1.2 mL/kg/min, $P = 0.03$). There was a slight and non-significant increase in +LVEDV patients (19.9 ± 1.1 vs. 20.8 ± 1.5 mL/kg/min; $P = 0.13$) (Table 3 and Figure 4).

Quality of life

Minnesota Living with Heart Failure Questionnaire scores improved significantly with BiV pacing compared to sham pacing in the whole patient group ($P = 0.001$) (online supplementary

Table 2 Acute semi-supine exercise data

Test variable	Sham	BiV	P-value
Rest (n = 29)			
+LVEDV patients (n = 14)			
LVEF (%)	74 ± 3.0	76 ± 2.4	0.58
Heart rate (bpm)	59 ± 2.1	64 ± 2.7	0.19
Systole _{dur} (s)	0.37 ± 0.02	0.32 ± 0.02	0.13
Diastole _{dur} (s)	0.57 ± 0.05	0.59 ± 0.04	0.81
Final 2/3 filling (%)	51 ± 4.4	66 ± 3.5	0.01*
E _{LV} (mmHg/mL)	2.96 ± 0.5	2.59 ± 0.4	0.57
-LVEDV patients (n = 15)			
LVEF (%)	71 ± 3.4	72 ± 2.5	0.87
Heart rate (bpm)	63 ± 2.6	67 ± 3.6	0.29
Systole _{dur} (s)	0.38 ± 0.03	0.34 ± 0.02	0.14
Diastole _{dur} (s)	0.61 ± 0.05	0.56 ± 0.06	0.19
Final 2/3 filling (%)	52 ± 4.4	69 ± 4.9	0.02*
E _{LV} (mmHg/mL)	2.44 ± 0.3	2.84 ± 0.4	0.43
Exercise (n = 29)			
+LVEDV patients (n = 14)			
LVEF (%)	76 ± 3.6	75 ± 3.4	0.85
Heart rate (bpm)	87 ± 4.6	87 ± 4.6	0.98
Systole _{dur} (s)	0.32 ± 0.01	0.26 ± 0.02	0.05*
Diastole _{dur} (s)	0.35 ± 0.04	0.38 ± 0.04	0.47
Final 2/3 filling (%)	66 ± 3.7	76 ± 3.0	0.04*
E _{LV} (mmHg/mL)	3.15 ± 0.5	3.10 ± 0.5	0.93
-LVEDV patients (n = 15)			
LVEF (%)	71 ± 3.1	73 ± 2.7	0.66
Heart rate (bpm)	91 ± 3.9	93 ± 4.5	0.69
Systole _{dur} (s)	0.33 ± 0.01	0.27 ± 0.01	0.02*
Diastole _{dur} (s)	0.34 ± 0.02	0.44 ± 0.03	0.002*
Final 2/3 filling (%)	62 ± 4.3	80 ± 3.2	0.003*
E _{LV} (mmHg/mL)	3.62 ± 0.5	3.54 ± 0.5	0.91

Values are mean ± standard error of the mean.

BiV, biventricular pacing; Diastole_{dur}, duration of diastole; E_{LV}, left ventricular end-systolic elastance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; Systole_{dur}, duration of systole; VVI 30, ventricular pacing and sensing at 30 bpm (sham pacing).

*P < 0.05.

Table S2), and this was true for the -LVEDV subgroup (P = 0.02), with a strong trend observed in +LVEDV patients (P = 0.05) (Table 3).

Left ventricular dyssynchrony

The two parameters of systolic dyssynchrony, SD_{t6s} and Yu index, did not demonstrate reduced dyssynchrony scores following 4 months of BiV pacing compared to sham (P = 1.00 and P = 0.25, respectively) (online supplementary Table S2). Te-SD, the measure of diastolic dyssynchrony, was also similar with each pacing mode (P = 1.00).

Discussion

In this study we show that BiV pacing increased exercise capacity and improved quality of life in patients with non-obstructive HCM who have severe exercise limitation due to breathlessness despite

