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REVIEW

Current therapies for hypertrophic cardiomyopathy: a systematic review and meta-analysis of the literature

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Abstract

Aims The aim of this study was to synthesize the evidence on the effect of the current therapies over the pathophysiological and clinical characteristics of patients with hypertrophic cardiomyopathy (HCM).

Methods and results A systematic review and meta-analysis of 41 studies identified from 1383 retrieved from PubMed, Web of Science, and Cochrane was conducted. Therapies were grouped in pharmacological, invasive and physical exercise. Pharmacological agents had no effect on functional capacity measured by VO2max (1.11 mL/kg/min; 95% CI: −0.04, 2.25, $P < 0.05$). Invasive septal reduction therapies increased VO2max (+3.2 mL/kg/min; 95% CI: 1.78, 4.60, $P < 0.05$). Structured physical exercise programmes did not report contraindications and evidenced the highest increases on functional capacity (VO2max + 4.33 mL/kg/min; 95% CI: 0.20, 8.45, $P < 0.05$). Patients with left ventricular outflow tract (LVOT) obstruction at rest improved their VO2max to a greater extent compared with those without resting LVOT obstruction (2.82 mL/kg/min; 95% CI: 1.97, 3.67 vs. 1.18; 95% CI: 0.62, 1.74, $P < 0.05$). Peak LVOT gradient was reduced with the three treatment options with the highest reduction observed for invasive therapies. Left ventricular ejection fraction was reduced in pharmacological and invasive procedures. No effect was observed after physical exercise. Symptomatic status improved with the three options and to a greater extent with invasive procedures.

Conclusions Invasive septal reduction therapies increase VO2max, improve symptomatic status, and reduce resting and peak LVOT gradient, thus might be considered in obstructive patients. Physical exercise emerges as a coadjuvant therapy, which is safe and associated with benefits on functional capacity. Pharmacological agents improve reported NYHA class, but not functional capacity.

Keywords Hypertrophic cardiomyopathy; Functional capacity; Left ventricular outflow tract obstruction; Cardiopulmonary exercise test; Therapies

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common and best characterized inherited heart disease for which prevalence in the general population is 1:500.[1–3] In most patients, it is due to pathogenic genetic variants in the heart muscle proteins of the sarcomere and it is inherited in an autosomal dominant pattern, having an heterogeneous clinical presentation.[4] Its natural history includes the development of progressive, life-limiting symptoms due to left ventricular outflow tract obstruction (LVOTO) or diastolic dysfunction, atrial arrhythmias (atrial fibrillation and flutter), which can result in thromboembolic stroke, heart failure associated with systolic dysfunction and risk of ventricular arrhythmias, which are the main cause of sudden cardiac death.[3] Current therapies include pharmacological agents, invasive therapies (myectomy, alcohol septal ablation, or right ventricular pacing), and physical conditioning.

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For symptomatic patients, conventional medical therapy consists of beta-blockers and non-dihydropyridine calcium channel blockers, which reduce myocardial energy demand. Other alternative drugs, which affect the myocardial energy metabolism at different levels (perhexiline, trimetazidine, and ranolazine)[5–7] or inhibit aldosterone production (losartan, candesartan, and spironolactone),[8–11] have been used.

For patients with LVOTO whose symptoms persist, there are invasive therapies available such as surgical myectomy, alcohol septal ablation, or right ventricular pacing. A new cardioselective drug emerged during the past few years, mavacamten, inhibits myosin binding to actin with good tolerance and has yielded promising results reducing obstruction and improving functionality.[12]

Physical conditioning is an established recommendation to prevent and treat the main modifiable cardiovascular risk factors, improve functional capacity, and reduce morbidity and mortality. Recent studies[13] refute the sedentary lifestyle usually prescribed to HCM patients with unfounded certainty showing safety, good tolerance, and benefits from physical conditioning.[14,15]

This study brings the first systematic review and meta-analysis to analyse the influence of the current therapies for HCM on functional capacity and echocardiographic variables.

Methods

Search strategy

A systematic review of the literature was conducted on PubMed, Web of Science and Cochrane in November 2021. Topics for the search included keywords regarding three main interest areas. The search equation in PubMed was (ti: title, ab: abstract): (HCM[ti] OR oHCM[ti] OR "hypertrophic cardiomyopathy"[ti]) AND (myectomy[ti/ab] OR pacing[ti/ab] OR pacer[ti/ab] OR pacemaker[ti/ab] OR DDD[ti/ab] OR drug[ti/ab] OR medication[ti/ab] OR therapy[ti/ab] OR training[ti/ab] OR exercise[ti/ab]) AND ("functional capacity"[ti/ab] OR "exercise tolerance"[ti/ab] OR oxygen [ti/ab] OR VO2max[ti/ab] OR assessment OR evaluation) and then adapted with the same terms for Web of Science and Cochrane. Two authors (A. B. R. and J. G.) independently screened for inclusion the articles retrieved from the search. When disagreements occurred, a consensus was reached with the rest of the authors.

Eligibility criteria

The eligibility criteria were (1) sample included patients with obstructive or non-obstructive hypertrophic cardiomyopathy; (2) interventions included pharmacological treatment, invasive surgery, alcohol septal ablation, pacing or an exercise training protocol; (3) functional capacity was reported pre- and post-intervention, whether in Watts, maximal oxygen consumption (mL/kg/min), metabolic equivalents (METs) or duration of the test; (4) case–control, cohort, randomized controlled trial or clinical trial designs; dissertations and conference proceedings were excluded. When studies compared different interventions, each group was individually included (e.g. myectomy and pacing). Studies combining physical exercise with other lifestyle modifications were excluded (e.g. exercise training and diet).

Data extraction and synthesis

The following variables were extracted from the studies included publication date, sample (size, age and gender) and intervention characteristics (type and duration); and the main outcomes of interest were: pre- and post-treatment functional capacity, resting LVOTO, peak LVOT gradient, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF%), resting systolic blood pressure (SBP), resting diastolic blood pressure (DBP), peak SBP and New York Heart Association index for symptomatic status (NYHA). When functional capacity was expressed in METs, it was recalculated to mL/kg/min of oxygen consumption as previously indicated[16]; for example, a maximal work rate reached at 7 METs was multiplied by 3.5 to be recalculated into 24.5 mL/kg/min. For meta-analyses, pre- and post-intervention mean values and standard deviation (SD) of the outcomes of interest were extracted.

Statistical analysis

Mean differences (MD) between pre- and post-intervention in the outcomes of interest were obtained conducting random effects meta-analyses and subgroup analyses using Review Manager (RevMan), V.5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Subgroup analyses examined the differences between treatment strategies (pharmacological therapies, invasive treatments and exercise training) and between treatment possibilities for pharmacological and invasive options. Because functional capacity was reported in different units (i.e. maximal oxygen consumption in mL/kg/min, METs, time on ergometer or Watts), only mL/kg/min and METs (recalculated into mL/kg/min) were included in the statistical analysis of differences in functional capacity. Alpha was set to 0.05.

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Results

Study identification and characteristics

The database search yielded 1383 articles and 62 full texts were read after initial screening. Forty-one publications were included in qualitative synthesis (31 trials and 10 cohort studies) and 40 in quantitative analysis (*Figure 1*), with information on exercise capacity with a total of 47 groups evaluated; 1830 patients (41.3% women) with a mean age of 51 ± 13 years underwent functional assessment before and after different therapies. Twenty study groups were treated with pharmacological agents, 24 studies evaluated the response to invasive septal reduction procedures (10 alcohol septal ablation, 9 pacing, and 5 surgical myectomy), and 3 studies implemented physical exercise programmes.

