Pacing for hypertrophic obstructive cardiomyopathy: an update and future directions

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PACING FOR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: AN UPDATE AND FUTURE DIRECTIONS

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ABSTRACT (222 words)

In hypertrophic cardiomyopathy (HCM) patients with symptoms caused by left ventricular outflow tract obstruction (LVOTO), treatment options include negative inotropic drugs, myectomy, septal alcohol ablation and AV sequential pacing with or without implantable cardioverter defibrillator (ICD). In spite of its relative simplicity and promising results pacing is rarely used even in elderly patients. In this review the current evidence of beneficial effects of AV sequential pacing in observational, randomised studies and long and very long term follow up are given in view of present guidelines recommendations. These studies indicate that AV sequential pacing improves symptoms and quality of life through decreases in LVOTO, systolic anterior movement (SAM) and mitral regurgitation. Effects on morbidity and mortality are lacking. We describe the mechanisms of action, the prerequisites for successful pacing and practical advice on the how to optimise this therapy. Moreover, role of the ICD for primary and secondary prevention is discussed with reference to the ESC HCM guidelines and risk score for sudden cardiac death. In summary, AV sequential pacing for HOCM is underused in clinical practise despite evidence from two randomised controlled studies. We want to highlight the current evidence and new interest for this therapy. AV sequential pacing in HOCM will be compared to TASH in a planned randomised controlled study and in an ongoing study comparing CRT to AAI pacing.

Key Words (6)

Hypertrophic obstructive cardiomyopathy, left ventricular outflow tract obstruction, cardiac pacing, exercise tolerance, quality of life, prognosis.

INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HOCM) has always fascinated cardiologists because it combines genetic determinants, complex anatomical and dynamic mechanisms, specific risks and original treatments[1]. In the late 1980s[2]-early 90s[3-6] observational studies indicated that right ventricular (RV) apical pacing with full ventricular capture limited the dynamic obstruction of the left ventricular outflow tract (LVOT) and reduced the gradient. But the enthusiasm fell when three small randomized crossover studies failed to demonstrate that pacing therapy was superior to control for exercise capacity in severely symptomatic HOCM patients [7-9] even though LVOTO was reduced. These results may have been negatively influenced by the fact that pacing therapy delivery was not universally optimized in these studies. Later findings indicate that the effectiveness of pacing can greatly improve by individual optimization[10]. Moreover, the favourable results from long or very long-term observational studies[11-14] and the increasing use of implantable cardioverter defibrillators (ICD) for prevention of arrhythmic death in HOCM patients[15] call for a reassessment of this simple therapy and of its place in guidelines. The purpose of this review article is to put the pacing therapy in perspective with other treatments of LVOT obstruction and to consider the current place of implantable cardioverter defibrillator in HOCM patients.

TREATMENT MODALITIES FOR LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

In HCM patients with symptoms caused by LVOTO, treatment options include negative inotropic drugs[16-18], surgery[19], septal alcohol ablation[20] and AV sequential pacing. Beta-blockers[16] is the first choice, followed by verapamil[17] if beta-blockers are not tolerated. Both reduce symptoms and improve exercise tolerance by reducing LVOTO. Disopyramide[18] can be combined with beta-blockers if an insufficient improvement is achieved. Approximately 60–70% of patients improve by medical therapy alone[15] and these drug therapies all were given Class I level of evidence B in the 2014 ESC / HCM guidelines despite the fact that they mostly are based on observational studies[15]. For patients with drug-refractory symptoms, open chest surgery (septal myectomy) or septal alcohol ablation (TASH) performed through transcutaneous coronary intervention or AV sequential pacing are therapeutic options. They all reduce LVOTO and improve functional status with more profound effects by myectomy and TASH. Septal thickening is only reduced by myectomy and TASH.

Myectomy and TASH has not been studied in RCT. Thus, no RCTs to date compared myectomy or TASH to control therapy and none myectomy to TASH or TASH to AV sequential pacing. In contrast, three RCTs compare AV sequential pacing to control[7-9]. Nonetheless, myectomy is considered the gold standard for HOCM patients

with refractory symptoms and is more commonly adopted in the US. In contrast, TASH is more commonly performed in Europe. None of these interventions is free from risks and complications. Clinical results and risk minimization depend on proper patient selection and the performance at highly experienced centres[15]. Myectomy has a surgical mortality rate of 3-4 % and carries a risk of ventricular septal defects (VSD), aortic incompetence and mitral valve leaflet damage. The mortality risk with TASH is lower and was recently reported to be 1- 1.3 %[21,22]. TASH also carries a risk for VSD when the septal thickness is ≤ 15 mm. Moreover, un-controlled myocardial infarction and ventricular fibrillation (VF) may occur if alcohol leaks out into left anterior descending coronary artery (LAD). Importantly, these interventions can damage intraventricular conduction: myectomy can induce RBBB and TASH ~~may induce~~ LBBB with the potential risk for AV block. TASH in particular is associated with risk of AV-block requiring a permanent pacemaker implantation reported to be 7%[21] with the greatest risk in patients with pre-existing conduction disease. Later studies in real life confirm that this risk may be even higher. In a Scandinavian TASH registry[23] high degree AV block evolved during the procedure in 36% and post procedural in 23% of the patients. Ten-year survival was, however, very favourable and comparable to an age and sex matched population and hospital mortality was only 0.3%.