Table 3 Exercise and quality of life data following 4-month pacing intervention

Test variable	Sham	BiV	P-value
Quality of life			
+LVEDV patients (n = 14)			
MLWHF Questionnaire score	45 ± 6.2	38 ± 5.5	0.05
-LVEDV patients (n = 15)			
MLWHF Questionnaire score	50 ± 5.0	35 ± 5.9	0.02*
Exercise			
+LVEDV patients (n = 14)			
Resting heart rate (bpm)	67 ± 3.3	67 ± 3.4	1.00
Peak heart rate (bpm)	128 ± 6.8	123 ± 6.5	0.56
Peak systolic BP (mmHg)	159 ± 6.1	168 ± 5.9	0.48
Exercise duration (s)	462 ± 28	469 ± 28	1.00
RER	1.08 ± 0.02	1.09 ± 0.02	1.00
VE/VCO ₂	36.3 ± 1.4	35.1 ± 1.4	0.82
Peak VO ₂ (mL/kg/min)	19.9 ± 1.1	20.8 ± 1.5	0.13
-LVEDV patients (n = 15)			
Resting heart rate (bpm)	63 ± 2.9	59 ± 2.1	0.28
Peak heart rate (bpm)	111 ± 5.8	118 ± 5.7	0.50
Peak systolic BP (mmHg)	158 ± 7.6	163 ± 6.7	1.00
Exercise duration (s)	409 ± 26	461 ± 25	0.008*
RER	1.09 ± 0.03	1.09 ± 0.02	1.00
VE/VCO ₂	34.3 ± 2.8	36.0 ± 1.6	1.00
Peak VO ₂ (mL/kg/min)	16.2 ± 0.9	17.6 ± 1.2	0.03*

Values are mean ± standard error of the mean.

BiV, biventricular pacing; BP, blood pressure; LVEDV, left ventricular end-diastolic volume; MLWHF, Minnesota Living with Heart Failure; RER, respiratory exchange ratio; VCO₂, carbon dioxide production; VE, minute ventilation; VO₂, oxygen consumption.

*P < 0.05.

optimal, maximally-tolerated standard therapies. The magnitude of improvement in peak VO₂ was comparable to that seen in cardiac resynchronization trials in systolic heart failure.³¹

In patients with systolic heart failure, the predominant mechanism of improvement of cardiac performance by BiV pacing has been considered to be due to the relief of mechanical dyssynchrony. In this study, QRS duration was normal and LVEF was at least 50% at rest in all patients. Furthermore, the degree of resting systolic mechanical dyssynchrony present in these patients was much less marked than in patients with systolic heart failure who undergo BiV pacemaker implants.³² No significant changes in these measures of systolic dyssynchrony (at rest) were observed with BiV pacing. Furthermore, there was no significant effect of BiV pacing on LVEF or on LV end-systolic elastance (a relatively load-independent measure of LV contractile function) at rest or with exercise. These findings argue against a substantial beneficial effect of BiV pacing on LV contractile function (at the 'chamber' level) that might explain the improved volume response on exercise and the increase in exercise capacity observed.

Importantly, BiV pacing had marked effects on the filling of the left ventricle with exercise, and this was closely related to the baseline exercise LVEDV response used to assign patient groups (Figure 3B). In health, LVEDV increases during exercise, and thereby the Frank-Starling mechanism contributes to the increase in stroke

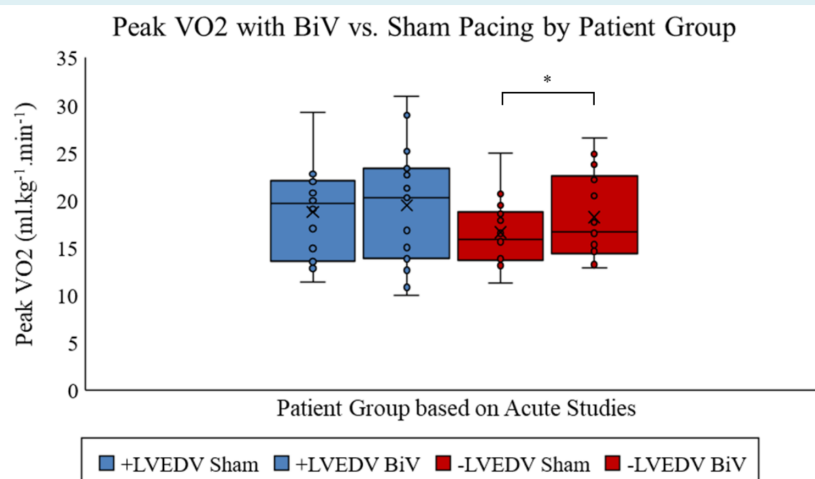


Figure 4 Change in peak oxygen consumption (VO_2) during 4 months of biventricular (BiV) vs. 4 months of sham pacing by patient group. Compared to sham, BiV pacing increased peak VO_2 in patients with decreased left ventricular end-diastolic volume ($-LVEDV$) by 1.4 mL/kg/min (16.2 ± 0.9 vs. $17.6 \pm 1.2 \text{ mL/kg/min}$) and this was statistically significant ($P = 0.03$). A small increase was seen in patients with increased LVEDV ($+LVEDV$) (19.9 ± 1.1 vs. $20.8 \pm 1.5 \text{ mL/kg/min}$), but this was not statistically significant ($P = 0.13$).

