Effects of permanent dual-chamber pacing on mitral regurgitation in hypertrophic obstructive cardiomyopathy


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Aims To assess the effects of chronic dual-chamber pacing on mitral regurgitation in hypertrophic obstructive cardiomyopathy.

Methods and Results Twenty-three patients with hypertrophic obstructive cardiomyopathy and mitral regurgitation, treated with DDD pacing for 16 ± 14 months, were included in the study. Mitral regurgitation was assessed by Doppler-echocardiography using semi-quantitative analysis (grades I–IV) and by measuring the maximum regurgitant jet area/left atrial area ratio. At the end of follow-up, DDD pacing reduced the outflow gradient from 93 ± 37 mmHg to 31 ± 30 mmHg (P<0.001). Nine of the 14 patients who initially had grade II mitral regurgitation improved by at least one grade, two of them exhibiting dramatic improvement (from grade IV and III to grade I). The regurgitant jet area/left atrial area ratio was reduced with DDD pacing from 20 ± 13% to 11 ± 6% (P<0.001). Patients who had significant mitral regurgitation despite pacing were those whose outflow gradient remained high or those with mitral valve organic abnormalities (mitral annulus calcification or mitral valve prolapse). In the absence of organic abnormalities other than leaflet elongation, there was a significant correlation between the gradient value achieved with DDD pacing and the extent of mitral regurgitation (P<0.05).

Conclusion In the absence of organic mitral valve abnormalities, DDD pacing reduces in parallel mitral regurgitation and left ventricular outflow gradient. In such patients therefore, significant mitral regurgitation is not a contraindication to pacing.

Key Words: Hypertrophic obstructive cardiomyopathy, Dual-chamber pacing, Mitral regurgitation.

See page 109 for the Editorial comment on this article

Introduction
Mitral valve structural abnormalities and mitral regurgitation are commonly found in hypertrophic obstructive cardiomyopathy. Significant mitral regurgitation associated with left ventricular outflow gradient often leads surgical teams to recommend mitral valve replacement, either alone or associated with myotomy–myectomy[1], even if the latter by itself may reduce both outflow gradient and mitral regurgitation[2]. In most cases, mitral regurgitation is related to the systolic anterior motion of the mitral valve[3,4] whose magnitude is correlated to that of the pressure gradient[5]. Dual-chamber pacing with complete ventricular capture from the right ventricular apex decreases the systolic motion of the mitral valve and the outflow gradient[6,7]. However, its effect on mitral regurgitation has not been documented, particularly when considering important mitral regurgitation and additional mitral valve abnormalities.

This study assesses the influence of chronic DDD pacing on mitral regurgitation and left ventricular outflow gradient in hypertrophic obstructive cardiomyopathy and associated mitral valve abnormalities.

Patients and methods

Patient selection
Patients were selected according to the following criteria: (1) hypertrophic cardiomyopathy with echo-
cardiographic evidence of left ventricular hypertrophy (septum wall or left ventricular free wall thickness ≥13 mm) without dilatation, in the absence of any other cardiac or systemic cause likely, on its own, to induce left ventricular hypertrophy[8]; (2) left ventricular outflow obstruction at baseline resulting from systolic anterior motion of the mitral valve with peak outflow gradient at rest ≥30 mmHg, as assessed by continuous Doppler echocardiography; (3) significant mitral regurgitation before pacemaker implantation. Mitral regurgitation was diagnosed and quantified by Doppler echocardiography. Patients with trivial mitral regurgitation (very restricted jet area with colour Doppler, low spectrum density with continuous Doppler) were excluded from the study; (4) incapacitating and drug-resistant symptoms justifying the indication of DDD pacing; (5) DDD pacing treatment for at least 3 months. This time period was chosen because the decrease in gradient sometimes varied with chronic pacing[6-9]; (6) patients in permanent sinus rhythm at the time of the study.

Patients with echo data of unsufficient quality for comparison between baseline and end follow-up were excluded.