Even though immediate results on LVOTO are more profound by TASH than by AV sequential pacing long term comparison with 7- 8 years follow up show a similar reduction in LVOTO [24]. These results indicate that AV sequential pacing should not be forgotten as a first step. This is particularly the case in grown up or elderly patients[11] and in those with contraindications or unwilling to undergo any of these interventions. Still pacing has not been widely adopted even in elderly patients.

THE ICD: A CENTRAL PLACE IN ELECTRICAL HCM TREATMENT?

Sudden cardiac death (SCD) due to unpredictable ventricular tachyarrhythmia remains the most feared complication in HCM. Young asymptomatic patients under the age of 35, including competitive athletes, are at higher risk[25]. The implantable cardioverter defibrillator (ICD) is the only treatment effective in preventing SCD in high-risk patients. There is large consensus that HCM patients with prior documented cardiac arrest, ventricular fibrillation (VF), or hemodynamically significant ventricular tachycardia (VT) are at very high risk of subsequent lethal cardiac arrhythmias (reported to be 10% per year)[26-27] and should receive an ICD (Class I, level of evidence B)[15, 25].

On the other hand, primary prophylaxis remains a difficult challenge because the risk-benefit ratio of the ICD may seem modest when weighing the relatively low rate of appropriate therapies in implanted patients (3-4% per

year) and the relatively high rate of complications (4% per year) and of inappropriate shocks (20-25%)[26-28]. Until recently, the identification of individuals at high risk of SCD was based on a small number of established risk markers[25]. Risk algorithms based on risk markers only discriminate modestly between high- and low-risk patients[29]. Recently, a new SCD risk prediction model was developed and validated from a multicentre, longitudinal cohort study of 3675 patients[30]. Based on this the 2014 ESC / HCM guidelines recommend that all HCM patients undergo a standardized clinical evaluation that records a pre-defined set of prognostic variables, which are then used to estimate the 5-year risk of SCD using this HCM Risk-SCD model[15]. In addition to some of the risk markers already considered (family history of sudden cardiac death, maximum LV wall thickness, unexplained syncope, NSVT), the model introduces new variables: age, left atrial diameter and LV outflow gradient. LVOT obstruction is thus recognised as independent risk factor that may significantly contribute at increasing the risk score. Based on individual score, patients are classified in three categories: low risk (5-year risk<4%), intermediate risk (4-6%) and high risk (≥6%). Guidelines propose that prophylactic ICD implantation should be considered in high-risk patients (Class IIa), may be considered in intermediate-risk patients (Class IIb) and is not recommended in low-risk patients (Class III)[15]. The 2014 ESC / HCM guidelines also specify that patients must be informed of the risk of inappropriate shocks, implant complications and the social, occupational, and driving implications of the device[15] prior to ICD implantation. In initially non-implanted patients a reassessment of SCD risk is recommended on a periodic basis (every 12-24 months).

Device selection - practical aspects.

In HCM patients indicated for an ICD, guidelines discuss the possibility of implanting a single-, dual- or triple-chamber unit according to patient needs while ensuring an optimal risk-benefit ratio in each case[15]. If the only therapeutic objective is protection against the risk of life-threatening ventricular tachyarrhythmia, a single ventricular lead is enough since the use of a dual- compared to a single-chamber device was associated with a higher risk of device-related complications without improving clinical outcomes, [31].

Contrary to what previously presumed[32], patients with HCM do not have higher defibrillation thresholds than other ICD populations[33] [33]. When a single-chamber ICD is implantedcurrent clinical evidence indicate the S-ICD is safe and effective in patients with HCM[34-36] and support the 2014 ESC / HCM guidelines proposal that S-ICD may be considered in HCM patients who do not have an indication for pacing (Class IIb, level of evidence C)[15]. S-ICD could also be an option for high-risk HOCM patients treated by septal reduction intervention but scientific evidence is lacking.

In HCM patients indicated for an ICD, the choice of a dual-chamber ICD remains advised in patients in sinus rhythm with an indication for pacing, in patients with resting or provocable LVOT gradient ≥50 mm Hg in sinus rhythm and with drug-refractory symptoms, to reduce the LVOTO or to facilitate medical treatment with ß-blockers and/or verapamil (Class IIb level of evidence C)[15]but taking into account the much higher risk of perioperative complications than with single-chamber ICD[37]

PACING THERAPY FOR HOCM

How does it work?

