Left Ventricular Remodeling in Patients With Hypertrophic Obstructive Cardiomyopathy Treated With Percutaneous Alcohol Septal Ablation: an Echocardiographic Study

Socorro Rivera, Marta Sitges, Manel Azqueta, Alba Marigliano, Margarita Velamazán, Faustino Miranda-Guardiola, Amadeu Betriu, and Carles Paré

Institut d'Investigacions Biomèdiques August Pi i Sunyer, Institut de Malalties Cardiovasculars, Hospital Clínic, Universidad de Barcelona, Barcelona, Spain.

Introduction. In patients with hypertrophic obstructive cardiomyopathy, obstruction in the left ventricular outflow tract may generate more hypertrophy. Our aim was to evaluate the impact of reducing ventricular outflow tract obstruction on left ventricular hypertrophy and remodeling after alcohol septal ablation.

Patients and method. 20 patients with hypertrophic obstructive cardiomyopathy who underwent alcohol septal ablation were included. Doppler echocardiography was performed in all patients at baseline, immediately after alcohol septal ablation, and at 3 and 12 months' follow-up. Left ventricular diameters and wall thickness and pressure gradients in the ventricular outflow tract were determined.

Results. Immediately after alcohol septal ablation, ventricular outflow tract pressure gradient decreased from 63.0 ± 27.7 to 28.2 ± 24.7 mmHg ($p < 0.001$), without significant changes in left ventricular dimensions. However, after 12 months we observed an increase in left ventricular end-diastolic (from 47.1 ± 4.9 to 50.8 ± 4.5 mm) and end-systolic diameter (from 27.1 ± 3.0 to 33.7 ± 4.6 mm), as well as a reduction in septal (from 19.5 ± 4.0 to 15.5 ± 2.7 mm) and posterior wall thickness (from 14.0 ± 2.2 to 12.9 ± 1.3 mm) ($p < 0.01$ in all cases). Left ventricular end-diastolic and end-systolic volumes increased (from 106.4 ± 26.9 to 123.1 ± 28.7 ml and from 50.2 ± 17.3 to 56.7 ± 18.3 ml, respectively, $p < 0.01$ in both cases), without changes in left ventricular ejection fraction. The reduction in ventricular outflow tract pressure gradient at 12 months' follow-up correlated significantly with the increase in left ventricular end-systolic diameter ($r = 0.63$; $p < 0.01$).

Conclusions. In patients with hypertrophic obstructive cardiomyopathy who underwent alcohol septal ablation, relief of ventricular outflow tract obstruction is associated with an increase in left ventricular chamber diameters and volume. These findings suggest that middle- and long-term ventricular remodeling and regression of hypertrophy occur in these patients, which may contribute to their clinical improvement.

Key words: *Septal ablation. Hypertrophic cardiomyopathy. Remodeling.*

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Remodelado ventricular izquierdo tras ablación septal percutánea con alcohol en pacientes con miocardiopatía hipertrófica obstructiva: estudio ecocardiográfico

Introducción. Evaluamos el impacto de la reducción de la obstrucción en el tracto de salida del ventrículo izquierdo tras la ablación septal percutánea con alcohol sobre la hipertrofia y el remodelado del ventrículo izquierdo (VI).

Pacientes y método. Se incluyó a 20 pacientes con miocardiopatía hipertrófica tratados con ablación septal percutánea. Se realizó ecocardiograma Doppler en situación basal, inmediatamente después de la ablación septal percutánea y a los 3 y 12 meses de seguimiento, en el que se midieron los diámetros y grosores del VI y del gradiente de presión en el tracto de salida del ventrículo izquierdo.