**Echocardiography**

Measurements were performed with a Hewlett Packard (Sonos 1000) real-time, phase array, 90° ultrasonic scanner with a 2·5-MHz transducer. Peak outflow gradient was measured in a four-chamber apical view from the continuous Doppler recording (1·9 MHz transducer) of subaortic velocities, according to Bernouilli’s simplified formula. Mitral valve systolic anterior motion was quantified according to Gilbert’s classification[10]: grade 0=absent; grade 1=mild with no septum/mitral valve contact and minimum valve/septum distance >10 mm; grade 2=moderate with no septum/mitral valve contact but valve/septum distance ≤10 mm; grade 3=important with brief septum valve contact (<30% of systole); grade 4=severe with prolonged septum/mitral valve contact (≥30% of systole).

Mitral valve abnormalities were confirmed and specified by two-dimensional echocardiography. Mitral regurgitation was quantitatively assessed: (1) by semi-quantitative analysis based on visual assessment after integrating pulsed, continuous and colour Doppler data collected at various angles and which could be stratified in five grades: grade 0=absent or non-significant mitral regurgitation; grade I=mild; grade II=moderate; grade III=important; grade IV=severe; (2) by quantitative analysis based on left atrial regurgitant jet mapping and determination of the maximum regurgitant jet area/left atrial area ratio. These measurements were performed in a four-chamber apical view, on the image showing the largest jet extension[11]. Values acquired in sinus rhythm before pacemaker implantation were compared with those recorded at the end of follow-up with DDD pacing.

Data collection was conducted by one investigator using one protocol. Echo data were analysed according to a blind protocol by two different investigators — including the data collector — unaware of the clinical and pacing status of each patient. No significant discrepancies were observed between the investigators in the mitral regurgitation jet area measurements; quantitative results were averaged. Both observers arrived at the same semi-quantitative grading of mitral regurgitation, except in two cases in which a consensus was reached (two grade II mitral regurgitation classified as grade I).

**Statistical analysis**

Results are expressed as means ± standard deviation or as percentages. Comparison of the means was performed using the Wilcoxon signed rank test. Percentages were compared, when appropriate, using the Chi-square test. Statistical analysis of the correlations between measured variables (outflow pressure gradient, degree of systolic anterior motion and mitral regurgitation) was performed with standard linear regression. The significance threshold was *P*<0·05.

**Results**

**Baseline patients’ characteristics (Table 1)**

Twenty-three patients (13 men, 10 women, mean age 54±15 years; range 24–75) treated by dual-chamber pacing between June 1991 and June 1996 were included in the study. They were part of a larger population of 37 patients treated during the same period by DDD pacing in our institution. Fourteen patients were excluded for various reasons: one died from cancer, five presented without any mitral regurgitation, three had only latent obstruction (pressure gradient with provocation using trinitrin) and five had echo data of unsufficient quality.

All patients were symptomatic despite drug treatment. Peak left ventricular outflow gradient at rest was 93±37 mmHg (range 30–150 mmHg). All patients presented with asymmetrical septal hypertrophy, as defined by a septum/posterior wall thickness ratio >1·3. According to Maron et al.’s classification[12], hypertrophy was type III (affecting the septum and the left ventricular free wall) in 17 patients (74%), type II (whole septum) in three patients (13%) and type I (anterior septum) in another three (13%). The degree of hypertrophy varied from 13 to 33 mm. Coronary arteriography performed in 21 patients was normal or revealed non-significant coronary artery lesions.

**Follow-up**

After pacemaker implantation, drug therapy (beta-blockers, verapamil, amiodarone) was maintained or
even increased and particular attention was paid to atrioventricular synchrony optimization[13], which could justify increased medication or radiofrequency catheter ablation of the atrioventricular junction, the latter being performed in seven patients. The mean follow-up duration was 16 ± 14 months (range 3–33). Compared to baseline status, the drug regimen at the end of follow-up was unchanged in 17 patients but was increased in six. These six patients received beta-blockers alone before pacemaker treatment, then the following treatment association: beta-blocker + verapamil in three patients, beta-blockers + verapamil + amiodarone in the other three patients. There were no significant differences in heart rate between baseline and follow-up (61 ± 13 beats . min\(^{-1}\) vs 65 ± 13 beat . min\(^{-1}\); P=ns).

