NONSURGICAL REDUCTION OF THE INTERVENTRICULAR SEPTUM IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

Background In patients with hypertrophic cardiomyopathy and obstruction of the left ventricular outflow tract, nonsurgical reduction of the septum is a treatment option when medical therapy has failed. We investigated the long-term effects of nonsurgical reduction of the septum on functional capacity and electrocardiographic and echocardiographic characteristics.

Methods Sixty-four consecutive patients with hypertrophic cardiomyopathy and a mean (±SD) age of 48.5±17.2 years underwent nonsurgical reduction of the septum by injection of ethanol into the septal perforator branch of the left anterior descending coronary artery. These patients were assessed by exercise testing, electrocardiography, and resting and dobutamine (stress-induced) echocardiography after a mean period of 3.0±1.3 years.

Results At follow-up, patients had significant improvements in New York Heart Association class, peak oxygen consumption (from 18.4±5.8 to 30.0±4.4 ml per kilogram of body weight per minute, P<0.001), and left ventricular outflow tract gradients (resting gradient, from 64±36 to 16±15 mm Hg; P<0.001; stress-induced gradient, from 132±34 to 45±19 mm Hg; P<0.001). Procedure-related complications included right bundle-branch block in all patients, complete heart block in 31 patients (48 percent), and significant increases in QRS and corrected QT intervals. Seventeen patients (27 percent) required permanent pacing. R-wave amplitude was significantly decreased (from 32±8 to 17±7 mV, P<0.001). The dimensions of the left ventricular cavity increased, and the interventricular septal thickness was reduced.

Conclusions Nonsurgical septal reduction leads to sustained improvements in both subjective and objective measures of exercise capacity in association with a persistent reduction in resting and stress-induced left ventricular outflow tract gradients. It is also associated with a high incidence of procedure-related complete heart block, however, often requiring permanent pacing. (N Engl J Med 2002;347:1326-33.)

D YNAMIC obstruction of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy has been recognized for 40 years.[1-3] Despite advances in our understanding of its pathogenesis and diagnosis, the progressive nature of hypertrophic cardiomyopathy has not been remedied. Pharmacologic agents (beta-blockers, calcium-channel blockers, and disopyramide),[4] dual-chamber pacing,[5-7] and surgical myomectomy have all been used to treat hypertrophic cardiomyopathy. Both pacemaker implantation and surgical myomectomy provide hemodynamic and clinical benefits in patients with drug-resistant hypertrophic cardiomyopathy.[6-8]

In the past decade, Knight et al. introduced a novel catheter-based nonsurgical technique[9,10] for the reduction of the left ventricular outflow tract gradient in patients with hypertrophic cardiomyopathy that has proved refractory to pharmacologic treatment. By the injection of 100 percent ethanol into the first (and sometimes the second) septal perforator branches of the left anterior descending artery, a controlled myocardial infarction of the interventricular septum was produced, thereby reducing the left ventricular outflow tract gradient. This technique, known as nonsurgical reduction of the septum, was subsequently adopted by several other centers as a potential alternative to surgery for the treatment of hypertrophic cardiomyopathy. Previous short-term follow-up studies[9] have demonstrated both hemodynamic and symptomatic benefits of nonsurgical reduction of the septum.

We investigated the long-term effects of nonsurgical reduction of the septum on electrocardiographic characteristics, functional capacity, and resting and stress-induced left ventricular outflow tract gradients in patients with hypertrophic cardiomyopathy. We also attempted to determine the potential effect of septal reduction on ventricular remodeling, a phenomenon

known to occur after acute myocardial infarction or the initiation of dual-chamber pacing.[11-16]

METHODS

Study Patients

Between June 1994 and May 1997, a total of 72 patients with a diagnosis of hypertrophic cardiomyopathy were referred to our institutions for possible treatment by nonsurgical septal reduction for symptoms that were refractory to optimal medical treatment. Nonsurgical reduction was considered when all the following criteria were fulfilled: there were symptoms that were refractory to optimal medical treatment, there was echocardiographic evidence of asymmetric septal hypertrophy with a resting left ventricular outflow tract gradient greater than 30 mm Hg, and the stress-induced left ventricular outflow tract gradient was greater than 60 mm Hg. Patients with coronary artery disease, severe valvular disease, uncontrolled arrhythmia, and other coexisting conditions were excluded from the study. The study was approved by the relevant institutional review boards, and written informed consent was obtained from all patients.