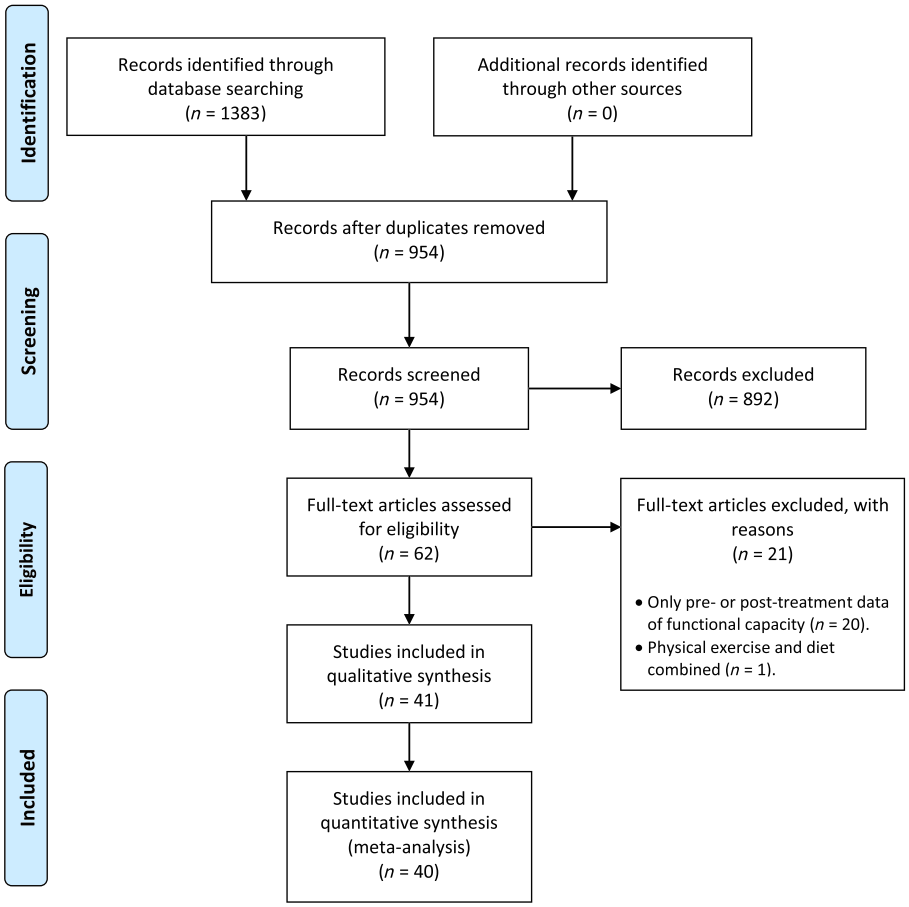
Interventions and time to follow-up ranged from 1 week to 7 years: 1 week to 5 years for medications, 3 months to 7 years for invasive therapies and 3 to 4 months for exercise programmes. *Table 1* summarizes key study and patient characteristics.[5–7,9–13,17–49]

Functional capacity

Since this parameter was sometimes reported as workload achieved or duration of the test, only VO2max values were included in meta-analysis. Pharmacological therapies did not produce any beneficial or detrimental effects on VO2max when considered together in 356 patients (*Figure 2*). Nevertheless, calcium channel blockers increased this value by ~3 mL/kg/min ($P < 0.05$) (*Figure S1*). No significant differences were observed between pharmacological therapies ($P = 0.34$). Absolute change from pre- to post-treatment ranged from −3.2 to +9.0 mL/kg/min and relative change from −9% to +47%.

Invasive therapies produced a significant beneficial effect on VO2max, which ranged from 0.5 to 11.6 mL/kg/min and from 3% to 66% relative to baseline capacity in 912 patients (*Figure S2*). Mean increment was 3.2 mL/kg/min (95% CI: 1.78, 4.60). All three invasive therapies increased VO2max considered separately with significant between-group differences ($P = 0.02$). Septal ablation produced greater benefits than surgical myectomy and pacing (4.53; 95% CI: 2.10, 6.97

Figure 1 Flow diagram.



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Table 1 Current therapies used in hypertrophic cardiomyopathy