Symptoms

The NYHA class decreased from 2·9 ± 0·5 before pacemaker implantation to 1·6 ± 0·5 with pacing (P<0·0001). At the end of follow-up, no patient was in class III or IV. All patients performed an exercise test on a cycloergometer (11 patients) or treadmill (12 patients) according to the same modalities as before pacemaker implantation. The mean exercise time increased significantly from 9·7 ± 5·5·min before pacemaker implantation to 11·2 ± 5·1 min with pacing (P<0·05). In 13 patients, the exercise test could be coupled to respiratory gas exchange measurements. All but one of these 13 patients performed their exercise test on treadmill with a modified Bruce protocol. The VO\(_2\) peak was higher with pacing (17·1 ± 5·1 ml . min\(^{-1}\) . kg\(^{-1}\) vs 15·4 ± 6·3 ml . min\(^{-1}\) . kg\(^{-1}\); P<0·05). At the end of follow-up, patients achieved 51 ± 19% (range 32–94) of their age, sex and body surface area predicted VO\(_2\) max, whereas this ratio was 45 ± 21% (range 15–84) at baseline (P=0·08).

Left ventricular outflow pressure gradient

Compared to baseline state (sinus rhythm), DDD pacing at discharge — immediately after pacemaker implantation — reduced the outflow gradient from 93 ± 37 mmHg to 50 ± 24 mmHg (P<0·0001) (Fig. 1). At the end of follow-up, the gradient fell to 31 ± 30 mmHg (P<0·01). It was less than 30 mmHg in 16 patients. The degree of systolic anterior motion of the mitral valve (Gilbert’s classification) also decreased from 3·1 ± 0·8 in sinus rhythm before pacemaker implantation to 1·5 ± 1·3 at the end of follow-up with DDD pacing (P<0·0001). The degree of systolic anterior motion and the outflow pressure gradient were linearly correlated both at baseline in sinus rhythm (R=0·54; P<0·007) and at the end of follow-up with DDD pacing (R=0·82; P<0·0001), although the relation was weaker in the former case.

Mitral regurgitation

Baseline characteristics of mitral regurgitation

Mitral regurgitation was mostly grade I (nine patients) or grade II (12 patients) but was grade III in one patient.
and grade IV in another. In the study population, three types of abnormalities were shown qualitatively: (1) mitral leaflet elongation in five patients; (2) important mitral annulus calcifications in five patients; (3) mitral valve prolapse in one patient. Patients with mitral annulus calcifications tended to be older than the others (median 69 years, range 64–73) and patients with mitral leaflet elongation were younger (median 36 years, range 24–71).

**Effect of DDD pacing on the magnitude of mitral regurgitation**

With pacing, mitral regurgitation was ≤ grade I in 17 patients and grade II in the other six (Fig. 2). According to the semi-quantitative analysis, mitral regurgitation decreased in 10 patients (43%) and particularly in two who exhibited the greatest regurgitation (grade III and IV respectively) and were reclassified as grade I (Fig. 3). Of the 14 patients who initially presented with mitral regurgitation ≥ grade II, nine (64%) were improved by at least one grade. Mitral regurgitation worsened from grade I to grade II in only one patient, who had a mitral valve prolapse.

The maximum regurgitant jet area/left atrial area ratio was significantly decreased from 20 ± 13% in sinus rhythm before pacemaker implantation to 11 ± 6% with DDD pacing (P<0.0001). Seen in relation to the mitral regurgitation grade, the ratio before implantation was 10 ± 3% for grade I, 23 ± 5% for grade II, 28% for grade III and 67% for grade IV. With pacing, the same ratio was 10 ± 4% for grade I and 17 ± 2% for grade II.