Study Design

All potentially eligible patients underwent a base-line clinical examination, standard 12-lead electrocardiography, cardiopulmonary exercise testing, resting and dobutamine stress echocardiography, and cardiac catheterization including coronary angiography. Patients underwent nonsurgical reduction of the septum when the predefined criteria were met. All the studies performed before the procedure, except cardiac catheterization, were repeated at six weeks and again more than two years after the procedure.

Electrocardiography

Twelve-lead electrocardiography was performed while the patient was at rest at a paper speed of 25 mm per second before and immediately after nonsurgical reduction of the septum and at the short-term and long-term follow-up visits. Electrocardiograms were analyzed for basic rhythm, QRS axis, PR interval, Q waves, QRS and QT intervals, bundle-branch block, and ST-segment changes.

Resting Transthoracic Echocardiography

Echocardiography was performed with the use of a 2.5-MHz transthoracic ultrasound probe connected to a cardiovascular ultrasound system (SONOS 2000, Hewlett–Packard). M-mode recording of the short axis of the left ventricle was used to measure the dimensions of the left ventricular cavity. The left ventricular end-diastolic diameter was measured at the onset of the Q wave on the simultaneously recorded electrocardiogram, and left ventricular end-systolic diameter was measured at the onset of the aortic component of the second heart sound (A_2) on the phonocardiogram. The left ventricular ejection fraction was estimated as the percentage difference between the cube of the left ventricular end-diastolic diameter and the cube of the left ventricular end-systolic diameter. Left ventricular filling velocities were measured from the pulsed Doppler recordings of the transmitral inflow, according to the recommendations of the American Society of Echocardiography.[17]

Dobutamine Stress Echocardiography

Resting and stress-induced left ventricular outflow tract gradients were determined by dobutamine stress echocardiography according to a standard protocol. Dobutamine was administered by means of an infusion pump at a starting rate of 5 μg per kilogram of body weight per minute, with increments of 5 μg per kilogram per minute every three minutes to a maximal dose of 40 μg per kilogram per minute. Each increment corresponded to one stage of the test protocol. The stress-induced echocardiographic end point for healthy subjects is the achievement of either 85 percent of the predicted target heart rate (220 beats per minute minus their age in years) or the end of the eighth stage of the dobutamine protocol. In patients with hypertrophic cardiomyopathy, chest pain, dyspnea, a drop in arterial pressure of 20 mm Hg or more, and an ST-segment shift of 1 mm or more were also considered as end points.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing with the use of a treadmill was performed according to the modified Bruce protocol[18,19] to determine peak oxygen consumption as an objective measure of patients' maximal functional capacity. During exercise, patients breathed through a mouthpiece and a one-way valve attached to a mass spectrometer and a calibrated pneumotachographic system (AMIS 2000, Innovision)[20] for breath-by-breath gas analysis.

Nonsurgical Reduction of the Septum

Retrograde and transseptal catheterization was performed by the Brockenbrough technique.[21] Left ventricular outflow tract gradients were measured at rest and after the Valsalva maneuver and infusion of dobutamine. A coaxial balloon catheter of 2.0 to 2.5 mm in diameter was introduced into the first septal perforator branch of the left anterior descending coronary artery, the second septal perforator branch, or both and was inflated; the hemodynamic effects of temporary inflation of the balloon were measured. The distribution of the first septal branch, the second septal branch, or both and their contribution to the left ventricular outflow tract gradient were confirmed. With the balloon remaining inflated at the origin of the septal artery, 2 to 5 ml of absolute ethanol was slowly injected into the septal artery and left in situ for five minutes with the use of diacetylmorphine analgesia. Angiography was repeated after the balloon was deflated in order to confirm blockage of the target artery. Measurements of the left ventricular outflow tract gradients were then repeated as described above. If a single large first septal branch was not found or the reduction in the gradient after the ethanol injection was insufficient, a second septal branch, a third septal branch, or both were ablated.

Statistical Analysis

Results are reported as means ±SD. An overall analysis of variance was performed to compare the means at the three time points (before the procedure, six weeks after the procedure, and more than two years after the procedure). We compared the distributions of patients with respect to New York Heart Association (NYHA) class at the three time points. The two-sample Student's t-test was used to compare changes in the patients who had complete heart block with changes in those who did not have complete heart block. For each variable, we analyzed the difference between the measurement obtained before the procedure and that obtained six weeks after the procedure and also the difference between the measurement obtained six weeks after the procedure and that obtained at long-term follow-up. For this purpose, a mixed model was used to take into account the intrapatient and interpatient variability in an outcome attributable to repeated measurements and to allow the inclusion of patients with missing values. Dunnett's test was used to calculate the P values, with adjustment for multiple comparisons. The Proc Mixed program in the SAS software was used to analyze the data (SAS Institute). P values lower than 0.05 were considered to indicate statistical significance.