Author, year	*N*	Age	%W	Treatment	Duration	Functional capacity	
						Pre	Post
Abozguia, 2010[5]	24	55 ± 1	16	Perhexiline	5 months	22.2 ± 0.2	24.3 ± 0.2
Coats, 2019[6]	26	50 ± 14	29	Trimetazidine	3 months	17.4 ± 3.9	17.7 ± 3.5
Olivotto, 2018[7]	40	53 ± 14	42	Ranolazine	5 months	16.9 ± 5.0	17.4 ± 5.9
Antianginal	**90**	**53 ± 11**	**32.2**			**1.34 (−0.00, 2.68)**	
Frenneaux, 1992[17]	10	35	40	Amiodarone	6 weeks	27 ± 5	30 ± 6
Amiodarone	**10**	**35**	**40**			**3.00 (−1.84, 7.84)**	
Axelsson, 2016[9]	67	52 ± 13	35	Losartan	12 months	27 ± 8.4	26.3 ± 8.8
Penicka, 2009[10]	12	43 ± 13	54	Candesartan	12 months	9.6 ± 2.5′	12.5 ± 2.7′
ARA	**79**	**51 ± 13**	**36.7**			**−0.70 (−3.61, 2.21)**	
Bratt, 2015(a)[18]	10	13 ± 2	30	Propanolol	12 months	35.4 ± 5.8	32.2 ± 2.6
Bratt, 2015(b)[18]	9	13 ± 2	12	Metoprolol	12 months	36.8 ± 3.0	34.3 ± 3.3
Frank, 1983[19]	32	47	34	Propanolol	5,7 ± 3,3 years	16.8 ± 8.7	24.6 ± 8
Lösse, 1983(a)[20]	12	40 ± 3	-	Propanolol	3 months	72.7 ± 8 W	72.9 ± 7 W
Nistri, 2012[21]	27	36 ± 15	19	Nadolol/Bisoprolol	12 months	24.5 ± 6	24.2 ± 4.9
Beta-blockers	**90**	**36 ± 8**	**25.6**			**0.33 (−3.98, 4.65)**	
Bonow, 1985[22]	55	47	47	Verapamil	4 weeks	5.9 ± 3.6′	8.7 ± 4.7′
Hanrath, 1983[23]	18	45 ± 10	22	Verapamil	7 weeks	626 ± 296 W	779 ± 363 W
Lösse, 1983(b)[20]	25	45 ± 3	-	Verapamil	5 months	80 ± 6 W	90 ± 5 W
Tokushima, 1996[24]	23	55 ± 10	13	Nisoldipine	6 months	9.4 ± 1.7′	10.1 ± 1.7′
Toshima, 1986(a)[25]	32	42 ± 15	25	Diltiazem	1 week	23.8 ± 5	26.5 ± 7
Toshima, 1986(b)[25]	32	42 ± 15	25	Verapamil	1 week	24.0 ± 5	27.3 ± 6.6
Ca^{+2}-channel blck.	**185**	**46 ± 11**	**30.6**			**3.01 (0.94, 5.08)***	
Maron, 2018[11]	26	40 ± 13	23	Spironolactone	12 months	30 ± 7	29 ± 8
Diuretics	**26**	**40 ± 13**	**23.1**			**−1.00 (−5.09, 3.09)**	
Heitner, 2019(a)[12]	11	56	36	Mavacamten	12 weeks	20.7 ± 7.4	24.2 ± 3.2
Heitner, 2019(b)[12]	10	58	50	Mavacamten + BB	12 weeks	19.4 ± 4.6	21.1 ± 2.2
Mavacamten	**21**	**57**	**57**			**2.25 (−0.38, 4.88)**	
Pharmacol.	**501**	**46 ± 11**	**31.5**			**1.11 (−0.04, 2.25)**	
Diodati, 1992[26]	30	43	43	Myectomy	6 months	17.1 ± 4.4	19.1 ± 4.3
Lösse, 1983(c)[20]	21	42 ± 3	-	Myectomy	10 months	64.3 ± 5 W	86.9 ± 6 W
Ommen, 1999(a)[27]	20	42 ± 14	30	Myectomy	14 months	19.4 ± 6.4	22.2 ± 6.5
Redwood, 1979[28]	29	18–65	-	Myectomy	6 months	16 ± 5	21 ± 4.6
Smith, 2020[29]	295	50 ± 14	44	Myectomy	6 months	18.8 ± 6.6	19.6 ± 6.7
Myectomy	**395**	**49 ± 13**	**43.2**			**2.43 (0.44, 4.42)***	
Ahmed, 2020[30]	29	55	44	Pacemaker	4 months	18.0 ± 1.2	19.1 ± 1.7
Begley, 2001[31]	14	34 ± 16	50	Pacemaker	4,8 ± 2,9 years	6.6 ± 2.8′	7.4 ± 2.1
Gadler, 1997[32]	41	67 ± 13	58	Pacemaker	12 months	94.5 ± 36 W	110 ± 43 W
Galve, 2010[33]	50	62 ± 11	48	Pacemaker	5.0 ± 2.9 years	281 ± 112 m	348 ± 78 m
Maron, 1999[34]	33	53 ± 17	54	Pacemaker	12 months	16.2 ± 5	16.7 ± 4
McDonald, 1988[35]	7	23–66	45	Pacemaker	4–24 months	7.7′	10.1′
Nishimura, 1997[36]	8	58	47	Pacemaker	3 months	19.4 ± 6.7	20.0 ± 6.5
Ommen, 1999(b)[27]	19	59 ± 13	47	Pacemaker	14 months	19.6 ± 6.5	20.1 ± 6.5
Simantirakis, 1998[37]	8	56 ± 7	37	Pacemaker	12 months	20.1 ± 3	24.9 ± 6
Pacemaker	**209**	**58 ± 13**	**50.2**			**1.10 (0.41, 1.79)***	
Faber, 2000[38]	25	55 ± 15	52	Septal ablation	24 ± 3 months	67 ± 74 W	111 ± 50 W
Faber, 2007[39]	100	54 ± 15	40	Septal ablation	12 months	18 ± 4	21 ± 6
Faber, 2011[40]	88	54 ± 12	37	Septal ablation	12 ± 12 months	17 ± 5	20 ± 6
Gietzen, 2002[41]	129	58 ± 15	57	Septal ablation	7 ± 3 months	14.3 ± 4.5	16.4 ± 5.8

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Table 1 (continued)

Author, year	*N*	Age	%W	Treatment	Duration	Functional capacity	
						Pre	Post
Kim, 1999[42]	12	44 ± 3	40	Septal ablation	12 months	19 ± 2	23 ± 2
Lakkis, 2000[43]	50	53 ± 17	50	Septal ablation	12 months	4.5 ± 1.8′	6.8 ± 3.5′
Malek, 2008[44]	23	44 ± 14	43	Septal ablation	7.2 ± 1 years	18 ± 4	22 ± 6
Ruzyllo, 2000[45]	25	49 ± 13	40	Septal ablation	6 months	14.8 ± 4.1	18.9 ± 6
Seggewiss, 2007[46]	100	53 ± 16	50	Septal ablation	4.8 ± 1 years	90 ± 49 W	121 ± 45 W
Shamim, 2003[47]	64	49 ± 17	30	Septal ablation	3.0 ± 1.3 years	18.4 ± 5.8	30.0 ± 4.4
Septal ablation	**616**	**53 ± 15**	**45.3**			**4.53 (2.10, 6.97)***	
Invasive	**1220**	**53 ± 14**	**45.6**			**3.19 (1.78, 4.60)†**	
Klempfner, 2015	20	62 ± 13	30	Physical exercise	-	16.5 ± 7.7	25.2 ± 9.8
Saberi, 2017[13]	57	50 ± 13	42	Physical exercise	4 months	21.3 ± 1.6	22.7 ± 1.8
Wasserstrum, 2019[49]	32	58 ± 14	31	Physical exercise	3 months	18.7 ± 7.4	23.6 ± 8
Physical exercise	**109**	**55 ± 13**	**36.7**			**4.33 (0.20, 8.45)***	
All	**1830**	**51 ± 13**	**41.3**			**2.41 (1.72, 3.10)†**	

Note: Data are expressed as mean (±SD) for each individual study. Functional capacity is expressed in mL/kg/min of VO2max unless different units are specified for those reporting maximum Watts or minutes lasted. For each group of therapies, mean difference from pre to post treatment (95% CI) as extracted from meta-analysis are indicated in bold numbers. Age is reported in years. Subscripts shown together with the year of the studies indicate that there was more than one group with different therapies in the trial. Corresponding groups for the original trial can be identified regarding the treatment indicated for each. Grey rows summarize the information of the corresponding therapies shown above each and the name found in bold letters corresponds to the name of the group of medicines or invasive therapy.

Abbreviations: %W, percentage of women in the study group; VO2max, maximal oxygen consumption; LVOT, left ventricular outflow tract gradient; LVEF%; left ventricular ejection fraction; NYHA, New York Heart Association symptomatic score; ARA, angiotensin II receptor antagonists; Pharmacol., pharmacological therapies; BB, beta-blockers; N/E, not estimable.

*$P < 0.05$.

[1]†$P < 0.001$.