Resultados. Inmediatamente después de la ablación septal percutánea, el gradiente de presión en el tracto de salida del VI disminuyó de 63,0 ± 27,7 a 28,2 ± 24,7 mmHg ($p < 0,001$), sin que se apreciaran cambios significativos en las dimensiones del VI. Doce meses después se observó un incremento en los diámetros telediastólico (de 47,1 ± 4,9 a 50,8 ± 4,5 mm; $p < 0,01$) y telesistólico del VI (de 27,1 ± 3,0 a 33,7 ± 4,6 mm; $p < 0,01$) y una reducción en los grosores del septo (de 19,5 ± 4,0 a 15,5 ± 2,7 mm; $p < 0,01$) y de la pared posterior del VI (de 14,0 ± 2,2 a 12,9 ± 1,3 mm; $p < 0,01$). Los volúmenes telediastólico y telesistólico del VI aumentaron (de 106,4 ± 26,9 a 123,1 ± 28,7 ml; $p < 0,01$, y de 50,2 ± 17,3 a 56,7 ± 18,3 ml; $p < 0,01$, respectivamente), sin que se observaran cambios en la fracción de eyección del VI. La reducción del gradiente de presión en el tracto de salida del ventrículo izquierdo observada a los 12 meses de la ablación septal percutánea se correlacionó de manera significativa con el incremento del diámetro telesistólico del VI ($r = 0,63$; $p < 0,01$).

Correspondence: Dra. M. Sitges.
Institut de Malalties Cardiovasculars. Hospital Clínic.
Villarroel, 170. 08036 Barcelona. España.
E-mail: msitges@clinic.ub.es

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ABBREVIATIONS

ASA: alcohol septal ablation.
HOCM: hypertrophic obstructive cardiomyopathy.
LV: left ventricle.
LVOT: left ventricular outflow tract.
PG: pressure gradient.
PSA: percutaneous septal ablation.

Conclusiones. La reducción de la obstrucción en el tracto de salida del ventrículo izquierdo en pacientes con miocardiopatía hipertrófica tratados con ablación septal percutánea se acompaña de un incremento de los diámetros y volúmenes del VI en el seguimiento. Esto indica el desarrollo de un remodelado cardíaco y de una regresión en la hipertrofia del VI de estos pacientes que podría contribuir a su mejoría sintomática.

Palabras clave: *Ablación. Miocardiopatía hipertrófica. Remodelado.*

INTRODUCTION

In hypertrophic obstructive cardiomyopathy (HOCM), the left ventricular outflow tract (LVOT) is narrowed by septal hypertrophy. Further narrowing occurs because blood flow through the LVOT causes systolic anterior motion of the anterior leaflet of the mitral valve due to the Venturi effect. Thus both functional and anatomical narrowing of the LVOT occurs. Obstruction of the LVOT may be a new stimulus for further secondary hypertrophy, leading to a vicious circle with greater myocardial growth.[1]

Treatment of LVOT obstruction in patients with HOCM usually starts with the use of negative inotropic drugs such as beta-blockers or calcium antagonists.[2,3] Surgical myectomy has proved successful if symptoms persist, although the effectiveness of this technique depends on the number of patients treated by each surgical team. Use of the technique therefore tends to be concentrated in highly specialized centers.[4-8] Recently, some groups have started to use dual-chamber pacemakers for ventricular stimulation to treat patients with HOCM, although the results are controversial.[9,10] Another new technique is percutaneous septal ablation (PSA) with alcohol to treat LVOT obstruction in patients with HOCM whose symptoms are refractory to medical treatment.[11-14] The results with this technique have been excellent; indeed, studies with medium-term follow-up have found the technique to have success rates similar to those of surgical myectomy.[15] Relief of LVOT obstruction leads to an improvement in symptoms, probably through better cardiac output and coronary perfusion, and a decrease in mitral regurgitation.[16] Likewise, a decrease in LVOT obstruction might break the vicious cycle of left ventricular hypertrophy by removing the stimulus responsible for secondary ventricular hypertrophy. Therapy that decreases septal thickness may thus be beneficial and lead to some regression of ventricular hypertrophy in patients with HOCM and some remodeling of the left ventricle. Symptoms in treated patients may therefore improve because of the greater distensibility of the left ventricle. The aim of our study was to evaluate the impact on remodeling and left ventricular hypertrophy of the decrease in LVOT obstruction after alcohol septal ablation (ASA) in patients with HOCM.