volume.³³ This is in part a consequence of an increase in the rate of LV active relaxation during exercise.³⁴ We have previously shown that the rate of LV active relaxation paradoxically slows during exercise in many patients with HCM, and that amelioration of cardiac energetic impairment with the metabolic modulator perhexiline reverses this abnormality.³⁵ Approximately 50% of the patients in this study had an abnormal fall in LVEDV during exercise ($-LVEDV$), and an associated fall in stroke volume. This pattern was associated with more severe exercise limitation than those in whom LVEDV increased as expected on exercise ($+LVEDV$). BiV pacing substantially corrected these abnormal LVEDV and stroke volume responses in $-LVEDV$ patients, and significantly increased peak VO_2 (by 1.4 mL/kg/min), but no significant effect on LVEDV or stroke volume during exercise was observed in $+LVEDV$ patients. The increase in peak VO_2 was also smaller and was not statistically significant. Thus, the improved cardiac performance on exercise and exercise capacity in $-LVEDV$ patients is principally due to partial restoration of the ability to use the Frank–Starling mechanism to increase stroke volume with exercise.

Potential explanatory mechanisms underlying improved augmentation of diastolic filling on exercise include a reduction in intrinsic LV stiffness, an increase in diastolic filling time, or a reduction in external constraint to LV filling. Diastolic dyssynchrony has been reported in HCM³⁶; however, we observed no significant effect of BiV pacing on measures of diastolic dyssynchrony at rest, and BiV pacing reduced the first-third filling fraction at rest and on exercise (the period that includes active relaxation), which argues against this being an important mechanism. We have previously shown that external constraint to LV filling by the pericardium³⁷ (pericardial constraint) and by the right ventricle through the interventricular septum (DVI) is observed in patients with chronic heart failure who have elevated LV end-diastolic pressures (typically $>15 \text{ mmHg}$).¹⁴ In a previous study of patients with severe chronic heart failure,

we showed that both BiV and LV pacing reduced this external constraint to LV filling and recruited LV preload, presumably by shifting the timing of LV filling in relation to the right ventricle.¹¹

In the present study we report a paradoxical increase in LVEDV during application of lower body negative pressure in four patients (all $-LVEDV$ patients), suggesting the presence of significant DVI at rest. In three of these patients, this paradoxical increase in LVEDV during application of lower body negative pressure was normalized by BiV pacing, suggesting alleviation of DVI. Although only a minority of patients with HCM have pulmonary hypertension and markedly raised LVEDP at rest, both pulmonary artery pressure and LVEDP markedly rise during exercise in many patients with symptomatic HCM,¹⁵ therefore *a priori* DVI might be expected to be a frequent occurrence on exercise in these patients, by analogy with our recent findings in patients with heart failure with a preserved ejection fraction.³⁸ We suggest that the partial restoration of the Frank–Starling mechanism on exercise by BiV pacing in $-LVEDV$ patients is most likely explained by relief of DVI. DVI is typically associated with a restrictive LV filling pattern, in which rapid early filling ceases with the onset of external constraint. Of note, BiV pacing during exercise reduced the rate of early filling but markedly increased LV filling in the later part of diastole, consistent with our hypothesis. Larger randomized controlled trials are needed to confirm these findings and determine whether they translate to improved survival. Indeed, the EchoCRT study of patients with systolic heart failure and a short QRS duration was halted early by the data and safety committee for futility with a potential for harm with cardiac resynchronization therapy/BiV pacing.³⁹ Whether similar adverse effects might occur in our patients is unknown; however, there were no significant adverse events or significant adverse device events during the 4-month BiV pacing arm of our study.