The mechanism of action by which AV sequential pacing or short AV delay DDD pacing limits outflow tract narrowing and dynamic obstruction are not completely elucidated. Hypotheses to explain the beneficial effects include: 1) Negative inotropic effect and reduced hyper-contractility of the left ventricle 2) Asynchronous septal activation and delayed septal thickening, 3) Limitation of abnormal mitral valve motion, 4) Interaction with left ventricular filling, and 5) Ventricular remodelling.

1) Reduced hyper-contractility:

Most HCM patients have normal or supra-normal left ventricular ejection fraction (LVEF) in spite of reduced myocardial shortening velocities[38,39]. It is classically recognized that patients with LVOTO have higher LVEF and that paradoxically LVEF is increasingly higher as the obstruction is more severe[40]. LVOTO is a dynamic process which depends largely on cardiac contractility and loading conditions. Augmentation of cardiac contractility increases LVOTO, since a more vigorous contraction is more likely to result in contact between the septum and mitral leaflets. RV pacing reduces hyper-contractility by inducing asynchronous ventricular activation and contraction.

HCM patients have abnormal response to RV pacing compared to normal hearts. Acute hemodynamic studies with PV loops analysis have shown that AV sequential pacing shifts the end-systolic pressure-volume relation (ESPVR) rightward increasing LV end-systolic volume substantially, reduces intra-cavitary pressure gradients, limits cavity obliteration and lowers total chamber workload[41]. Evidence for a net negative contractile effect is supported by a significant decline in LV dP/dtmax[41,42]. These effects are present in all HCM patients but in those with LVOTO, a significant reduction in LVOT gradient is observed and shown to be the direct consequence of the negative contractile effect. Global effects of pacing can be compared with those of negative inotropic drugs like beta-blockers, verapamil and in particular disopyramide. Net results of pacing and such drugs could be additive. However, it is not clear whether these acute haemodynamic changes persist over time

and contribute to the long-term benefit of AV sequential pacing.

2) Delayed septal activation and thickening:

RV pre-excitation profoundly alters timing and dynamics of ventricular contraction. Provided complete ventricular capture is achieved, pacing at the RV apex reverses the activation sequence of the left ventricle. Instead of starting at the basal septum, it begins in the apical region. The delayed thickening of the already bulging proximal septum limits outflow tract narrowing and contributes to prevent dynamic obstruction as demonstrated by Doppler-echocardiographic studies[43-44]. However, it must be noted that septal contraction is a relatively late systolic event while systolic anterior motion (SAM) of the mitral valve and mitral valve to septum contact occurs early in systole[45]. Consequently, the pacing-induced paradoxical septal motion is probably not the main favourable mechanism of pacing.

3) Limitation of abnormal mitral valve motion

LVOTO is mainly caused by SAM of the mitral valve towards the hypertrophied septum. The drag forces across the mitral valve pull the leaflets anteriorly to the basal septum[45] and lead to both LVOTO and mal-coaptation of the mitral valve leaflets which may result in mitral insufficiency

AV sequential pacing significantly reduces the severity of SAM both acutely and long-term. After individually optimised AV sequential pacing mean severity of SAM (graded 0-4) dropped from 3·1$\pm$0·8 to 1.5$\pm$1.3 with a strong correlation between individual changes in SAM grade and LVOT gradient[46]. The LVOT gradient decreased on average by 46% acutely and 67% after 12-14 months of pacing. A significant reduction in mitral regurgitation (MR) severity was also observed particularly in patients with baseline MR $\geq$2. In such patients the MR jet/left atrial area ratio decreased by a mean of 45% with DDD pacing. A possible explanation to these beneficial effects is the early activation of the anterior papillary muscle by pacing pulling the leaflet out of the left ventricular outflow tract which thus reduces SAM by mitigating excess slack.

4) Interaction with left ventricular filling

Diastolic dysfunction with impaired left ventricular filling is commonly observed in HCM and contributes largely to symptoms[1, 40.] Rapid or early diastolic filling is reduced whereas, the atrial contribution to ventricular filling is increased in HCM, on average the double of normal hearts[47,48]. This balance may be disturbed by AV sequential pacing [42,49] in particular if too short AV intervals are programmed. Too short AV delays create left AV dyssynchrony which reduces or even suppresses the atrial contribution to LV filling. Preserving optimal LV filling through a fully efficient left atrial systole is crucial for getting optimal result by pacing.

5) Reverse remodelling

There is no evidence to support that reverse myocardial remodelling contributes to the long-term beneficial effects of pacing therapy. In long-term studies with a follow-up time of up to 18 years [11-14] no significant decrease in septal thickness or increase in cavity dimensions was observed. In contrast, a modest but significant, 8-10% decline in LVEF has been documented in two studies[12,13] in concert with previous observations in anti-bradycardia-paced patients[50] and patients with primary preventive ICDs[51]. Over very long observation times this may mean that some patients paced for HOCM may develop HF. But since the mean age of studied patients[12,13] was relatively high in these studies (59-62 years), it is difficult to assess to which extent this decrease in LVEF was explained by the natural history of the disease or by a possible negative effect of pacing. In summary AV sequential pacing does not decrease of septal thickening but does reduce LVOT gradient, SAM and mitral regurgitation.