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Table 1 (continued)

Author, year	Rest LVOT (mmHg)		Peak LVOT (mmHg)		LVEF%		NYHA	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Abozguia, 2010[5]	-	-	-	-	68 ± 0.5	67 ± 0.5	-	-
Coats, 2019[6]	6.5 ± 4.2	5.9 ± 3.1	-	-	63 ± 9	64 ± 8	-	-
Olivotto, 2018[7]	9 ± 7	-	-	-	-	-	-	-
Antianginal	**N/E**		**N/E**		**−1.0 (−1.3, −0.7)†**		**N/E**	
Frenneaux, 1992[17]	18 ± 32	-	-	-	75 ± 8	-	1.5 ± 0.5	-
Amiodarone	**N/E**		**N/E**		**N/E**		**N/E**	
Axelsson, 2016[9]	-	-	-	-	75 ± 7	73 ± 7	1.3 ± 0.5	-
Penicka, 2009[10]	7.5 ± 3.1	8.2 ± 5.1	-	-	69 ± 5	68 ± 6	2.0 ± 0.9	1.3 ± 0.5
ARA	**N/E**		**N/E**		**−1.8 (−3.9, 0.3)**		**−0.7 (−1.3, −0.1)***	
Bratt, 2015(a)[18]	-	-	-	-	-	-	-	-
Bratt, 2015(b)[18]	-	-	-	-	-	-	-	-
Frank, 1983[19]	-	-	-	-	-	-	2.2 ± 0.8	0.8 ± 0.7
Lösse, 1983(a)[20]	45 ± 11	-	110 ± 15	-	-	-	2.8 ± 0.6	2.6 ± 0.6
Nistri, 2012[21]	14 ± 7	-	77 ± 28	35 ± 22	67 ± 6	-	1.2 ± 0.4	1.1 ± 0.3
Beta-blockers	**N/E**		**−42.0 (−55.4, −28.6)†**		**N/E**		**−0.6 (−1.4, 0.3)**	
Bonow, 1985[22]	-	-	-	-	71 ± 9	71 ± 9	-	-
Hanrath, 1983[23]	-	-	-	-	-	-	-	-
Lösse, 1983(b)[20]	36 ± 7	-	100 ± 12	-	-	-	2.8 ± 0.6	2.4 ± 0.5
Tokushima, 1996[24]	-	-	-	-	-	-	-	-
Toshima, 1986(a)[25]	-	-	-	-	82 ± 8	81 ± 10	-	-
Toshima, 1986(b)[25]	-	-	-	-	81 ± 9	82 ± 8	-	-
Ca^{+2}-channel blck.	**N/E**		**N/E**		**0.1 (−2.2, 2.4)**		**−0.4 (−0.7, −0.1)***	
Maron, 2018[11]	11 ± 29	-	-	-	65 ± 3	-	1.6 ± 0.7	1.7 ± 0.8
Diuretics	**N/E**		**N/E**		**N/E**		**0.1 (−0.3, 0.5)**	
Heitner, 2019(a)[12]	60 ± 28	12.2 ± 31	103 ± 50	19 ± 13	70 ± 7	55 ± 4	2.4 ± 0.5	1.5 ± 0.7
Heitner, 2019(b)[12]	86 ± 63	37.5 ± 47.5	86 ± 43	61 ± 26	75 ± 5	69 ± 2	2.5 ± 0.5	1.5 ± 0.1
Mavacamten	**−47.9 (−70.0, −25.9)†**		**−54.6 (−112.4, 3.4)**		**−10.3 (−19.2, −1.5)***		**−0.97 (−1.2, −0.7)†**	
Pharmacol.	**N/E**		**−49.5 (−78.0, −21.0)***		**−2.5 (−4.8, −0.3)***		**−0.6 (−0.94, −0.2)***	
Diodati, 1992[26]	83 ± 38	17 ± 24	119 ± 28	-	-	-	-	-
Lösse, 1983(c)[20]	66 ± 7	-	140 ± 7	-	-	-	2.8 ± 0.6	1.5 ± 0.5
Ommen, 1999(a)[27]	76 ± 57	9 ± 17	-	-	-	-	2.8 ± 0.6	1.3 ± 0.5
Redwood, 1979[28]	-	-	-	-	-	-	-	-
Smith, 2020[29]	61 ± 40	17 ± 14	-	-	71 ± 6	65 ± 8	2.9 ± 0.5	-
Myectomy	**−56.6 (−74.7, −38.6)†**		**N/E**		**−6.0 (−7.1, −4.9)†**		**−1.4 (−1.6, −1.2)†**	
Ahmed, 2020[30]	-	-	-	-	62 ± 2	-	-	-
Begley, 2001[31]	84 ± 31	43 ± 36	-	-	-	-	2.8 ± 0.1	1.9 ± 0.4
Gadler, 1997[32]	56 ± 24	-	92 ± 35	39 ± 25	-	-	2.9 ± 0.5	1.9 ± 0.5
Galve, 2010[33]	86 ± 29	28 ± 24	114 ± 53	38 ± 24	76 ± 10	65 ± 15	3.1 ± 0.3	1.7 ± 0.7
Maron, 1999[34]	82 ± 33	48 ± 32	-	-	-	-	-	-
McDonald, 1988[35]	-	-	-	-	-	-	3.0 ± 0.6	1.6 ± 0.5
Nishimura, 1997[36]	76 ± 61	55 ± 38	-	-	-	-	2.9 ± 0.4	2.4 ± 0.7
Ommen, 1999(b)[27]	77 ± 61	55 ± 39	-	-	-	-	2.9 ± 0.4	2.4 ± 0.8
Simantirakis, 1998[37]	70 ± 18	24 ± 11	-	-	-	-	-	-
Pacemaker	**−42.7 (−54.2, −31.1)†**		**−64.2 (−86.4, −41.9)†**		**−11.0 (−16.0, −6.0)†**		**−1.0 (−1.3, −0.7)†**	
Faber, 2000[38]	60 ± 38	3 ± 6	147 ± 56	12 ± 19	-	-	2.8 ± 0.6	1.2 ± 1.0
Faber, 2007[39]	59 ± 32	8 ± 15	120 ± 42	28 ± 32	78 ± 9	-	2.9 ± 0.4	1.5 ± 0.7
Faber, 2011[40]	62 ± 30	11 ± 19	121 ± 26	43 ± 40	79 ± 11	76 ± 11	2.9 ± 0.4	1.6 ± 0.6
Gietzen, 2002[41]	56 ± 24	13 ± 16	149 ± 41	44 ± 41	72 ± 8	70 ± 8	3.1 ± 0.2	1.6 ± 0.6

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Table 1 (continued)

Author, year	Rest LVOT (mmHg)		Peak LVOT (mmHg)		LVEF%		NYHA	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Kim, 1999[42]	58 ± 8	4 ± 1	143 ± 11	30 ± 6	66 ± 2	64 ± 3	2.8 ± 0.6	1.3 ± 0.5
Lakkis, 2000[43]	74 ± 23	6 ± 18	-	-	74 ± 7	73 ± 7	3.0 ± 0.5	0.5 ± 0.5
Malek, 2008[44]	82 ± 29	21 ± 23	-	-	76 ± 9	65 ± 10	-	-
Ruzyllo, 2000[45]	85 ± 31	32 ± 26	141 ± 45	62 ± 47	75 ± 10	66 ± 18	2.8 ± 0.5	1.5 ± 0.5
Seggewiss, 2007[46]	76 ± 37	19 ± 21	131 ± 9	20 ± 5	-	-	2.8 ± 0.6	1.6 ± 0.7
Shamim, 2003[47]	64 ± 36	16 ± 15	132 ± 34	45 ± 19	-	-	2.8 ± 0.7	1.1 ± 0.2
Septal ablation	**−53.7 (−58.5, −48.8)†**		**−99.8 (−110.1, −89.5)†**		**−3.3 (−5.4, −1.1)***		**−1.47 (−1.6, −1.3)†**	
Invasive	**−51.8 (−56.0, −47.6)†**		**−92.9 (−104.7, −81.1)†**		**−4.7 (−7.2, −2.4)†**		**−1.3 (−1.45, −1.17)†**	
Klempfner, 2015	50 ± 24	-	-	-	53 ± 15	-	2.7 ± 0.5	2.1 ± 0.7
Saberi, 2017[13]	15 ± 3	18 ± 7	48 ± 11	44 ± 13	63 ± 2	63 ± 2	-	-
Wasserstrum, 2019[49]	-	-	-	-	60 ± 14	59 ± 13	2.0 ± 0.7	-
Physical exercise	**N/E**		**−4.6 (−8.9, −0.31)***		**0.3 (−0.6, 1.1)**		**−0.6 (−1.0, −0.2)†**	
All	**−51.7 (−55.8, −47.6)†**		**−77.6 (−104.5, −50.7)†**		**−3.2 (−4.5, −1.8)†**		**−1.06 (−1.3, −0.9)†**	