PATIENTS AND METHODS

We evaluated patients diagnosed with HOCM by two-dimensional echocardiography with a septal thickness ≥15 mm and no other apparent cause of left ventricular hypertrophy. Our patients had a maximum instantaneous LVOT gradient of ≥40 mmHg at rest or ≥60 mm Hg after provocation maneuvers but with no systolic dysfunction of the left ventricle (LV), and ejection fraction ≥50% determined echocardiographically. We treated all patients in our center with the same therapeutic approach, consisting of three steps. First, medical treatment was optimized by increasing pharmacological therapy with beta-blockers and calcium channel blockers to the maximum tolerated doses. If symptoms and LVOT obstruction persisted, a dual-chamber pacemaker was implanted. Finally, if the LVOT pressure gradient (PG) and the symptoms persisted despite dual-chamber pacing, the patient was offered either surgical myectomy or ASA according to comorbidity, coexistent abnormalities of the mitral valve and age.

The present study included only patients treated with ASA. Of these, only patients for whom the ASA procedure had been successful were analyzed in order to provide specific information on how the decrease in LVOT obstruction affects LV volumes and hypertrophy. Success was defined as a decrease in LVOT pressure gradient of ≥50% with respect to the pressure gradient before the intervention. All patients included in the study were symptomatic, functional class III of the New York Heart Association, despite medical treatment at the maximum tolerated dose and the implantation of a dual-chamber pacemaker. The mean time from implantation of the pacemaker to the ASA procedure and inclusion in the study was 21±15 months.

Percutaneous septal ablation with alcohol

A balloon catheter was introduced into the septal perforator, a branch of the anterior descending coronary artery, by standard angioplasty techniques. The septal branch was occluded proximally by inflating

the balloon and contrast (Levograf®, dilution, 4g/10 mL, 2 mL, Juste, SAQF, Madrid) was injected through the catheter under two-dimensional echocardiographic control to verify the region perfused by the artery. After confirmation that the artery perfused the region of the basal septal segment, which is responsible for maximum LVOT obstruction, and not a different myocardial region, 1 to 3 mL of alcohol was injected. We continuously monitored whether LVOT obstruction was present and the degree of obstruction by hemodynamic monitoring with catheters and echo-Doppler to ensure success. The same interventional cardiologist performed the procedure in all patients.

Echocardiography

Transthoracic echocardiography was performed using commercially available equipment (Sonos 5500, Phillips, Holland; Sequoia, Siemens, Germany) with 2.5-3.5 MHz transducers. An echocardiogram was performed before PSA (baseline), immediately after PSA (within 24 hours of the procedure), after three months and after 12 months. Left ventricular diameters at end-diastole and end-systole, ventricular septal thickness, LV posterior wall and anteroposterior diameter of the left atrium were all determined according to the recommendations of the American Echocardiographic Society.[17] The end-diastolic and end-systolic LV volumes were determined with the Simpson method in the 4-chamber apical view.[17] The LV mass was estimated with the formula of the Penn Convention.[18] Continuous-wave Doppler was used to measure the peak flow through the LVOT, and the maximum pressure gradient was calculated using the modified Bernoulli equation with the patient at rest and after the Valsalva maneuver.[19] Color-Doppler techniques were used for semi-quantitative evaluation of mitral regurgitation.[20] To assess intra-observer and inter-observer variability, the measurements for 20 random examinations were repeated by 2 observers. The measurements were compared by linear regression analysis and the variability expressed as a percentage of mean error±standard deviation (SD) and the error range. In our laboratory, the intra-observer correlation for calculation of the LV mass was 0.92, the inter-observer correlation was 0.83, and the mean difference between the two was 9±34 g. The remaining LV measurements showed an intra-observer variability of 3.5% (2%-4.5%) and an inter-observer variability of 4.6% (2.8%-5.3%).