Current clinical evidence and recommendations

In initial observational studies [3-6,52,53] (**Table 1**) AV sequential pacing reduced LVOT gradients and reported positive but no consistent effects on symptoms and quality of life (**Table 1**). Thereafter, three small randomised, placebo-controlled crossover studies of DDD versus AAI pacing were performed[7-9,54] **(Table 2).** They all included patients with drug refractory symptoms and with a LVOT gradient of 30-50 mmHg at rest or during provocation. The outcome measures were LVOT gradient, quality of life, exercise tolerance and Peak$V0_2$ but the studies were not dimensioned for morbidity or mortality. The majority of patients experienced improvements in LVOT gradients within 3 months of active pacing with progressive improvements over the next 9 months of active pacing accompanied with improvements in quality or life and or NYHA class. Surprisingly, in ~~one of these:~~ the PIC-study even pacemaker implantation without activation of AV sequential pacing lowered the LVOTO but subsequent activation of pacing in the same patients showed further reductions. Moreover, there were significant improvements in some quality of life dimensions also during the inactive pacing phase although significantly greater improvements in all areas of quality of life were achieved during AV sequential pacing[55,56]. These improvements emphasize the placebo effect of device implantation which is now widely recognized meaning that there is no possibility to prove a benefit of a given therapy including device therapy without a control group.

In the PIC study exercise tolerance was only improved in those with initial severe impairment[8]. In the MPATHY trial similar observations were made. No improvements in exercise time or Peak VO_2 were observed during the randomised phase of this study but during the un-blinded 12 months follow up with AV sequential pacing the patients with lower baseline exercise time experienced an improvement by at least 10% [9]. The MPATHY authors

retrospectively defined a response to pacing as the combination of improvement > 1 NYHA class, > 10% exercise time and ≥10 points in the Minnesota Living with Heart failure score. By this strict definition only 6 of 48 randomised patients were responders. These results may have contributed to the negative interpretation of study results and the concept of AV sequential pacing as a treatment alternative.

Looking at the responders in the MPATHY study they were significantly older 69±4 years than non-responders with a mean age 51±16 years and had a lower baseline exercise time (9.7±3.4 min) and Peak $V0_2$ (12.4 ml/kg/min) than non-responders (17.1±5.5 ml/kg/min) p<0.0005). The authors therefore concluded that DDD pacing could be an option for patients > 65 years if they reject other therapeutic options[9].

Despite these inconsistent short term results, it is noteworthy that long term studies all report sustained effects of pacing. Such sustained effects were first demonstrated in the 3 year longitudinal follow up of the PIC study[54] and in very long-term observational studies with follow up ranging between 5- 21.8 years[12-14] **(Table 3)**. In one of these studies l 5 year longevity was remarkably high[13] and the need for septal interventions low suggesting a therapeutic role much larger than presently adopted. Moreover, if adjunct therapies such as AV nodal ablation were given to patients with insufficient RV capture the need for more advanced therapies such as TASH or myectomy was very small[13].

Recommendations in ESC/EHRA/HCM guidelines

The 2013 ESC/EHRA guidelines for cardiac pacing and CRT[57] summarize that there is sufficient evidence to suggest that permanent AV sequential pacing with short AV-delay can reduce outflow tract obstruction and improve symptoms in selected patients who are unsuitable or unwilling to consider invasive septal reduction therapies and give it a Class IIb level of evidence B. For those who are at high risk of developing AV block following septal myectomy or alcohol ablation the recommendation is Class IIb level of evidence C. These guidelines also add that in case systolic dysfunction and symptoms of heart failure are developed a CRT may be considered despite absence of randomized trials.

In the 2014 ESC / HCM guidelines [15] the level of evidence for AV sequential pacing was C despite the evidence from two randomised trials[8,9] and a Cochrane analysis[58]. The latter recognises that AV sequential pacing induces benefits for LVOTO reductions and improvements in quality of life and NYHA class but found the evidence for improvements in exercise tolerance morbidity, mortality and cost-effectiveness based on two RCTs[8-9] was insufficient.

Individual optimization of AV sequential pacing

The original concept was based on pre-excitation of the left ventricle by stimulating the right ventricular apex, achieving complete ventricular capture by programming a short AV delay during VDD / DDD stimulation to over-ride intrinsic conduction[2-4]. With this stimulation pattern, observational and randomized studies showed huge inter-individual variations in effects of acute and chronic pacing indicating a clear need for individual optimization. In practice, optimization should focus on three main points: ventricular stimulation site, ventricular capture and left AV synchrony.