RESULTS

Study Patients

After preliminary investigations, 8 of the 72 patients were excluded from the study. Three of these patients had an insufficient stress-induced left ventricular outflow tract gradient for eligibility, two had normal exer-

cise tolerance, and three had septal perforator branches of the left anterior descending coronary artery that were unsuitable for nonsurgical septal reduction. The remaining 64 patients, who underwent nonsurgical septal reduction, had a mean age of 48.5±17.2 years; 45 were men and 19 were women. No deaths were recorded by a mean follow-up of 3.0±1.3 years (range, 2.1 to 5.9). Twenty-two patients did not complete the predefined long-term follow-up studies. The findings before and after the procedure and at the short-term follow-up visit in these patients (19 of the 22 patients had short-term follow-up data) were similar to those in the 42 patients in whom long-term follow-up studies were completed. Complete heart block had developed in 14 of these 42 patients by six weeks. All patients had an increase in serum creatine kinase levels

(increase, 1616±1317 U per liter; range, 345 to 7609) after the ablative procedure.

Clinical Status

There were significant improvements in NYHA class from before the procedure to six weeks after the procedure and during long-term follow-up (P<0.001). Before the ablative procedure, 2 patients were in NYHA class I, 16 were in class II, 39 were in class III, and 7 were in class IV. Six weeks after the procedure, 50 patients were in NYHA class I, 9 were in class II, 3 were in class III, none were in class IV, and 2 had no follow-up data. Four patients were lost to follow-up before the long-term follow-up visit. Of the remaining 60 patients, 57 were in NYHA class I, 3 were in class II, and none were in class III or IV. Whereas 46

TABLE 1. RESULTS ON ECHOCARDIOGRAPHY, CARDIOPULMONARY EXERCISE TESTING, AND ELECTROCARDIOGRAPHY.

VARIABLE	BEFORE THE PROCEDURE	6 WK AFTER THE PROCEDURE	AT LONG-TERM FOLLOW-UP	P VALUE*		
				COMPARISON BETWEEN BEFORE PROCEDURE AND 6 WK	COMPARISON BETWEEN 6 WK AND LONG-TERM FOLLOW-UP	THREE-WAY COMPARISON
	mean ±SD (no. of patients)					
Echocardiography						
Left ventricular end-diastolic diameter (cm)	4.2±0.7 (45)	4.8±0.7 (49)	4.8±0.8 (49)	<0.001	0.42	<0.001
Left ventricular end-systolic diameter (cm)	2.6±0.6 (48)	3.3±0.9 (48)	3.2±0.8 (48)	<0.001	0.35	<0.001
Fractional shortening (%)	37±11 (45)	32±10 (48)	31±9 (48)	0.008	0.35	0.002
Interventricular septal thickness (cm)	2.4±0.8 (50)	1.7±0.6 (50)	1.4±0.4 (47)	<0.001	<0.001	<0.001
Left atrial diameter (cm)	4.2±0.7 (47)	4.2±0.6 (47)	4.0±0.7 (47)	0.37	<0.001	<0.001
Isovolumic relaxation time (msec)	87±30 (50)	84±27 (49)	80±30 (50)	0.008	0.04	<0.001
Left ventricular filling time (msec)	479±138 (45)	458±114 (45)	444±125 (42)	0.17	0.35	0.07
Ratio of early diastolic filling velocity to atrial filling velocity	1.1±0.6 (41)	0.9±0.5 (41)	0.7±0.7 (41)	0.16	0.007	<0.001
Left ventricular mass (g)	410±195 (45)	331±127 (49)	287±108 (49)	0.008	<0.001	<0.001
Resting left ventricular outflow tract gradient (mm Hg)	64±36 (49)	16±14 (49)	16±15 (49)	<0.001	0.97	<0.001
Stress-induced left ventricular outflow tract gradient (mm Hg)	132±34 (49)	46±20 (48)	45±19 (48)	<0.001	0.87	<0.001
Cardiopulmonary exercise testing						
Exercise time (min)	6.1±2.8 (49)	9.5±3.4 (49)	10.0±3.2 (49)	<0.001	0.01	<0.001
Peak heart rate (beats per min)	123±19 (52)	120±19 (52)	126±18 (50)	0.05	0.03	0.09
Peak oxygen consumption (ml/kg of body weight/min)	18.4±5.8 (48)	29.2±4.6 (48)	30.0±4.4 (48)	<0.001	0.26	<0.001
Slope of the ventilatory response to carbon dioxide	32.3±5.1 (49)	26.7±3.0 (49)	26.8±3.1 (49)	<0.001	0.94	<0.001
Anaerobic threshold (ml/kg/min)	9.2±2.2 (44)	13.3±2.4 (44)	13.7±2.3 (44)	<0.001	0.46	<0.001
Electrocardiography						
Heart rate (beats per min)	69±13 (59)	72±14 (55)	69±12 (55)	0.15	0.14	0.13
PR interval (msec)	181±26 (59)	186±35 (55)	183±26 (55)	0.41	0.63	0.49
QRS duration (msec)	106±17 (59)	147±19 (55)	148±19 (55)	<0.001	0.90	<0.001
QT interval (msec)	429±53 (58)	441±51 (53)	437±53 (53)	0.02	0.78	0.03
QTc interval (msec)†	454±35 (58)	476±40 (53)	473±45 (53)	0.002	0.89	0.002
QRS axis	20±60 (59)	76±96 (49)	57±85 (49)	0.007	0.35	0.001
R-wave amplitude (mV)‡	32±8 (59)	20±8 (59)	17±7 (59)	<0.001	0.003	<0.001