Clinical follow-up

All patients were monitored in the out-patient clinic of our center, and were interviewed to assess their functional class, determined according to the classification of the New York Heart Association (NYHA).

Statistical analysis

All values are expressed as the mean±SD for quantitative variables. Student's *t* test was used for paired data to compare echocardiographic measurements before and after PSA, and the Bonferroni correction was applied for multiple comparisons. Discrete variables are presented as percentages and compared with the χ^2 test. Functional class before and after the intervention was compared with the Wilcoxon sign test. The relationship between changes in different echocardiographic parameters was analyzed by simple linear regression. A *P* value of <.05 was considered significant.

RESULTS

During the inclusion period of the study (1999-2001) PSA was performed in 24 patients with HOCM. Ablation was effective in 22 of them, but only 20 were able to complete one year of echocardiographic follow-up. Ablation was not effective for 2 patients: in one the PSA did not reduce the LVOT obstruction at any time, and in the other the gradient was eliminated initially but reappeared after 6 months of follow-up.

Mean age of the 20 patients (seven men and 15 women) included in the analysis was 58.5±20.6 years. All were diagnosed as having HOCM, and PSA with alcohol had been effective in all of them (greater than 50% decrease in LVOT pressure gradient with respect to pressure gradient prior to PSA). Seventeen patients (85%) were in functional class III according to the NYHA system, and three (15%) were in class IV before PSA. Table 1 shows the ventricular sizes and echocardiographic characteristics at baseline for the patients. Before the procedure, the thickness of the ventricular septum was 19.53±4.0 mm and that of the posterior ventricular wall was 14.0±2.2 mm. The LVOT pressure gradient was 63.0±27.7 mm Hg under baseline conditions and 96.1±15.2 mm Hg after provocation maneuvers. Most patients had mild or moderate mitral regurgitation (18 patients, 90%).

Immediately after the ablation procedure, the basal LVOT gradient decreased to 28.2±24.7 mm Hg (*P*<.001) and to 56.5±36.6 mm Hg (*P*<.01) after the Valsalva maneuver, although significant differences in the LV size were not seen (Table 1).

After 3 months of follow-up, the basal LVOT pressure gradient and the gradient after the Valsalva maneuver continued to decrease compared to baseline values. Thickness of the ventricular septum decreased and the LV end-systolic diameter increased significantly with respect to the baseline value (Table 1).

After 12 months of follow-up, the gradient in the outflow tract decreased by 85±18% from the pre-abla-

TABLE 1. **Changes in heart size and pressure gradients determined by echocardiography after PSA**

	Baseline	Post-ASP	3 months	12 months
LVEDD, mm	47.1±4.9	47.0±4.1	47.6±4.5	50.8±4.5[a]
LVESD, mm	27.1±3.0	27.5±3.1	29.5±4.4[a]	33.7±4.6[b]
Baseline LVOT PG, mm Hg	63.0±27.7	28.2±4.7[b]	9.2±22.5[b]	9.1±12.6[b]
Provoked LVOT PG, mmHg	96.1±15.2	56.5±36.6[b]	37.4±37.3[b]	23.4±25.2[b]
Septal thickness, mm	19.5±4.0	18.5±2.7	17.8±2.8[b]	15.5±2.7[b]
Thickness posterior LV wall, mm	14.0±2.2	13.8±2.0	14.0±2.1	12.9±1.3[b]
LV mass, g	522.5±135.3	502.2±129.5	490.7±94.0[a]	466.3±60.1[a]
Diameter, mm	47.2±6.5	45.9±7.6	46.2±6.6	45.6±6.4[a]

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PG, pressure gradient; LVOT, left ventricular outflow tract; LV, left ventricular.
[a]*P*<.05 with respect to baseline. [b]*P*<.01 with respect to baseline.

tion value. The decrease in outflow tract obstruction was accompanied by an increase in end-diastolic and end-systolic LV diameters and a decrease in the thickness of the septum and the posterior LV wall (Table 1). Akinesis of the basal septal segment was observed in all patients 24 hours after ablation. One year later this segment was narrower, but no aneurysms were observed (Figures 1A and B).