**Influence of mitral valve abnormalities and decrease in left ventricular outflow gradient on mitral regurgitation**

From the nine patients whose mitral regurgitation significantly persisted despite pacing, quantitatively expressed as a jet area/left atrial area ratio >15% (the six grade II and three grade I), four had a persistent high left ventricular outflow gradient (>60 mmHg) including three with elongated mitral leaflets. The other five had minimal gradient (<20 mmHg) but mitral valve organic abnormalities were observed: severe calcification of the mitral annulus in four patients and mitral valve prolapse in one (Fig. 4).

After excluding the six patients who had mitral valve organic abnormalities other than mere leaflet elongation (i.e. severe mitral annulus calcification or mitral valve prolapse), there was a significant linear correlation between the magnitude of the left ventricular outflow gradient and the maximum regurgitant jet area/left atrial area ratio measured at the end of follow-up with DDD pacing (r=0.7; P=0.002) (Fig. 5). A similar correlation was found between the grade of systolic anterior motion and the quantitative index of mitral regurgitation (R=0.64; P=0.005) (Fig. 6). Conversely, there were no significant correlations when comparing the changes in gradient or in grade of systolic anterior motion between baseline and follow-up studies to the changes in the severity of mitral regurgitation (semi-quantitative or quantitative assessment) observed at the same time.

**Discussion**

This study has demonstrated the effectiveness of dual-chamber pacing in decreasing mitral regurgitation in parallel with the effect on left ventricular outflow gradient in hypertrophic obstructive cardiomyopathy, provided the regurgitation is due to the abnormal systolic motion of the mitral valve and no major structural abnormalities of the mitral valve apparatus exist. These results must be interpreted in the context of our therapeutic approach, where dual-chamber pacing is combined with drug treatment and atrioventricular synchrony is optimized individually.

When pacing, in the absence of severe mitral annulus calcifications or mitral valve prolapse, systolic anterior motion and pressure gradient were found to be correlated with the extent of mitral regurgitation. The absence of a significant correlation between changes in systolic anterior motion or gradient and changes in mitral regurgitation with pacing (i.e. the differences between baseline and end follow-up quantitative measurements of each variable) is explained by the fact that some patients had high pressure gradients without
really important mitral regurgitation at baseline. This is particularly relevant in elderly patients in whom the mechanism of systolic anterior motion is usually different. Indeed, in most elderly patients, the systolic contact between the mitral valve and septum results from a combination of anterior motion of the mitral valve and posterior excursion of the septum\[14\]. Thus, anterior excursion of the mitral leaflets is more restricted and the leaflets' coaptation failure could be reduced. In these patients, major changes in the importance of mitral regurgitation could not be shown even after a dramatic decrease in gradient. However, it was important to include such patients, and especially those with mild mitral regurgitation, as pacing by itself might have induced mitral regurgitation.  

Hypertrophic cardiomyopathy is a complex cardiac disease in which several pathophysiological mechanisms concur to determine symptoms, such as left ventricular diastolic dysfunction, myocardial ischaemia, outflow obstruction and mitral regurgitation\[15\]. Dual-chamber pacing with complete and permanent ventricular capture from the right ventricular apex reduces the
left ventricular outflow gradient and improves symp-
toms in patients with hypertrophic obstructive cardio-
myopathy[6,7,16]. The mechanism by which the dynamic
outflow obstruction is decreased by DDD pacing is
uncertain, but is related to a decrease in the systolic
anterior displacement of the mitral valve leaflet(s). It
could be expected that relieving outflow obstruction
and systolic anterior displacement of the mitral leaflet(s) by
pacemaker therapy would alleviate or abolish mitral
regurgitation. Indeed, the main mechanism of mitral
regurgitation in hypertrophic obstructive cardiomy-
opathy is the abnormal coaptation of mitral leaflets in
relation to mitral valve systolic displacement. Mitral
leaflets are generally elongated and the coaptation point
is localized within the leaflet bodies[3,17,18]. During sys-
tole, the free distal end of the leaflets can move forward
and upwards towards the septum by a Venturi effect[19]
and/or because of drag forces induced by leaflets inter-
fering with flow streamlines[20,21], producing the mitral
valve systolic anterior motion whose magnitude is cor-
related to that of the outflow pressure gradient[5]. The
result of this motion is a leaflet coaptation failure during
meso-telesystole, creating a posteriorly oriented funnel
responsible for mitral regurgitation[3].