Note: Data are expressed as mean (±SD) for each individual study. Functional capacity is expressed in mL/kg/min of VO2max unless different units are specified for those reporting maximum Watts or minutes lasted. For each group of therapies, mean difference from pre to post treatment (95% CI) as extracted from meta-analysis are indicated in bold numbers. Age is reported in years. Subscripts shown together with the year of the studies indicate that there was more than one group with different therapies in the trial. Corresponding groups for the original trial can be identified regarding the treatment indicated for each. Grey rows summarize the information of the corresponding therapies shown above each and the name found in bold letters corresponds to the name of the group of medicines or invasive therapy.

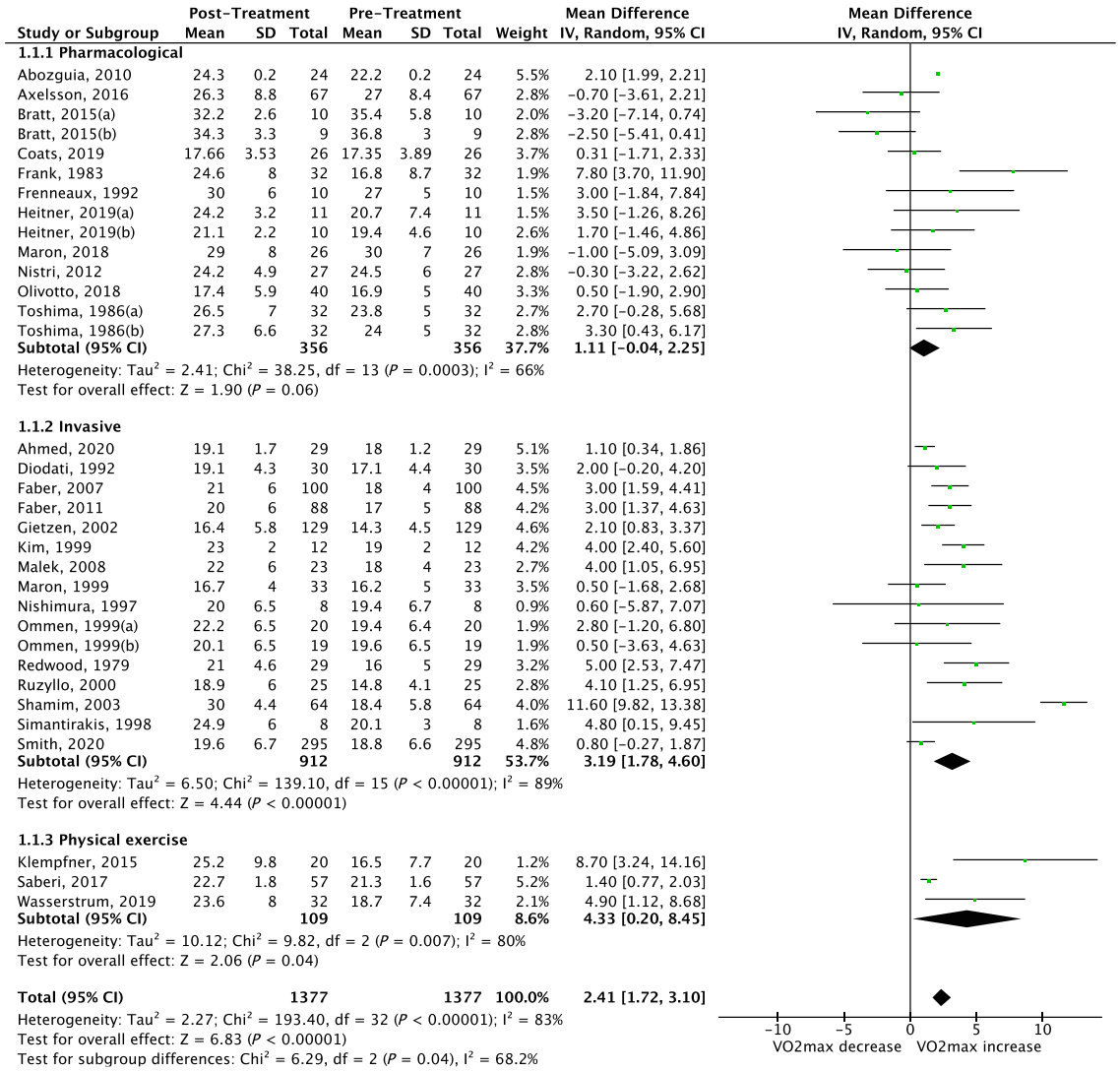
Abbreviations: %W, percentage of women in the study group; VO2max, maximal oxygen consumption; LVOT, left ventricular outflow tract gradient; LVEF%; left ventricular ejection fraction; NYHA, New York Heart Association symptomatic score; ARA, angiotensin II receptor antagonists; Pharmacol., pharmacological therapies; BB, beta-blockers; N/E, not estimable.

*$P < 0.05$.

†$P < 0.001$.

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Figure 2 Meta-analysis of the effect of pharmacological agents, invasive therapies, and physical exercise on VO2max. CI, confidence interval; IV, inverse variance; SD, standard deviation.



vs. 2.43; 95% CI: 0.44, 4.42 vs. 1.10; 95% CI: 0.41, 1.79; respectively), with no difference between the last two.

Studies using physical exercise showed the highest increase in VO2max in 109 patients, leading to an average increase of 4.33 mL/kg/min (95% CI: 0.20, 8.45). Absolute increase ranged from 1.4 to 8.7 mL/kg/min and relative increase from 7% to 53%. Between-group differences were statistically significant when compared with pharmacological and invasive therapies ($P = 0.04$).

Further analyses were performed to elucidate differences between patients with and without resting LVOT gradient (*Figure S3*). Six trials reported data for resting non-obstructive patients, whereas 23 studies did so for 27 obstructive groups. Patients with LVOTO at rest improved their functional capacity to a greater extent than those without resting LVOTO considering all treatment options together (2.82; 95% CI: 1.97, 3.67 vs. 1.18; 95% CI: 0.62, 1.74; $P < 0.01$).

Resting and peak LVOT gradient

The effect of pharmacological therapies on resting LVOT gradient in obstructive patients could not be estimated because data from a single study was available, in which a significant reduction was achieved with mavacamten (−47.9 mmHg, 95% CI: −70.0, −25.9; $P < 0.01$). Invasive therapies also achieved a significant average reduction of −51.8 mmHg (95% CI: −56.0, −47.6; $P < 0.01$), which ranged from −21 to −68 mmHg, and a relative reduction between −26% and

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−98% of the baseline obstruction (*Figure 3*). No significant differences were observed among the three invasive procedures (P = 0.20). The effect of physical exercise on resting LVOT gradient could not be estimated because only one study with non-obstructive patients offered pre- and post-treatment data.