Study limitations

The HCM phenotype can be caused by over 400 genetic mutations in the sarcomeric contractile apparatus.⁴⁰ The pattern and severity of hypertrophy and contractile dysfunction is often heterogeneous between patients and indeed between different areas of an individual patient's myocardium. However, all of our patients fulfilled the currently established criteria for HCM,⁴⁰ and as much as possible we have excluded the presence of HCM phenocopies such as infiltrative cardiomyopathies (e.g. amyloid) and glycogen storage disorders. We have also used 'chamber' level measures of contractile function, reducing the impact of regional variations. Highly symptomatic non-obstructive HCM is relatively uncommon, and identifying and recruiting appropriate patients remains difficult, despite recruitment from two large tertiary referral centres in the UK. However, the majority of randomized controlled trials in this patient subgroup involve similar patient numbers, and we attempted to maximize statistical power with a crossover study design. Despite achieving >80% power for the primary endpoint, the relatively small number of patients in our study may have important effects on the results seen. Changes in peak VO_2 are greatly influenced by changes in heart rate,⁴¹ which can be quite variable in smaller sample sizes. Numerically, exercise peak heart rate was higher in +LVEDV patients than -LVEDV patients, and peak heart rate was numerically higher during BiV pacing in -LVEDV patients with no change in +LVEDV patients. This mirrored the improvement seen in peak VO_2 . It is important to note, however, that these differences were not statistically significant and the changes in cardiac volumes were much more marked. Whilst it is true that peak exercise heart rate was higher in -LVEDV patients (and slightly higher during BiV pacing than sham), BiV pacing corrected the fall in LVEDV and stroke volume in these patients. Therefore, the very large changes in LVEDV and stroke volume are much more likely to be responsible for driving the increase in exercise capacity in these patients.

We hypothesized that BiV pacing ameliorated DVI with exercise in -LVEDV patients, and that this resulted from exercise-induced pulmonary hypertension. Unfortunately, the tricuspid regurgitant jet in the majority of patients was insufficient to allow prediction of right heart pressures at rest. Indeed, right ventricular pressures during exercise are likely more important, and would have required invasive right heart catheterization, which was not undertaken in an already complex protocol for patients. Similarly, we did not attempt to optimize AV or VV delay during BiV pacing in our patients. In patients with systolic heart failure, AV optimization has been shown to improve response to cardiac resynchronization therapy, but does not change non-responders to responders.⁴² We also chose a specific VV delay of 40 ms from previous work demonstrating a potential benefit when the left ventricle is triggered slightly earlier than the right ventricle.¹¹ AV and VV optimization of BiV pacing in non-obstructive HCM represents an interesting topic for future studies.

Conclusion

Biventricular pacing improved symptoms and exercise capacity in patients with non-obstructive HCM. The benefit was greatest in

those patients with the most marked diastolic impairment during exercise, and the benefit was due to augmented diastolic filling on exercise, enhancing utilization of the Frank–Starling mechanism. We suggest that the most likely mechanism of this improvement in diastolic filling is relief of DVI. Larger studies of BiV pacing in non-obstructive HCM are indicated.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Left ventricular end-diastolic volume response to acute submaximal exercise with VVI 30 (sham) and biventricular pacing.

Table S1. Change in left ventricular volumes during acute studies.

Table S2. Chronic follow-up data for whole patient group.

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References

1. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 1995;**92**:785–789.
2. Maron BJ. Hypertrophic cardiomyopathy. *Lancet* 1997;**350**:127–133.
3. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;**10**:733–742.
4. Lele SS, Thomson HL, Seo H, Belenkie I, McKenna WJ, Frenneaux MP. Exercise capacity in hypertrophic cardiomyopathy. Role of stroke volume limitation, heart rate, and diastolic filling characteristics. *Circulation* 1995;**92**:2886–2894.
5. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy: a prognostic study with fourier phase analysis of radionuclide angioscintigraphy. *J Am Coll Cardiol* 2002;**40**:2022–2030.
6. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**124**:2761–2796.
7. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ; MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–1072.
8. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;**105**:438–445.
9. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**:1834–1840.
10. Gorcsan J 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, Bax JJ. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 2007;**50**:1476–1483.