Mitra regurgitation is therefore frequent in
hypertrophic obstructive cardiomyopathy and detected
by angiography in about 2/3 of cases[19]. In the absence

![Figure 4](image1.png)

**Figure 4** Scatterplot showing individual relationship be-
tween peak left ventricular outflow gradient and the extent
of mitral regurgitation at the end of follow-up with DDD
pacing. Extent of mitral regurgitation is expressed as the
maximum regurgitant jet area/left atrial area ratio
measured with colour Doppler from a four-chamber apical
view. Patients whose mitral regurgitation remained sig-
nificant (ratio >15%) either had an important residual
outflow gradient with pacing (four patients with gradient
>60 mmHg) — associated with important mitral leaflets
elongation in three of them — or had organic mitral valve
disease (one with mitral valve prolapse and four with
important mitral annular calcifications). □ = normal valve;
○ = elongation of the mitral leaflets; ○ = mitral
annular calcification; * = mitral valve prolapse.

![Figure 5](image2.png)

**Figure 5** Correlation between peak left ventricular out-
flow gradient and extent of mitral regurgitation at the end
of follow-up with DDD pacing after excluding patients
with organic mitral valve disease, except those with mitral
leaflets elongation (i.e. patients with mitral annular calci-
fications or mitral valve prolapse). Extent of mitral regur-
gitation is expressed as the maximum regurgitant jet
area/left atrial area ratio measured with colour Doppler in
a four-chamber apical view.

![Figure 6](image3.png)

**Figure 6** Correlation between the grade of systolic an-
terior motion according to Gilbert[10] and extent of mitral
regurgitation at the end of follow-up with DDD pacing
after excluding patients with organic mitral valve disease,
except those with mitral leaflets elongation (i.e. patients
with mitral annular calcifications or mitral valve pro-
lapse). Extent of mitral regurgitation is expressed as the
maximum regurgitant jet area/left atrial area ratio
measured with color Doppler in a four-chamber apical
view.
mitral regurgitation. When the gradient is abolished by pharmacological manipulation, mitral regurgitation is reduced or abolished in up to 80% of cases\[19\]. Myotomy–myectomy is accompanied by reduced mitral regurgitation severity in 50 to 75% of cases, even in marked cases\[2,22\]. Dual-chamber pacing with complete ventricular capture reduces mitral valve systolic anterior motion and left ventricular outflow gradient\[6,7\] but its beneficial effect on the magnitude of mitral regurgitation still has to be studied in more depth\[9\].

In our experience, it appears that mitral regurgitation, even severe, can be reduced or abolished by pacing, in parallel with a reduction of mitral valve systolic anterior displacement and left ventricular outflow gradient if the mechanism of mitral valve regurgitation is precisely related to this abnormal mitral valve motion. However, beside these dynamic abnormalities of the mitral valve, a number of organic disorders can be observed in hypertrophic obstructive cardiomyopathy and reduce the effectiveness of pacing. These may be mitral valve malformations directly linked to the disease, such as valve leaflet elongation or abnormal insertion of the papillary muscle into the anterior mitral leaflet\[18\]; mitral valve prolapse, whose combination with hypertrophic obstructive cardiomyopathy can be fortuitous\[23\], mitral valve annulus calcification, especially in elderly patients\[24\], infectious endocarditis\[25\] or more rarely rupture of chordae tendineae\[26\].