Peak LVOT gradient was also reduced with all three major therapies (*Figure S4*). Pharmacological therapies allowed an average reduction of −49.5 mmHg (95% CI: −78.0, −21.0), which ranged from −84 to −25 mmHg (−29% to −82% of the baseline gradient). Among medicines, beta-blockers induced a significant reduction of 42.0 mmHg (95% CI: −55.4, −28.6; $P < 0.01$), whereas the overall effect of mavacamten (mavacamten and mavacamten plus beta-blocker groups) did not reach significance, although mavacamten alone did (−84.0 mmHg; 95% CI: −114.5, −53.5; $P < 0.01$).

Invasive therapies also promoted an average reduction in peak LVOT gradient of −92.9 mmHg (95% CI: −104.7, −81.1; $P < 0.01$), which ranged from −135 to −53 mmHg (−56% to −92% of the baseline gradient). Significant differences were found between alcohol septal ablation and pacing (−99.8; 95% CI: −110.1, −89.5 vs. −64.2; 95% CI: −86.4, −41.9, respectively; P = 0.004), whereas no data was available for surgical myectomy.

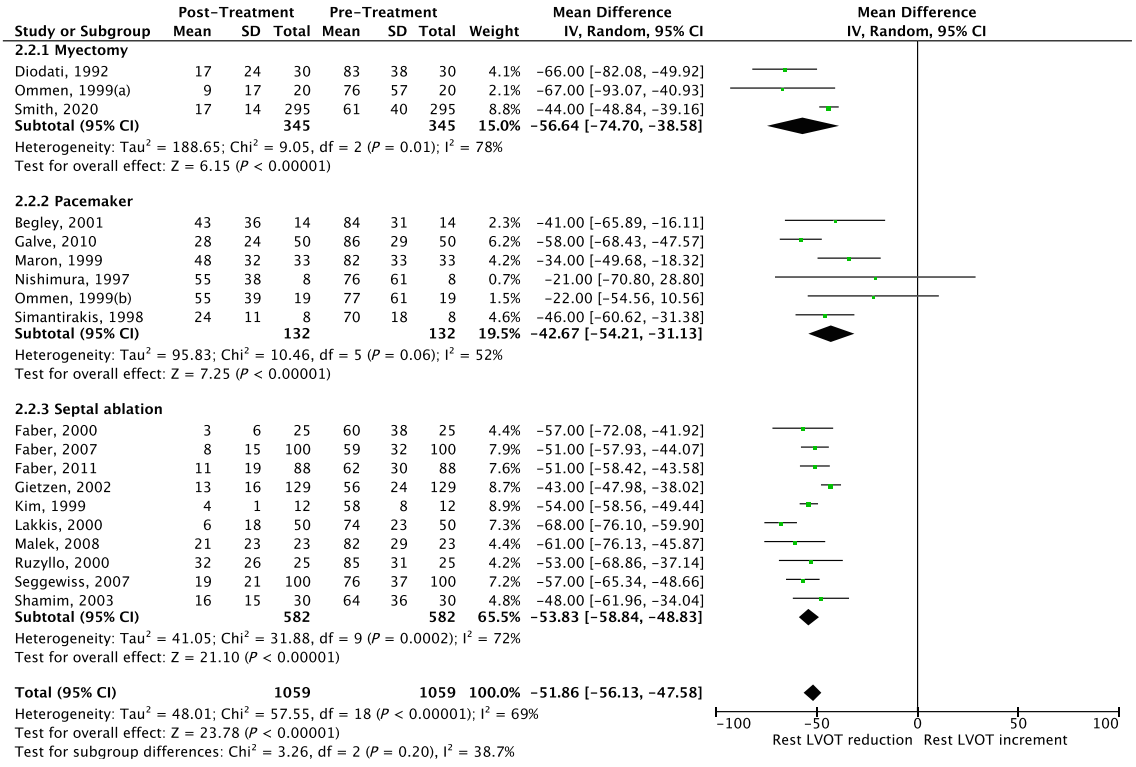
Physical exercise also showed a very mild but significant reduction of this parameter (−4.6; 95% CI: −8.9, −0.31; $P < 0.05$). Overall reduction of all therapies was −77.6 mmHg (95% CI: −104.5, −50.7; $P < 0.01$) and significant between-group differences were found. Invasive therapies allowed a greater reduction than drugs and physical exercise ($P < 0.01$), whereas drugs also showed greater effect than training ($P < 0.01$).

Left ventricular ejection fraction

LVEF% was significantly reduced considering all pharmacological therapies together (−2.5; 95% CI: −4.8, −0.3; $P < 0.05$). Absolute reduction ranged from −15% to 1%. No significant differences were found among drugs; however, angiotensin II receptor antagonists and calcium channel blockers did not produce a significant reduction (−1.8; 95% CI: −3.9, 0.3; and 0.1; 95% CI: −2.2, 2.4, respectively), but antianginals and mavacamten did (−1.0; 95% CI: −1.3, −0.7; $P < 0.01$; and −10.3; 95% CI: −19.2, −1.5; $P < 0.01$). No data was available for amiodarone, beta-blockers and diuretics.

Invasive therapies caused a significant reduction in LVEF% as well (−4.7; 95% CI: −7.2, −2.4; $P < 0.01$). Absolute reduction ranged from −11% to −1%. Significant differences were found between the three procedures ($P < 0.001$) (*Figure S5*). All of them reached significance individually, and pacing

Figure 3 Meta-analysis of the effect of the different invasive options on resting LVOT gradient.



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reduced this parameter to a greater extent than surgical myectomy and alcohol septal ablation (−11.0; 95% CI: −16.0, −6.0 vs. −6.0; 95% CI: −7.1, −4.9 vs. −3.3; 95% CI: −5.4, −1.1, respectively; $P < 0.05$ all). Differences were also significant in the comparison of surgical myectomy and alcohol septal ablation ($P < 0.01$).

Finally, physical exercise did not show any detrimental effect on this parameter (0.3; 95% CI: −0.6, 1.1), and significant differences were found between the three major treatment strategies ($P < 0.001$ pharmacological vs. invasive vs. physical exercise).