*All P values are based on repeated-measures analysis for incomplete measurements.

†QTc interval denotes corrected QT interval.

‡The R-wave amplitude was used as an indicator of left ventricular hypertrophy.

patients (72 percent) were classified in NYHA class III or IV before the procedure, none were in these categories two years after the procedure.

Echocardiographic Follow-up

Echocardiographic examination showed changes in the septal thickness, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter and a decrease in the left ventricular outflow tract gradient, as shown in Table 1 and Figures 1 and 2. There were decreases in both the resting left ventricular outflow tract gradient (from 64 ± 36 to 16 ± 15 mm Hg, $P<0.001$) and the stress-induced left ventricular outflow tract gradient (from 132 ± 34 to 45 ± 19 mm Hg, $P<0.001$) between the preprocedural measurement and two-year follow-up. The estimated left ventricular mass decreased from 410 ± 195 g before the procedure to 331 ± 127 g six weeks after the procedure and to

287 ± 108 g at long-term follow-up ($P<0.001$ for the three-way comparison).

Left Ventricular Outflow Tract Gradient According to the Catheter Technique

As measured by the catheter technique immediately after nonsurgical reduction of the septum, the resting gradient had decreased from 59 ± 29 to 10 ± 13 mm Hg, and the stress-induced gradient decreased from 131 ± 37 to 35 ± 26 mm Hg ($P<0.001$).

Cardiopulmonary Exercise Testing

An initial increase in peak oxygen consumption after nonsurgical septal reduction (from 18.4 ± 5.8 to 29.2 ± 4.6 ml per kilogram per minute, $P<0.001$) was maintained during long-term follow-up (Table 1 and Fig. 2).
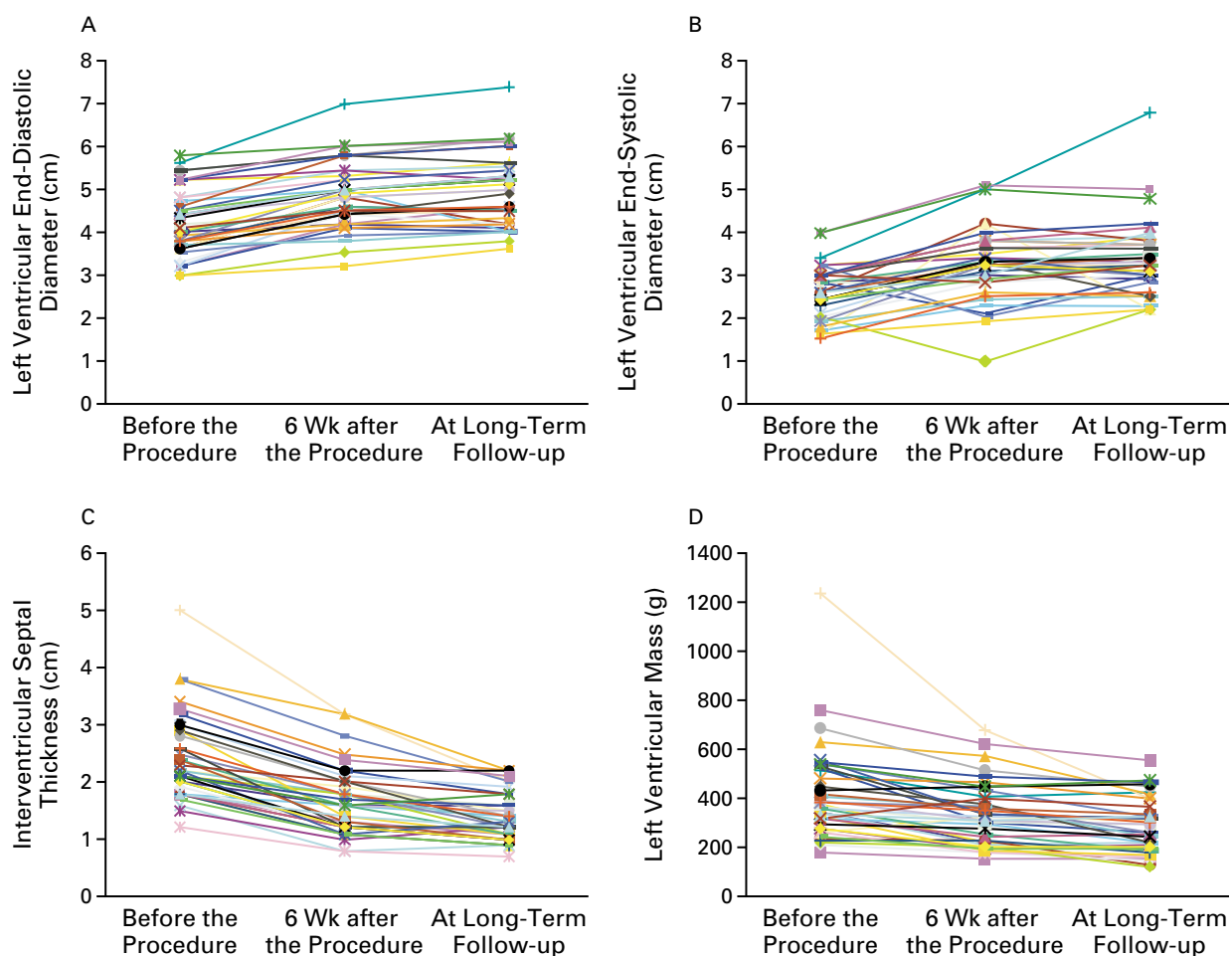