Mitral valve leaflet elongation adds to other anatomical or dynamic features for the determination of systolic anterior displacement of mitral leaflets and hence of outflow obstruction and mitral regurgitation\[17,19–21\]. In such cases, reduced mitral regurgitation is directly related to the decrease in left ventricular outflow pressure gradient obtained with pacing. In our experience, however, the reduced systolic motion of the mitral valve and subsequent decrease in outflow gradient and mitral regurgitation are sometimes less marked with DDD pacing when mitral leaflet elongation is marked: three of five patients with that valve abnormality maintained outflow gradient >60 mmHg and grade II mitral regurgitation. In contrast, in other cases of mitral valve organic abnormalities, the effect of pacing on mitral regurgitation was often incomplete even if the gradient was abolished. Such was the case in this study in some patients who had mitral valve prolapse or severe mitral annulus calcification. The latter condition may be a cause of significant mitral regurgitation\[27\]. Reduced mobility of the mitral valve and chordae and loss of the normal systolic spheric action of the mitral ring are believed to be responsible for the valvular failure.

In consideration of these facts, it appears that mitral regurgitation associated with hypertrophic obstructive cardiomyopathy does not constitute a contraindication for DDD pacing, even in the case of marked regurgitation, provided there are no major organic abnormalities of the mitral valve apparatus other than mere mitral leaflet elongation. Severe mitral regurgitation secondary to an intrinsic abnormality of the valve should indicate surgery and mitral valve replacement in highly symptomatic patients\[28\]. When mitral regurgitation is a consequence of the abnormal systolic anterior displacement of the valve, it is relieved or reduced by DDD pacing and the decrease in mitral regurgitation is then parallel to that of outflow obstruction. Identification of patients whose mitral regurgitation is dependent on abnormal mitral valve dynamics and can be alleviated by pacing therapy should be based on: (1) the absence of major abnormalities of the mitral valve apparatus other than leaflets elongation; (2) a parallel decrease in gradient and mitral regurgitation when acute haemodynamic testing is performed. However, it is worth noting that the long-term effect of pacing on left ventricular outflow gradient is usually more important than that observed during acute haemodynamic tests performed before pacemaker implantation. This phenomenon can be explained by the better results obtained after secondary optimization of atrio-ventricular synchrony\[13\] and by unknown long-term effects of pacing on left ventricular function. Indeed, gradual or varied reduction of the outflow gradient has been observed with chronic pacing\[6,9\]. Therefore, absence of a significant decrease in gradient and mitral regurgitation alike during acute pacing will not preclude a favourable long-term effect.

**Limitations of the study**

A ‘quantitative’ method based on the measurement of the maximum regurgitant jet area/left atrial ratio was used to assess the severity of mitral regurgitation. In the absence of a real gold standard, this parameter was chosen for its simplicity and reproducibility. However, it is well known that this parameter relies on the severity of the regurgitation, but other factors can influence the area of the regurgitant jet. This parameter can provide an inaccurate estimation of the regurgitation especially when the jet is eccentric, as usually observed in hypertrophic obstructive cardiomyopathy. We were aware of these limitations of the method. Nevertheless, the severity of mitral regurgitation was also assessed with a semi-quantitative method, integrating other transthoracic echo-Doppler parameters. Despite the limitations mentioned above, correlations between semi-quantitative and quantitative measurements were well-matched (R=0.91, P<0.0001 at baseline and R=0.78, P<0.0001 at the end of follow-up). This does not imply that the regurgitant jet area is an accurate method for assessing the true severity of the regurgitation, as recommended in the original publication from Helmcke et al.\[11\], but rather than this area was proportional to the real extent of the regurgitation. Moreover, by comparing, in each patient, the effects of pacing on mitral regurgitation seems valid. Conversely, attempting to grade mitral regurgitation from the measurements of the regurgitant jet area/left atrial area ratio would have been inaccurate.
Conclusion

Dual-chamber pacing in hypertrophic obstructive cardiomyopathy reduces systolic anterior motion of the mitral valve and left ventricular outflow gradient. Provided mitral regurgitation is related to this abnormal systolic anterior motion of the mitral valve, pacing can reduce even severe regurgitation. Mitral valve organic abnormalities—except leaflet elongation—make results uncertain, according to the respective involvement of the mitral valve organic and dynamic abnormalities in the regurgitation mechanism. In the absence of major organic abnormalities of the mitral valve apparatus, marked mitral regurgitation does not constitute a contraindication for dual-chamber pacing.

References