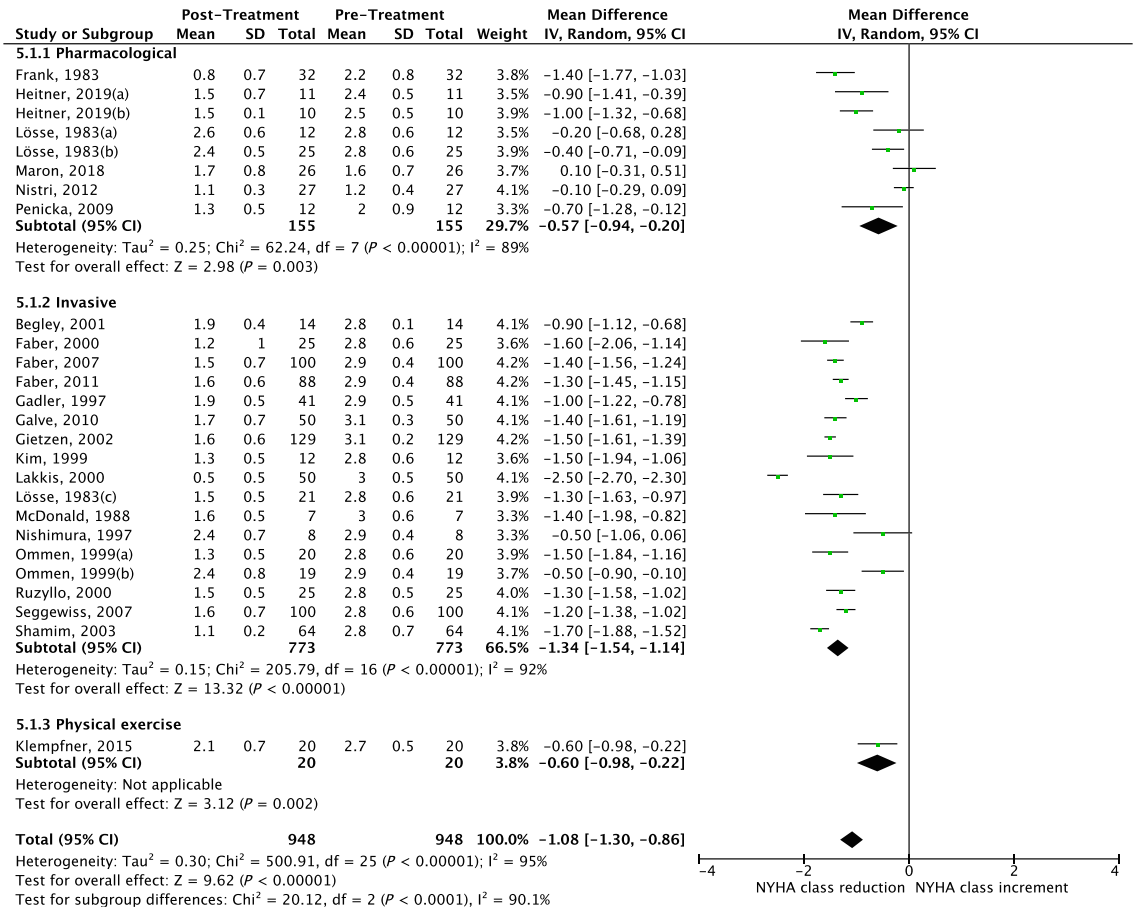
Reported functional NYHA class

Pharmacological therapies had a beneficial effect on symptomatic status. Changes ranged from −1.4 to +0.1 points (−64% to +6% of the baseline values). Mean effect was −0.6 (95% CI: −0.94, −0.2; $P < 0.05$); however, significant differences were found among the individual pharmacological agents ($P < 0.001$). Angiotensin II receptor antagonists, calcium channel blockers and mavacamten yielded significant reductions ($P < 0.05$ all), whereas beta-blockers and diuretics showed no effect (*Figure S6*). Changes could not be estimated for amiodarone and antianginals.

Invasive procedures were also effective improving symptomatic status (−1.3; 95% CI: −1.45, −1.17; $P < 0.001$). The absolute reduction of NYHA ranged from −2.5 to −0.5 points (−83% to −17% of the baseline score). The three strategies showed significant effects individually ($P < 0.001$ all), although between-group differences were observed ($P < 0.001$). Surgical myectomy and alcohol septal ablation had a greater effect than pacing ($P < 0.01$ for the two paired comparisons), whereas no differences were found between the first two (*Figures 4* and *S7*).

Physical exercise reduced this score too (−0.6; 95% CI: −1.0, −0.2; $P < 0.001$), and significant differences were found between the three major strategies ($P < 0.001$). In paired comparisons, physical exercise and pharmacological strategies showed no different effect, whereas invasive procedures improved symptomatic status to a greater extent ($P < 0.001$ for both invasive vs. pharmacological and inva-

Figure 4 Meta-analysis of the effect of pharmacological agents, invasive therapies, and physical exercise on NYHA class for symptomatic status.



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sive vs. physical exercise). Overall improvement with all therapies was ~1 NYHA class (−1.06; 95% CI: −1.3, −0.9; $P < 0.001$).

Other echocardiographic findings

LAVI and resting DBP were not included in the meta-analysis due to the small number of studies available with data for these parameters (n = 5 both). LVEDD (n = 13), peak SBP (n = 8), resting SBP (n = 9), and LVESD (n = 7) were analysed.

Therapies showed an overall positive effect on LVEDD (1.41; 95% CI: 0.07, 2.74; $P < 0.05$). Subgroup analysis was performed comparing drugs, invasive therapies and physical exercise. No significant differences were found (P = 0.12). Nevertheless, only invasive therapies reached significance individually (2.19; 95% CI: 0.43, 3.95; $P < 0.05$), whereas drugs and exercise showed no effect on their own (*Figure S8*). Subgroup analysis could not be performed for LVESD due to the limited number of studies, and no overall effect was found. No differences were found in resting SBP considering all therapies (P = 0.81). Regarding peak SBP, the effect of all therapies considered together did not reach significance (3.55; 95% CI: −6.70, 13.79; P = 0.50); however, a subgroup analysis was carried out distinguishing beta-blockers from other strategies and significant differences were found ($P < 0.0001$). Beta-blockers caused a reduction in peak SBP (−15.49; 95% CI: −23.99, −6.99; $P < 0.001$), whereas other therapies increased its value (14.76; 95% CI: 7.02, 13.79; $P < 0.001$).

Discussion

There is no specific treatment for patients with HCM which has been demonstrated to modify disease expression or its clinical course. The most commonly used drugs have an impact on the reduction of the LVOT gradient, on the improvement in functional class reported but not on the exercise capacity measured in VO2max. Only invasive septal reduction therapies significantly modify these three parameters. Mavacamten, a new selective myosin inhibitor shows an action profile similar to the invasive procedures.

This is the first systematic review of the different therapeutic tools used to treat this disease with the objective of evaluating their effects on different variables (mainly physical exercise capacity, LVOT gradient and functional class). For this, we analysed 41 publications and a total of 1830 patients who received medical treatment, underwent invasive therapies (pacemaker implantation, surgical myectomy or alcohol septal ablation) or followed a structured physical exercise programme.

Functional capacity

Functional capacity is reduced in more than 80% of HCM patients.[50,51] In these patients, VO2max analysis allows for an objective assessment of the exercise capacity.[52] In the study by Frenneaux et al.,[51] HCM patients showed a VO2max of 28.1 ± 7.5 mL/kg/min, whereas healthy individuals of the same age and gender ranged from 39 to 68 mL/kg/min. In our review, considering the pre-treatment values, 88.5% of patients showed a reduced functional capacity with VO2max below the threshold of 7 MET (24.5 mL/kg/min) and the average VO2max was 20.0 ± 3.0 mL/kg/min in HCM patients. The pathophysiology of such limitation is complex, with LVOTO, microvascular ischaemia, diastolic dysfunction, and chronotropic incompetence being the most widely recognized involved mechanisms.[2–4]

Despite the wide range of therapies available for HCM patients, in our study, none of the pharmacological agents showed significant benefits on the functional capacity measured by VO2max, with the only exception of calcium channel blockers, where a slight but significant increase in VO2max was observed in the short term. It should be noticed that some studies in which functional capacity was expressed in terms of maximal workload or duration of the test, where there may have been some benefit with pharmacological therapy, were excluded.

In contrast with the results of the traditional medication, a recently published trial with a novel drug called Mavacamten (EXPLORER-HCM) reported an increase in functional capacity of patients with obstructive HCM.[53] In our analysis, such therapy did not reach statistical significance for maximal VO2 increment, because the group of patients meeting inclusion criteria was relatively small (21 patients).