Figure 1. Changes in Echocardiographic Characteristics of Individual Patients, Including Left Ventricular End-Diastolic Diameter (Panel A), Left Ventricular End-Systolic Diameter (Panel B), Interventricular Septal Thickness (Panel C), and Left Ventricular Mass (Panel D).
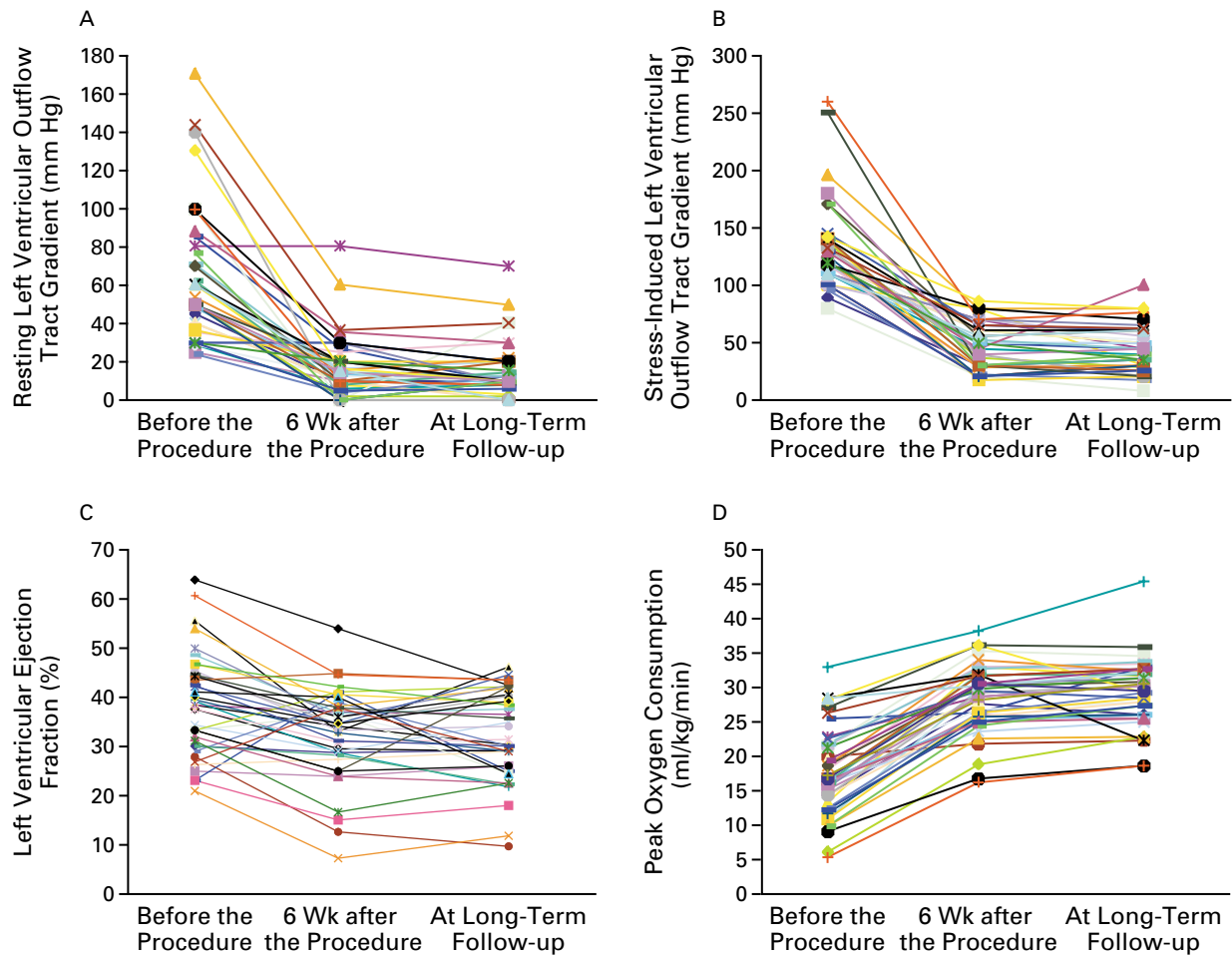
Figure 2. Changes in Individual Patients in Resting and Stress-Induced Left Ventricular Outflow Tract Gradients (Panels A and B, Respectively), Left Ventricular Ejection Fraction (Panel C), and Peak Oxygen Consumption (Panel D).