1) Optimal right ventricular pacing site

The crucial importance of the RV pacing site for reducing LVOTO was shown by Gadler[59] in an acute hemodynamic study comparing the effects of RV apical and RV septal pacing. Apical pacing reduced the LVOT gradient in all patients with a mean decrease from 96±33 mmHg at baseline to 38±24 mmHg with pacing. In contrast, the gradient did not change during septal pacing, remaining stable at 93±44 mm Hg (**Figure 1).** Hence, it is advisable to carefully place the lead tip at the apex or extreme apex of the right ventricle and check the position during implantation by fluoroscopy in right anterior oblique view or in sagittal view. It is important to emphasize this since reaching a true apical position may be challenging to obtain in HCM patients because of hypertrophied RV trabeculae and in some cases, RV apical obliteration[60].

More recently, biventricular pacing (BIV) or CRT using two transvenous leads, one placed at the RV apex and the other at the LV lateral wall was proposed in a dual objective to enhance the effect of RV apical pacing on LVOT obstruction and to better preserve LV function by correcting RV pacing-induced radial dyssynchrony[61,62]. In a preliminary report of only 9 patients Berruezo et al showed that BIV pacing reduced LVOT gradient from 74±23 mmHg at baseline to 50±27 mmHg acutely, while RV pacing had no effect (69±25 mmHg)[62]. The gradient continued to decrease during follow-up reaching 28±17 mmHg at one year to a similar magnitude already observed in several studies with chronic RV pacing[12-14]. Interestingly, gradient reduction was associated with reduced septum peak longitudinal displacement and earlier displacement of the lateral wall indicating improved ventricular synchrony. These apparently positive effects of chronic BIV pacing on LV structure (also including significant decrease in wall thickness and LV mass) should be interpreted very cautiously in view of the very few patients in the study. Finally, it should be noted that in this preliminary experiment, LV lead implantation failed in 3 patients, or 25% of the cases indicating that transvenous LV lead placement may be challenging in hypertrophied hyperkinetic hearts. Thus to date, there is no reason to believe that CRT is superior to RV pacing when AV sequential pacing is planned to HOCM patients.

2) *Full ventricular capture*

In spite of the programming of an « optimal » AV delay, incomplete ventricular capture with fusion between intrinsic conduction and paced activation is often observed (58% of patients for Berruezo et al[63]) and associated with worse response to pacing. In the series of Berruezo[63], the mean LVOT gradient decreased from 80±25 mmHg to 10±17 mmHg at end follow-up in patients without fusion while there were no significant changes (from 81±25 mmHg to 58±32 mmHg) in patients with fusion. Patients with fusion also did not improve in symptoms. Therefore, full ventricular capture should routinely be sought and checked peri-operatively. It is recommended to use temporary pacing in VOO mode at 20 bpm above the intrinsic rate to validate RV apical pacing and full ventricular capture on 12-lead surface ECG. RV apical pacing is defined by LBBB pattern and left superior axis deviation on paced QRS complexes. Full capture is identified as the widest paced QRS duration. This perioperative paced QRS duration and morphology will serve as reference of full ventricular capture during follow-up.

3) Optimal left AV synchrony

Full ventricular capture is best achieved by programming short AV delay during VDD/DDD pacing. In practice, this may be difficult since the AV-delay on the one hand must be short enough to fully capture the left ventricle from the RV apex, but on the other hand long enough to obtain a maximum atrial contribution to the LV filling. Beyond the critical role of the atrial contribution to preserve optimal LV filling, there is a strong interaction between LVOTO and left AV synchrony probably dependent on changes in loading conditions. This is well illustrated by ancient observations of patients with HOCM and high-degree AV block[64,65] showing major cycle-to-cycle variations in LVOT gradient according to temporal variations in AV timing. Briefly, the gradient decreases or is even abolished on ventricular cycles preceded by a P wave with an appropriate AV interval and conversely increases on cycles without correctly synchronised P wave (**Figure 2**).

Another proof of the subtle interaction between AV synchrony and LVOTO is provided by studies aimed to determine the optimal AV delay during VDD/DDD pacing. In a study by Sadoul et al[66], the optimal AV delay defined as that which provided the maximal decrease in LVOT gradient without reducing stroke volume, ranged between 47 and 87 mm in different patients. Interestingly, further shortening of the AV delay below the "optimal" value resulted in a paradoxical re-increase of the gradient.

In clinical practice, determining the optimal AV delay, which ensures complete ventricular capture without altering the LV filling can be a difficult challenge, depending on the electro-mechanical characteristics of each patient. It can be relatively easy in patients with long (around 10% of patients[67]) or normal PR interval.