There is a drug with metabolic cardiomyocyte action, called perhexiline, that has demonstrated to improve functional capacity in symptomatic patients with non-obstructive HCM.[5] However, its use is limited due to hepatic and neurotoxicity. Despite the reported benefits of ranolazine on symptoms of angina,[54] and the suggested role in the prevention of phenotype expression from the mice HCM model,[55] this inhibitor of the late sodium current failed to show benefit on exercise capacity in humans (RESTYLE-HCM) with non-obstructive HCM.[7]

LVOTO is one of the main determinants of exercise capacity in HCM patients. Invasive therapies have shown a significant increase in the functional capacity of these patients. In the subgroup analysis of our study, alcohol septal ablation was the technique which provided the greatest benefit on functional capacity (P = 0.02).

In our study, the 109 patients who were prescribed a structured physical exercise programme reached the highest increase in VO2max (mean increase was 4.33 mL/kg/min), reaching significant differences when compared with the other two groups of therapies.

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Obstruction

It is worth mentioning a recent study conducted with mavacamten, which demonstrated a significant reduction on baseline gradient.[12] In patients with obstruction during exercise, beta-blockers, achieved a significant reduction of the peak LVOT gradient. However, when beta-blockers were used together with mavacamten, part of the benefit was lost probably due to the heart rate limitations observed, because patients using beta-blockers had lower peak heart rates during exercise.[53]

Regarding invasive therapies, all of them reduced significantly LVOTO both at rest and at peak exercise and the benefit was maintained throughout time. There were no differences in the baseline gradient between the different invasive techniques, although there were indeed differences in the provoked gradient, with alcohol septal ablation being the most beneficial.

The results of the influence of physical exercise on obstruction are scarce. In our study, physical exercise reached a slight reduction of the peak gradient.

Reported functional class

HCM treatment has two main objectives: first, sudden cardiac death prevention in high-risk patients via implantation of an ICD[56] and second, the improvement of symptoms. The three therapeutic groups studied here caused a significant improvement of the NYHA functional class, being invasive therapies the most beneficial. This is likely associated to a reduction in the LVOT gradient, as this is a decisive factor in the onset of symptoms in the majority of HCM patients. Among the pharmacological agents, mavacamten stands out as the most beneficial regarding symptoms, which, together with the reduction of the LVOT gradient in patients with obstruction, turns it into a powerful therapeutic tool.

Impact of therapies on left ventricular ejection fraction

Among the echocardiographic parameters of left ventricular function, the most widespread LVEF% was reduced both with drug agents and invasive therapies. No changes were observed in LVEF% after structured physical exercise programme in HCM patients. The greatest impact on LVEF% in HCM has been reported after pacing. When the right ventricle (RV) is stimulated from the apical segments, the usual activation pattern of the heart's electrical system is altered, thus generating ventricular asynchrony, which may lead to decreased LVEF%. In other cardiac conditions, but rarely in HCM, longstanding asynchrony caused by ventricular pacing is associated with an increased risk of hospitalizations due to heart failure.[57]

In vitro and animal models have shown that mutant myosin molecules have a higher activity of the adenosine triphosphatase enzyme (ATPase), greater tension and increased actin sliding velocity; causing the hyperdynamic contraction characteristic of HCM,[58,59] which results in a LVEF% above normal values. Mavacamten, at the dose used in the clinical trials, reduced LVEF% by 10.3%; 95% CI: −19.2, −1.5; $P < 0.05$, relative reduction.[12] This small reduction in the LVEF% from baseline ("normalization") was not associated to any clinical relevant outcome.

New perspectives

The pharmacologic drugs traditionally used for HCM treatment have a limited and sometimes temporary effect. They achieve an improvement in symptoms and a partial reduction in exercise LVOT gradient but they have no significant impact on the exercise capacity measured by VO2max. The emergence of a new class of cardioselective drugs, well tolerated and whose effects are similar to the invasive procedures, provides new hope in the treatment of patients with HCM.

Changes in the patients' lifestyle, such as correcting overweight and physical exercise programmes, have shown a significant improvement both in reported functional class and in objective effort capacity which is more pronounced than with pharmacological agents. For many years, physical exercise was considered prohibited for HCM patients.[14,15] However, the results from recent studies support the current recommendations, which suggest that the promotion of supervised physical exercise results in an improved quality of life for the patients with this condition.[60] Moreover, in a recent meta-analysis from our group including 11 672 HCM patients, the mean VO2max was 22.3 ± 1.1 mL/kg/min (6.4 ± 1.1 MET),[61] which stands right below the classical threshold of functionality of 7 MET. Considering the pooled mean benefit of exercise on functional capacity observed in this study (4.33 mL/kg/min, 1.1 MET), physical training emerges as a non-invasive and non-pharmacological alternative that might potentially help HCM patients achieving a functional state without affecting other echocardiographic parameters such as LVEF%. However, the available exercise protocols are scarce regarding training variables and have focused on cardiorespiratory exercise. Nonetheless, sports physiologists have evidenced greater benefits on functional capacity derived from concurrent training, the combination of cardiorespiratory and resistance training.[62] This is yet to be investigated in HCM patients together with the role of myokines with potential cardioprotective effects which are enhanced with training.[63]

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Limitations

This study has limitations worth mentioning. The main of these is the heterogeneity of the study cohorts regarding the chosen therapies but especially the presence of LVOTO. Some studies did not mention the presence of LVOT gradient either at rest of after exercise or did not provide separated data for sub-cohorts of obstructive and non-obstructive patients. Other studies characterized their cohorts as non-obstructive at rest but did not provide data regarding the development of obstruction with exercise. Another limitation is the limited number of studies and patients that undergone physical exercise protocols.

There is also a limitation related to the outcomes of interest. Some of the studies did not report values for all the included outcomes and 14 of the 47 groups of patients analysed could not be included in the analysis of the effect on functional capacity because data were provided in Watts or duration of the test.

Conclusions

Invasive septal reduction therapies improve symptomatic status, increase functional capacity measured by VO2max and reduce resting and peak LVOT gradients in obstructive HCM patients. Pharmacological agents improve reported NYHA class, but not functional capacity, although promising results are expected from upcoming studies with mavacamten. Structured physical exercise programmes are safe and are also associated with improvements in functional capacity. Therefore, invasive therapies might be considered in obstructive HCM patients, whereas physical exercise emerges as a coadjuvant therapy to improve functional capacity and symptomatic status.

Conflicts of interest

None declared.

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Supporting information

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

Figure S1. Meta-analysis of the effect of **pharmacological agents** on VO2max.
Figure S2. Meta-analysis of the effect of invasive therapies on VO2max.
Figure S3. Meta-analysis of the effect of current therapies on VO2max in patients with obstructive vs. non-obstructive phenotype at rest.
Figure S4. Meta-analysis of the effect of **pharmacological agents**, invasive therapies, and physical exercise on peak **LVOTO**.
Figure S5. Meta-analysis of the effect of invasive therapies on LVEF%.
Figure S6. Meta-analysis of the effect of **pharmacological agents** on NYHA class for symptomatic status.
Figure S7. Meta-analysis of the effect of invasive therapies on NYHA class for symptomatic status.
Figure S8. Meta-analysis of the effect of **pharmacological agents**, invasive therapies, and physical exercise on peak LVEDD.

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