Peak oxygen consumption is measured in milliliters per kilogram of body weight per minute.

Electrocardiographic Follow-up

There were no significant early or late changes in the heart rate (P=0.15 for the comparison between the heart rate before the procedure and that measured six weeks after the procedure and P=0.14 for the comparison between the heart rate at six weeks and that measured at long-term follow-up). The PR interval was normal in 59 patients at base line but was prolonged in 5. Complete heart block developed in 31 patients during the procedure in the catheterization laboratory, and 17 of these patients eventually required dual-chamber pacemakers for persistent heart block. The PR interval did not change significantly between base line and long-term follow-up (from 181±26 msec to 183±26 msec, P=0.49 for the three-way comparison). There was initial prolongation of the QRS duration after the procedure (from

106±17 msec to 147±19 msec, P<0.001) with no further significant changes observed at long-term follow-up (148±19 msec). Complete right bundle-branch block developed in all patients after ablation. Electrocardiographic data are presented in Table 1 and in Figure 3.

In a subgroup analysis, patients in whom complete heart block developed were compared with those in whom it did not develop (Table 2). Nonsurgical septal reduction resulted in broadly similar improvements in NYHA class, peak oxygen consumption, and left ventricular outflow tract gradients regardless of the presence or absence of complete heart block. There were no significant differences between these groups in echocardiographic measurements at follow-up. However, increases in QRS and QT intervals between base line and long-term follow-up were greater in patients
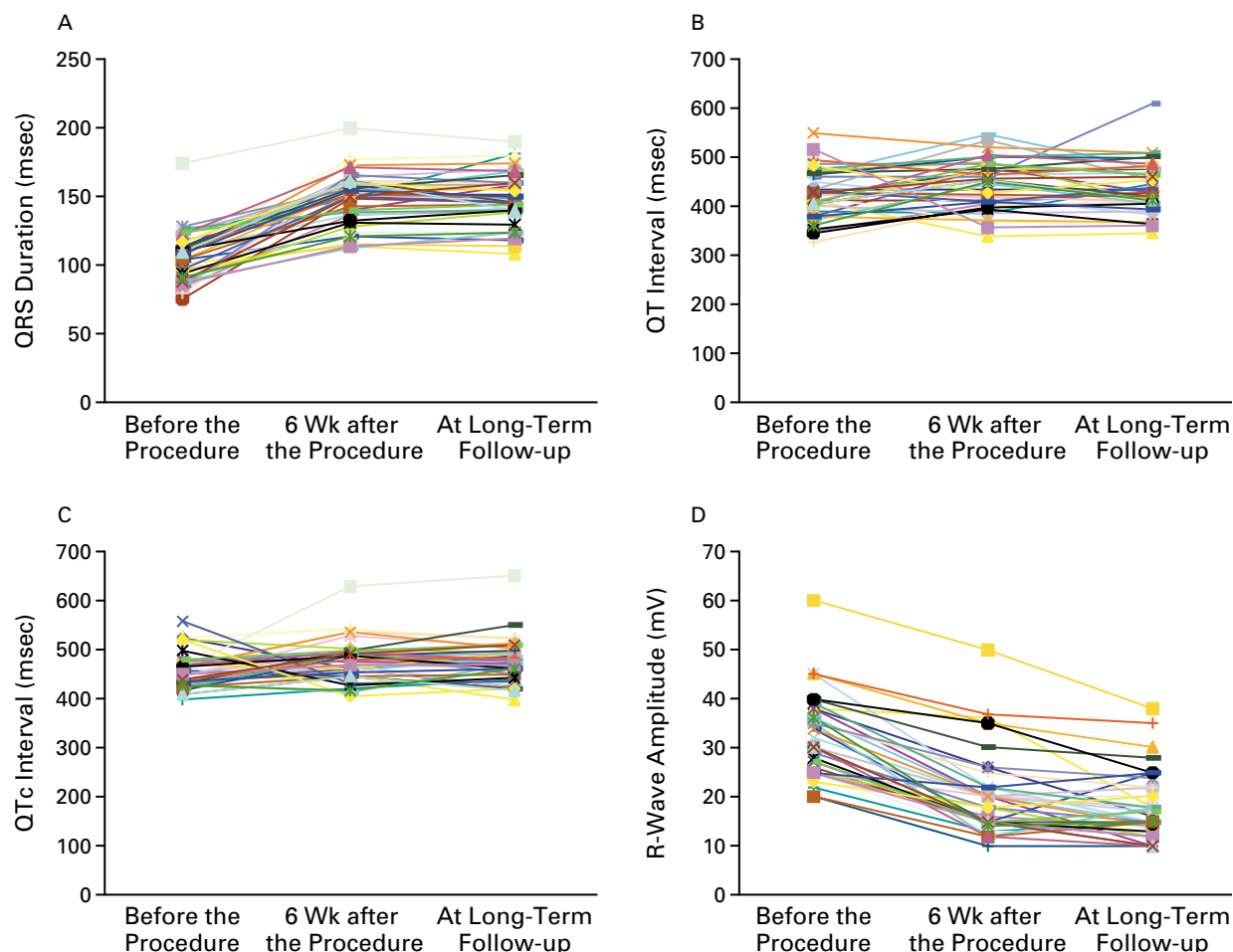