Conversely, it is much more challenging in case of short PR interval commonly seen in the young and in certain non-sarcomeric forms of HCM[15] as well as in older patients with inter-atrial conduction block delaying the left atrial activation[68,69]. Therefore to optimise AV-delay a step-by-step procedure may be recommended.

a) *During implantation*, the implanter can try to optimize the atrial lead position by looking for the latest activation site using intra-cardiac ECG mapping during spontaneous sinus rhythm (**Figure 3).** Delaying atrial detection enables programming of shorter AV delays to capture the ventricle in the VDD mode without compromising mechanical AV synchrony.

b) *Before discharge*, AV optimisation procedure should be carried out in each patient using 12-lead surface ECG and Doppler-echocardiography to determine transmitral flow. Optimal sensed and paced AV delays are determined during spontaneous atrial rhythm VDD (basic pacing rate programmed 10 bpm below spontaneous rate) then during paced atrial rhythm DDD pacing (overdrive pacing at 10 bpm above spontaneous rate) with step by step decrease in programmed AV delay value until ventricular fusion occurs. The optimal «electrical » AV delay is defined as the longest value that preserves full ventricular capture. Trans-mitral blood flow analysis allows to verify that the LV filling time is not excessively shortened (>50% of RR cycle) and that atrial contribution is preserved with a non-truncated A wave.

c) *During follow-up* in patients not improved functionally and with evidence of suboptimal AV-synchrony, several interventions can be discussed. The simplest is an attempt of pharmacological prolongation of AV conduction time by increasing the doses of negative inotropic drugs, beta-blockers and verapamil in particular or by combining them. Rhythm support provided by pacing allows a good tolerance to such changes in most cases.

d) In selected patients with refractory symptoms, *radiofrequency ablation*[68,69] or *modification*[70] of AV node conduction can be proposed. The advantage is to allow programming of a truly optimal electromechanical AV delay in each patient with full and permanent ventricular capture. The main limitation is the creation of pacemaker dependency, which is a concern in particular in younger patients. The value of this adjunct therapy was recently recognized by Berruezo et al[63] in non-responder patients with ECG fusion. AV node ablation further reduced LVOT gradient and significantly improved functional capacity and quality of life.

e) Patients with inter-atrial conduction delay might benefit from *bi-atrial* DDD pacing with implantation of an additional coronary sinus lead to sense and pace the left atrium[10]. It may allow anticipation of the left atrial contraction by the time interval corresponding to the interatrial conduction delay and program short AV delay without impairing left ventricular filling. The risk/benefit ratio of this technique needs to be further assessed. By applying this step-by-step optimization program in a prospective series of patients initial non-responders

derived similar long-term benefit of pacing therapy as responders[10]. In this study non-responders differed from responders at baseline by a lower age, higher LVOT gradient, shorter PR interval (115±15 ms vs 143±23 ms ; P=0.015) and shorter programmed AV delay for full ventricular capture (43±19 vs 92±20 ms ; P=0.001).

FUTURES DIRECTIONS

In view of these promising results we need stronger clinical evidence to validate the clinical benefit of HOCM electrical therapy, determine the optimal pacing configuration, demonstrate a favourable risk / benefit ratio, and identify subgroups of patients that can benefit most from the therapy.

These are the subjects of two ongoing or upcoming randomized trials: The « Triple Chamber Pacing in Hypertrophic Obstructive Cardiomyopathy Patients » -TRICHAMPION study (***ClinicalTrials.gov: NCT01614717***) is a prospective, randomized, single-blinded and multi-center trial which aims to evaluate the benefit of CRT in severely symptomatic HOCM patients, all implanted with a Cardiac Resynchronization Therapy - Pacing (CRT-P) device. The comparison will be optimized CRT pacing including the possibility of AV node ablation in case of fusion (active group) versus back-up AAI pacing (control group). The primary endpoint of the study is symptomatic improvement at 12 months post-implant defined as combined improvement in NYHA functional class by at least one class, quality of life questionnaire score by ≥ 10 points and exercise time during cardiopulmonary exercise test by ≥10%. The upcoming "Pacing Therapy for Hypertrophic Obstructive Cardiomyopathy"-HOCM PACE study is a French prospective, multi-center, controlled, randomized (1:1 ratio), non-inferiority, open-label and parallel-group trial with more ambitious objectives. It aims to demonstrate that individually optimized DDD pacing with a dual-chamber ICD is non-inferior to TASH for a clinical composite score of functional status (NYHA class), patient self-assessment and major clinical events over a two-year period in patients with symptomatic drug-resistant HOCM. Patients will be stratified at inclusion whether they have an indication for an ICD **(Figure 4**).To evaluate the risk-benefit balance of these procedures, the study has a safety co-primary endpoint of major procedure- or device-related complications at 1-month.