11. Bleasdale RA, Turner MS, Mumford CE, Steendijk P, Paul V, Tyberg JV, Morris-Thurgood JA, Frenneaux MP. Left ventricular pacing minimizes diastolic ventricular interaction, allowing improved preload-dependent systolic performance. *Circulation* 2004;**110**:2395–2400.
12. Choi HS, Vito RP. Two-dimensional stress-strain relationship for canine pericardium. *J Biomech Eng* 1990;**112**:153–159.
13. Shivakumar PN, Man CS, Rabkin SW. Modelling of the heart and pericardium at end-diastole. *J Biomech* 1989;**22**:201–209.
14. Atherton JJ, Moore TD, Lele SS, Thomson HL, Galbraith AJ, Belenkie I, Tyberg JV, Frenneaux MP. Diastolic ventricular interaction in chronic heart failure. *Lancet* 1997;**349**:1720–1724.
15. Losse B, Kuhn H, Loogen F, Schulte HD. Exercise performance in hypertrophic cardiomyopathies. *Eur Heart J* 1983;**4**:197–208.
16. Daubert JC, Leclercq C, Mabo P. Heart re-synchronization with biventricular stimulation: new treatment for refractory heart failure. *Bull Acad Natl Med* 2002;**186**:45–55 discussion 6–7.
17. Linde C, Braunschweig F, Gadler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy Study (MUSTIC). *Am J Cardiol* 2003;**91**:1090–1095.
18. John Sutton MG, Plappert T, Abraham WT, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;**107**:1985–1990.
19. Callahan RJ, Froelich JW, McKusick KA, Leppo J, Strauss HW. A modified method for the in vivo labeling of red blood cells with Tc-99m: concise communication. *J Nucl Med* 1982;**23**:315–318.
20. Thaman R, Elliott PM, Shah JS, Mist B, Williams L, Murphy RT, McKenna WJ, Frenneaux MP. Reversal of inappropriate peripheral vascular responses in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**46**:883–892.
21. Moore TD, Frenneaux MP, Sas R, Atherton JJ, Morris-Thurgood JA, Smith ER, Tyberg JV, Belenkie I. Ventricular interaction and external constraint account for decreased stroke work during volume loading in CHF. *Am J Physiol Heart Circ Physiol* 2001;**281**:H2385–H2391.
22. Massardo T, Gal RA, Grenier RP, Schmidt DH, Port SC. Left ventricular volume calculation using a count-based ratio method applied to multigated radionuclide angiography. *J Nucl Med* 1990;**31**:450–456.
23. Najjar SS, Schulman SP, Gerstenblith G, Fleg JL, Kass DA, O'Connor F, Becker LC, Lakatta EG. Age and gender affect ventricular-vascular coupling during aerobic exercise. *J Am Coll Cardiol* 2004;**44**:611–617.
24. Bruce RA, McDonough JR. Stress testing in screening for cardiovascular disease. *Bull N Y Acad Med* 1969;**45**:1288–1305.
25. Davies NJ, Denison DM. The measurement of metabolic gas exchange and minute volume by mass spectrometry alone. *Respir Physiol* 1979;**36**:261–267.
26. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure: content, reliability, and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. *Heart Failure* 1987;**3**:198–209.
27. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
28. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 2003;**91**:684–688.
29. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging: comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;**51**:1944–1952.
30. Cho GY, Song JK, Park WJ, Han SW, Choi SH, Doo YC, Oh DJ, Lee Y. Mechanical dyssynchrony assessed by tissue Doppler imaging is a powerful predictor of mortality in congestive heart failure with normal QRS duration. *J Am Coll Cardiol* 2005;**46**:2237–2343.
31. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;**42**:1454–1459.
32. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Cardiac Resynchronization-Heart Failure Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
33. Poliner LR, Dehmer GJ, Lewis SE, Parkey RV, Blomqvist CG, Willerson JT. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. *Circulation* 1980;**62**:528–534.
34. Nonogi H, Hess OM, Ritter M, Krakenbuehl HP. Diastolic properties of the normal left ventricle during supine exercise. *Br Heart J* 1988;**60**:30–38.
35. Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, Kaur K, Taylor J, Henning A, Ashrafian H, Watkins H, Frenneaux M. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* 2010;**122**:1562–1569.
36. Betocchi S, Hess OM, Losi MA, Nonogi H, Krakenbuehl HP. Regional left ventricular mechanics in hypertrophic cardiomyopathy. *Circulation* 1993;**88**:2206–2214.
37. Applegate RJ, Johnston WE, Vinten-Johansen J, Klopstein HS, Little WC. Restraining effect of intact pericardium during acute volume loading. *Am J Physiol* 1992;**262**:H1725–H1733.
38. Parasuraman SK, Loudon BL, Lowery C, Cameron D, Singh S, Schwarz K, Gollop ND, Rudd A, McKiddie F, Phillips JJ, Prasad SK, Wilson AM, Sen-Chowdhry S, Clark A, Vassiliou VS, Dawson DK, Frenneaux MP. Diastolic ventricular interaction in heart failure with preserved ejection fraction. *J Am Heart Assoc* 2019;**8**:e010114.
39. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Ghorcan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
40. Elliott PM, Anastakis A, Borgers MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
41. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986;**58**:281–291.
42. Barold SS, Ilteric A, Herweg B. Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization. *Europace* 2008;**10**:iii88–iii95.