The diameter of the left atrium decreased from 47.2±6.5 mm before ablation to 45.6±6.4 mm after 12 months (*P*<.05). The mean severity of mitral regurgitation did not vary significantly during the study, although it did tend to decrease (from 1.7±0.7 to 1.3±0.6; *P*=NS [0.14]).

A significant decrease in left atrium size was seen at 12 months (Table 1), as well as the decrease seen in LVOT obstruction and the steady change in the diameters and thicknesses of the LV during follow-up. Left ventricular mass also decreased progressively . It was significantly less 3 months after PSA and further reduced after 12 months of follow-up [pre 522.5±135.3 g, 3 months 490.7±94.0 g (*P*=.04), 12 months 466.3±60.1 (*P*=.04)].

At the end of follow-up both LV end-diastolic and end-systolic volumes had increased significantly (from 106.4±26.9 to 123.1±28.7 ml for LV end-diastolic volume, *P*<.01; and from 50.2±17.3 to 56.7±18.3 ml for LV end-systolic volume; *P*<.01). Left ventricular ejection fraction was unchanged 12 months after PSA (52.9±9.8 before PSA, 54.3±7.9% after PSA; *P*=NS [0.74]; Figure 2).

The decrease in LVOT pressure gradient at 12 months after the intervention correlated significantly with the increase in LV end-systolic diameter (r=0.63; *P*=.01) (Figure 3).

Of the 20 patients treated with PSA, 15 (75%) presented clinical improvement after one year of follow-up, whereas symptoms remained unchanged in 5 patients (25%) (Figure 4). The patients' mean functional class improved significantly from 3.1±0.3 at baseline to 1.7±0.8 after PSA (*P*<.01). The 5 patients who showed no clinical improvement had a significant increase in LV volumes and diameters, as well as a decrease in wall thickness.

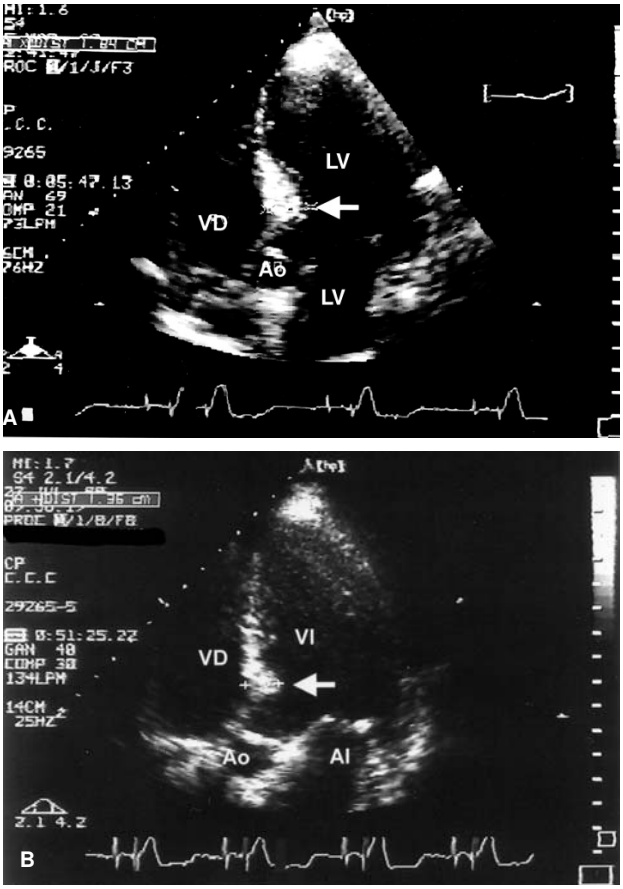

Fig. 1. A: Apical four-chamber two-dimensional echocardiogram of a patient with hypertrophic obstructive cardiomyopathy before percutaneous septal ablation with alcohol, in which the septal base thickness (arrow) was 18.4 mm. B: Apical 4-chamber two-dimensional echocardiogram of the same patient one year after septal ablation. Note marked narrowing of the septal base, with a maximum thickness of 13.6 mm. LA indicates left atrium; Ao, aorta; RV, right ventricle; LV, left ventricle.