CONCLUSION

Despite the fact that pacing has been subject to randomised controlled studies with favourable results in drug refractory elderly HOCM patients it remains a largely unutilized therapy. It is clear that AV sequential pacing has been forgotten despite evidence of short and long-term benefits. We believe that its value needs to be

reassessed for future therapeutic directions. The therapy in itself is less complex and invasive than myectomy and TASH. Logically, it could be suggested that the least complex and invasive therapy should be tried before the more definite and irrevocable TASH and myectomy options. Importantly, pacing does not preclude or hamper these therapies.

Nonetheless, this therapy needs careful implantation and optimization to achieve benefits which means that the therapy is best adopted in cardiomyopathy centers. More importantly, the scientific evidence is still relatively week and more studies are needed. The ongoing randomised trials comparing pacing to control or to TASH are highly needed to identify the role of AV sequential pacing with or without ICD therapy in the therapeutic possibilities for HOCM patients. Additional trials as well as prospective multi-center registries are needed.

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LEGENDS

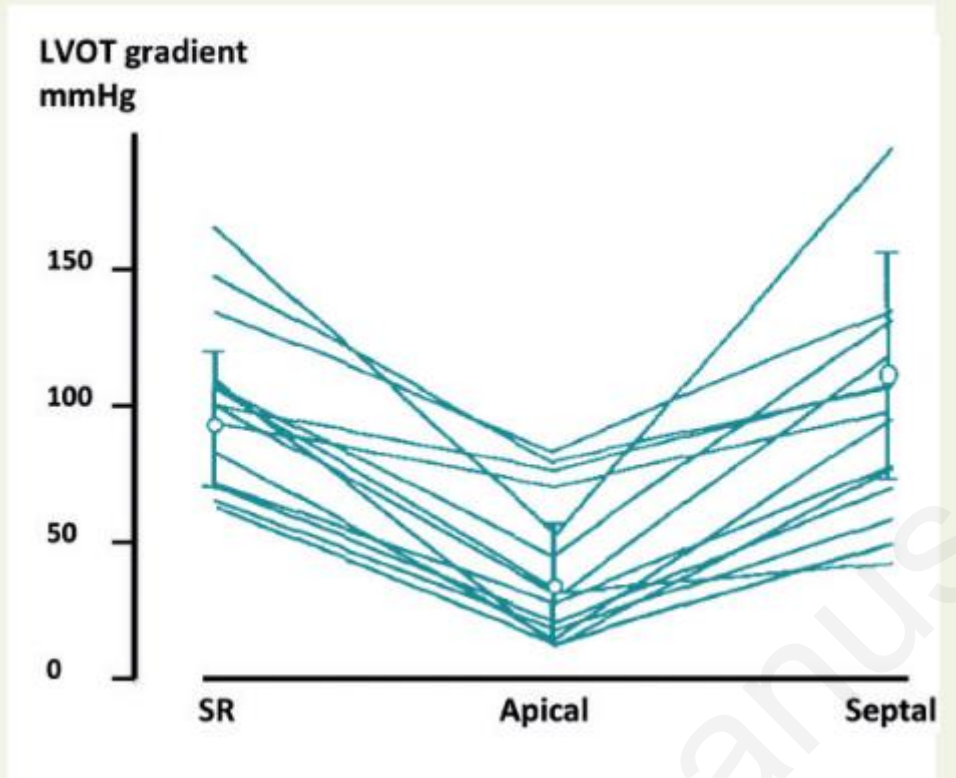

Figure 1. The maximal LVOT gradient during sinus rhythm (SR) and during DDD pacing with an optimal atrioventricular delay with the right ventricular apical (RVA) compared to the RV-high septal (RVS) position. RVA significantly reduced the gradient whereas RVS had no significant effect (Adapted from Gadler[59] with permission).

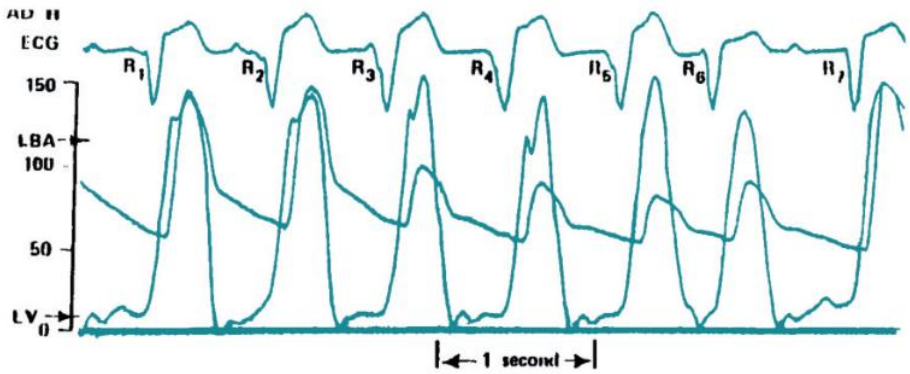

Figure 2. In this patient with HOCM, complete heart block and with permanent ventricular pacing a huge cycle-to-cycle variations in LVOT gradient depending on temporal variations in AV synchrony is seen. The gradient decreases or is abolished during ventricular cycles preceded by a P wave with an appropriate AV interval, even after a long cycle following a ventricular extra-beat*. Conversely the LVOT gradient increases on cycles without correctly synchronised P wave (Adapted from Johnson[65] with permission).