Figure 3. Changes in Electrocardiographic Characteristics of Individual Patients, Including QRS Duration (Panel A), QT Interval (Panel B), Corrected QT Interval (QTc) (Panel C), and R-Wave Amplitude (the Electrocardiographic Indicator of Left Ventricular Hypertrophy, Panel D).

who had complete heart block than in those who did not.

DISCUSSION

Our results demonstrate that nonsurgical septal reduction in patients with drug-resistant hypertrophic cardiomyopathy leads to rapid and long-term improvement in functional capacity (as assessed by subjective and objective measures), in association with reductions in resting and stress-induced left ventricular outflow tract gradients. Furthermore, we observed regression of left ventricular mass similar to that described in a recent report by Mazur et al.[22] Nonfatal complications associated with nonsurgical reduction of the septum in the current study included atrioventricular and other conduction-system blocks, prolongation of QRS and QT intervals, and ventricular remodeling.

The degree of reduction in the outflow tract gradient and in the severity of symptoms achieved by nonsurgical septal reduction in our series of patients was similar to that reported with septal myotomy–myectomy, which has been an established standard surgical treatment for patients with hypertrophic cardiomyopathy for more than 40 years.[23-25] Our findings showed a high incidence of complete heart block (nearly 50 percent) that occurred during the procedure and eventually required placement of a permanent pacemaker in a quarter of all patients. Reports from other centers show a similar rate.[26]

In our study, long-term relief of symptoms and improvement of outflow tract gradients in response to nonsurgical septal reduction occurred regardless of the presence or absence of complete heart block. Other centers have reported procedure-related mor-

TABLE 2. CHANGES FROM BASE LINE TO LONG-TERM FOLLOW-UP AMONG PATIENTS WITH COMPLETE HEART BLOCK AND PATIENTS WITHOUT COMPLETE HEART BLOCK.*