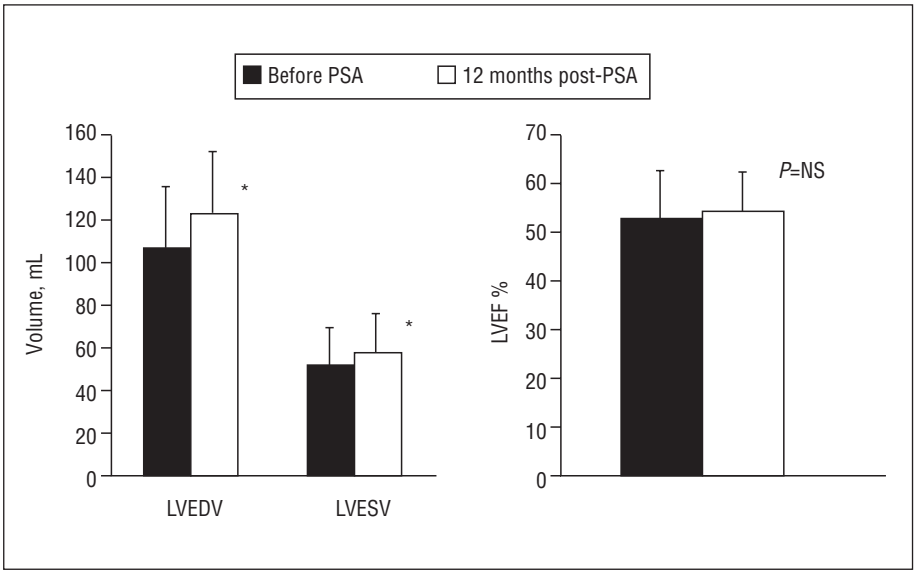

Fig. 2. Left: mean left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) before percutaneous septal ablation (black bars) and after 12 months of follow-up (white bars). Right: mean left ventricular ejection fraction (LVEF) before percutaneous septal ablation (black bar) and after 12 months of follow-up (white bar). **P*<.01.

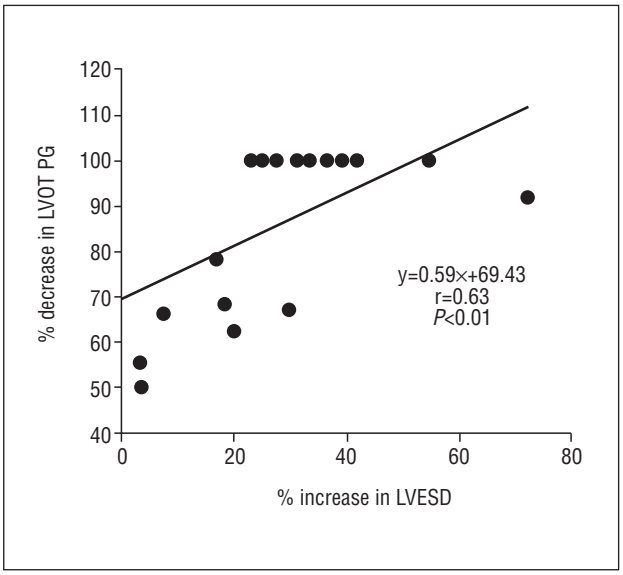

Fig. 3. Relationship between the increase in left ventricular end-systolic diameter (LVESD) and decrease in the pressure gradient (PG) in the left ventricular outflow tract (LVOT) after percutaneous septal ablation with alcohol in patients with hypertrophic obstructive cardiomyopathy.