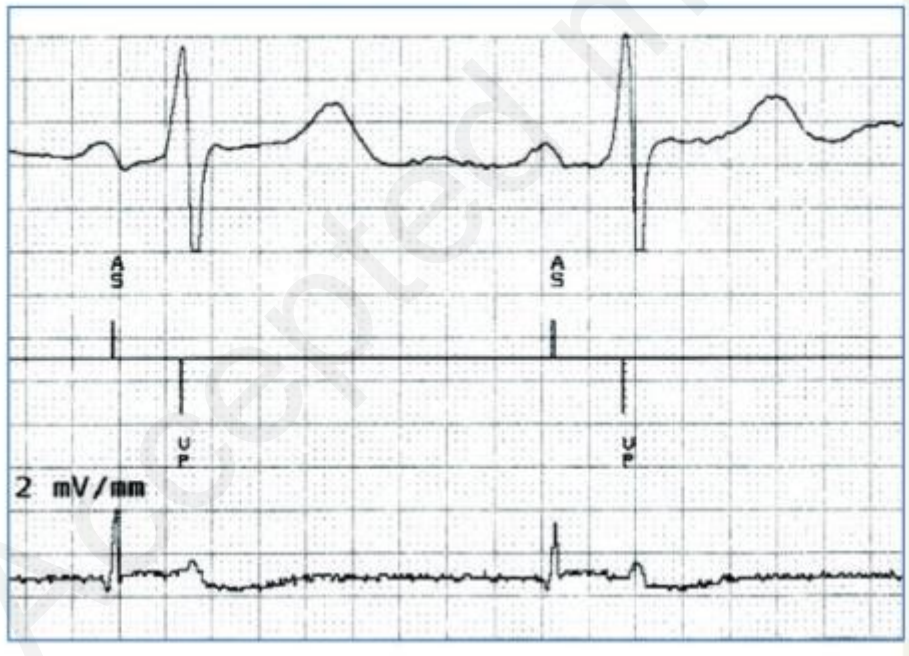

Figure 3. An ECG example from an optimized atrial lead position at the site of the latest activation site during spontaneous sinus rhythm. The intra-cardiac sensed atrial signal (AS) is delayed by 85 ms with respect to the onset of the P wave on the surface ECG. The delayed atrial sensing enables to program shorter AV delays to capture the ventricle in the VDD mode without compromising AV synchrony.

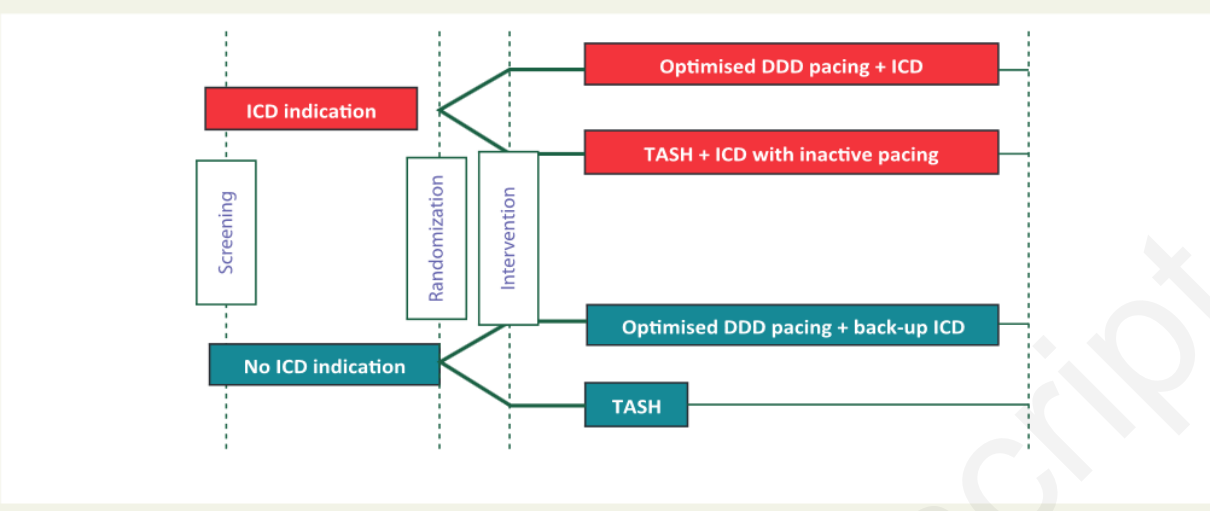

Figure 4. The design of the HOCM Pace study (for further details see text)