VARIABLE	MEAN CHANGE FROM BASE LINE TO LONG-TERM FOLLOW-UP		P VALUE
	PATIENTS WITHOUT COMPLETE HEART BLOCK (N=28)	PATIENTS WITH COMPLETE HEART BLOCK (N=14)	
NYHA class	2.2	2.3	0.08
Left ventricular end-diastolic diameter (cm)	1.0	0.9	0.12
Left ventricular end-systolic diameter (cm)	0.6	0.7	0.07
Left ventricular mass (g)	108	96	0.33
Resting left ventricular outflow gradient (mm Hg)	47	43	0.15
Stress-induced left ventricular outflow gradient (mm Hg)	86	78	0.06
Exercise time (min)	4.1	3.8	0.05
Peak oxygen consumption (ml/kg/min)	11.8	12.2	0.27
QRS duration (msec)	38	47	0.03
QT interval (msec)	28	33	0.05
R-wave amplitude (mV)†	16	15	0.64

*Data are means among patients with complete data. NYHA denotes New York Heart Association.

†The R-wave amplitude was used as an indicator of left ventricular hypertrophy.

tality of 1 to 4 percent with septal ablation, which is similar to that associated with surgery in experienced centers.[26,27] Nonsurgical septal reduction creates a potential arrhythmogenic substrate by virtue of healed myocardial infarction and subsequent electromechanical ventricular remodeling. Patients with hypertrophic cardiomyopathy are already predisposed to arrhythmogenesis. These issues raised concern regarding the long-term risk of nonsurgical septal reduction, especially in younger patients.[28]

The extent of left ventricular remodeling after myocardial infarction depends on the size of the infarct and has important clinical implications.[29,30] In addition, electrocardiographic changes such as prolongation of the QRS and QT intervals, which may occur after myocardial infarction, may be related to decreased survival rates.[31,32] Contrary to findings in patients after myocardial infarction, we found that nonsurgical septal reduction was associated with limited and almost nonprogressive changes in the size of the left ventricle and in the QRS and QT intervals after 2.1 to 5.9 years of follow-up. Using positron-emission tomography, Kuhn et al. have recently shown that nonsurgical septal reduction produces a well-demarcated area of septal necrosis.[33] Although these findings are reassuring, many years of follow-up may be required in order to identify proarrhythmic complications of nonsurgical septal reduction, since some patients with hypertrophic cardiomyopathy are at risk for sudden death for an extended time, and possibly throughout their lifetimes. Surgical myotomy–myectomy is also

associated with numerous fatal and nonfatal complications, such as myocardial infarction, rupture of the free wall of the ventricle, septal perforation, atrial fibrillation and conduction-system disturbances, cerebrovascular accident, thromboembolism, delayed cardiac tamponade, a need for pacemaker implantation, and recurrence of septal hypertrophy.[26,27]

Dual-chamber pacing is the other potential nonsurgical option for the treatment of drug-refractory obstructive hypertrophic cardiomyopathy. Several early reports suggest that dual-chamber pacing is associated with the improvement of symptoms and reduction in the outflow tract gradient.[34] Unconfirmed reports also indicate that pacing may lead to ventricular remodeling and regression of left ventricular hypertrophy. On the other hand, recent trials have reported that subjective improvement in symptoms during pacing occurs with little objective evidence of an increase in exercise capacity.[35] Moreover, a mean reduction in the outflow tract gradient during pacing is small — on the order of 25 percent — and varies among patients.

There are distinct advantages and disadvantages to each approach to the treatment of hypertrophic cardiomyopathy. Nonsurgical septal reduction is less invasive than surgery, requires a shorter hospital stay, and could be offered to elderly patients or those with coexisting disorders. On the other hand, surgery has proven long-term efficacy and provides greater flexibility than nonsurgical septal reduction for the relief of outflow tract obstruction when other structural ab-

normalities of the left ventricle or mitral-valve disease are present. Our patients were referred to us, and it is therefore difficult to be certain that they are representative of the general population of patients with hypertrophic cardiomyopathy. Patients who require surgery or nonsurgical septal reduction represent a small subgroup (5 percent) of the overall population of patients with hypertrophic cardiomyopathy.[36]

In summary, nonsurgical septal reduction, a potential alternative to surgery for the treatment of hypertrophic cardiomyopathy and outflow tract obstruction, provides substantial relief of symptoms and outflow tract obstruction and improves objective measures of exercise capacity. Further studies are required to determine whether late complications, such as serious cardiac arrhythmias or ventricular remodeling, may occur. Moreover, randomized, controlled trials are needed in order to compare nonsurgical septal reduction with myotomy–myectomy. Nonsurgical septal reduction may be considered an investigational therapeutic procedure offering an alternative to surgery for selected patients with obstructive hypertrophic cardiomyopathy, but it cannot yet be regarded as a primary approach to the treatment of this complex disorder.

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