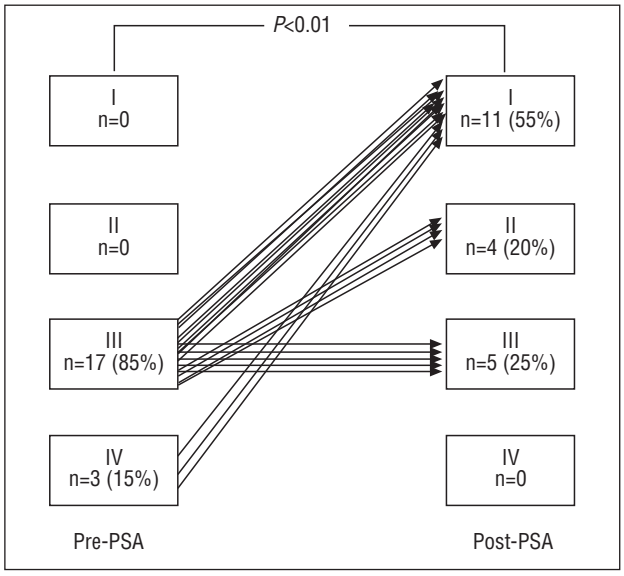

Fig. 4. Functional class before and after percutaneous septal ablation. The figures indicate number and percentage of patients in each class, and the arrows indicate the change in functional class for each of the patients from pre-PSA baseline (left) to end of follow-up after PSA (right). PSA: percutaneous septal ablation.

DISCUSSION

The present echocardiographic study demonstrates that the LV dimensions change as LVOT obstruction decreases in patients with HOCM who have undergone PSA. The decrease in LVOT obstruction is accompanied by a progressive increase in LV diameters and volumes, and gradual decrease in wall thickness and LV mass during follow-up. The size of the left atrium also decreased, possible reflecting improved distensibility of the LV and/or reduced severity of mitral regurgitation. These findings suggest that cardiac remodeling occurs after PSA in patients with HOCM, and that there is some decrease or regression in ventricular hypertrophy. The decrease in LVOT obstruction probably removes the stimulus for secondary hypertrophy in these patients regardless of the pathogenic mechanism responsible for primary myocardial hypertrophy.

Effect of treatment to reduce septal thickness on left ventricular remodeling

Earlier results for the regression of LV hypertrophy in patients with HOCM treated by surgical myectomy

were similar to ours. Curtius et al[21] reported a small but significant decrease in the thickness of the ventricular septum and the LV posterior wall in 30 patients with HOCM treated by myectomy, compared to 77 patients who received medical treatment and who did not have this decrease. Other authors described similar findings in 2 patients with HOCM treated by myectomy (Konno procedure), with significant decreases in both wall thickness (septum and posterior wall) and the size of the left atrium.[22]

More recently, some regression in LV hypertrophy has been reported with the recently introduced technique of percutaneous septal ablation with alcohol in patients with HOCM. Our results agree with those of Mazur et al,[23] who found decreases in wall thicknesses along with significant increases in LV volumes and sizes after PSA in 26 patients after 2 years of follow-up. In another study, 64 patients with HOCM treated with PSA showed sustained improvement in exercise capacity and LVOT obstruction during 3 years of follow-up. This was accompanied by a decrease, apparent as early as 6 weeks after the procedure, in septal thickness and LV mass, and an increase in LV diameter.[24] A decrease in wall thickness and LV mass was also observed in another recent study, which included 57 patients with HOCM treated by PSA and by surgical myectomy.[25] Our findings confirm the results of these studies, as LV remodeling was evident even with our shorter follow-up period. In fact, the study by Mazur et al[23] also showed significant changes in thicknesses and LV volumes one year after PSA, which became more pronounced after 2 years of follow-up. Our data shows that these changes occur progressively and that the decrease in septal thickness probably starts immediately after the procedure, because there was evidence of cardiac remodeling after 3 months of follow-up.

Effect of dual-chamber pacing on left ventricular remodeling

The effect of dual-chamber pacing on LVOT obstruction in patients with HOCM is controversial.[10,26-29] Left-ventricular outflow tract obstruction was removed after dual-chamber pacing in 65% of the patients, and partially reduced in a further 27% in the initial study by Fananapazir et al.[26] This substantial hemodynamic improvement was accompanied by a slight increase in LV end-systolic size and a decrease in ventricular septal thickness during the 2-year follow-up. Tascón et al[29] obtained favorable hemodynamic responses in 88% of the patients, but this response did not lead to significant ventricular remodeling after a mean follow-up of 36 months. They observed a decrease in septal thickness, but the thickness of the posterior wall and the LV diameters remained unchanged.[29] Other studies have, however, found rates of clinical efficacy of only 12% with dual-chamber pacing and no effect on heart size.[9,28]

Although the literature appears contradictory, some of the cardiac remodeling in our patients may have been due to the dual-chamber stimulation itself and not PSA. Before PSA, all patients included in our study had LVOT obstruction despite dual-chamber pacing (an inclusion criterion for the study). Therefore, an increase in LV diameters and volumes was not expected as a result of pacemaker implantation. Moreover, Fananapazir et al[26] reported changes in LV size with dual-chamber pacing after 2 years of follow-up, similar to the time elapsed since pacemaker implantation in our population. Therefore, even if remodeling did take place, this would have been evident in the baseline measurement before PSA, whereas we observed changes in heart size after PSA.

Complete atrioventricular block may have occurred in some patients, which would improve pacemaker function (although this should have been optimized from the moment of implantation). We think this is unlikely in most patients because the incidence of atrioventricular block for septal ablation procedures is less than 30%.[1] We therefore think that the heart remodeling seen in the present study is due to PSA of the intraventricular obstruction, and not to dual-chamber pacing.[9,28]

Study limitations

We did not perform serial measurements from different segments of the LV wall, and used only standard measurements obtained in M-mode, in accordance with the recommendations of the American Society of Echocardiography.[17] This might influence the results of the study, which may be attributable in part to the variability inherent in the method. However, the low variability described in our laboratory supports the reliability of results. Furthermore, because we have sequential control values for each patient, we can use each patient as his or her own control, which increases the reliability of the data. The calculation of volumes and, in particular, LV mass using geometrical assumptions established for conventional or symmetric models of ventricular chamber shape cannot be as accurate as other methods such as three-dimensional echocardiography or magnetic resonance. As noted above, because sequential measurements are available for each patient, changes in LV geometry can be measured accurately without the need for accurate absolute values. Finally, previous studies similar to ours have used the same methods because of the limited availability of three-dimensional techniques such as nuclear magnetic resonance or three-dimensional echocardiography, which would theoretically provide more accurate measures of the study variables.[22-25]

CONCLUSIONS AND CLINICAL

IMPLICATIONS

The results from this study are relevant for 2 reasons. First, they support the hypothesis that HOCM is not only a primary disease of the myocardium but can also be accompanied by hypertrophy secondary to LVOT obstruction itself. Second, the remodeling and regression of LV hypertrophy, along with the decrease in intraventricular obstruction, decrease in mitral regurgitation and improvement in diastolic function, can contribute to clinical improvement in these patients. Most of our patients (75%) improved clinically after ablation. The remaining 25% of the patients experienced no relief from symptoms despite the decrease in intraventricular gradient and LV remodeling, possibly because symptoms in HOCM are multifactorial[30-32] or because we did not investigate whether these patients had greater diastolic dysfunction. Studies with a longer follow-up may confirm the persistence of LV remodeling and, in particular, provide more information on its extent and effect on the clinical progression of this disease.

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