Percutaneous Radiofrequency Septal Reduction for Hypertrophic Obstructive Cardiomyopathy in Children

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Objectives
The aim of this study was to assess the efficacy of radiofrequency catheter ablation (RFCA) in the treatment of hypertrophic obstructive cardiomyopathy in children.

Background
Hypertrophic obstructive cardiomyopathy is an uncommon cause of left ventricular outflow tract obstruction in children. In symptomatic patients, open heart surgical myectomy has hitherto been the only therapeutic option.

Methods
In 32 children, at a median age of 11.1 (range 2.9 to 17.5) years and weight of 31 (15 to 68) kg, ablation of the hypertrophied septum was performed using a cool-tip ablation catheter via a femoral arterial approach. The median number of lesions was 27 (10 to 63) and fluoroscopic time was 24 (12 to 60) min.

Results
The majority of patients demonstrated an immediate decrease in the catheter pullback gradient (mean 78.5 ± 26.2 mm Hg pre-RFCA versus mean 36.1 ± 16.5 mm Hg post-RFCA, p < 0.01) and a further reduction in the Doppler echocardiographic gradient (mean 96.9 ± 27.0 mm Hg pre-RFCA versus 32.7 ± 27.1 mm Hg post-RFCA, p < 0.01) at follow-up. One patient died due to a paradoxical increase in left ventricular outflow tract obstruction, and another had persistent atrioventricular block that required permanent pacing. Six patients required further procedures (surgery, pacing, or further RFCA) during a median follow-up of 48 (3 to 144) months.

Conclusions
The preliminary results of RFCA for septal reduction in children with hypertrophic cardiomyopathy are promising and merit further evaluation. (J Am Coll Cardiol 2011;58:2501–10) © 2011 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) in childhood is a heterogeneous disease with variable progression (1,2). Left ventricular outflow tract obstruction (LVOTO), which is dynamic in nature, is partly caused by systolic anterior motion of the mitral valvular apparatus (3–5). Symptoms include tiredness, dyspnea with effort, chest pain, exercise-related syncope, or sudden arrhythmic death (6–8). Treatment is aimed at palliation. Whereas in adults myectomy results in elimination of symptoms and improved long-term survival, similar data in children are scarce (9–14). Percutaneous alcohol septal ablation (ASA) was developed as a therapeutic alternative in adult patients for relief of LVOTO (15–18). In children, however, this approach is technically not feasible. With the establishment of radiofrequency catheter ablation (RFCA) for arrhythmias, increasing the depth of the radiofrequency (RF) lesions has been achieved with a variety of advances in catheter technologies, including the use of cool-tip irrigated catheters (19–21).

We have previously demonstrated the ability of percutaneous RFCA to relieve symptomatic LVOTO and also to reduce or dissolve myocardial tumors (22–24). We report on the extended application of this technique in a series of children treated by 2 tertiary referral centers.

Methods
Patients. Between June 1999 and January 2011, 33 patients (20 males), age between 2.9 and 17.5 years (median 11.1 years), and weighing between 15 and 68 kg (median 31 kg), were considered for percutaneous RFCA. Patients were chosen for the RFCA procedure after having failed pharmacological therapy, and surgical myectomy was considered as indicated. RFCA was offered as an alternative to surgical myectomy in both institutions; apart from 2 children whose parents opted for surgery, the remaining patients underwent RFCA as the primary treatment during the study period. Presenting symptoms were increasing tiredness as reported by the parents or the patient (n = 28), dyspnea on exertion and exercise intolerance (n = 16), anginal chest pain with exertion (n = 3), and recurrent nonarrhythmic syncope (n = 8). One child had previously undergone surgical septal myectomy. Standard outpatient investigations included a 12-lead electrocardiogram and Holter, transthoracic Doppl-
echocardiography to document the degree of myocardial septal hypertrophy and the resting gradient across the left ventricular outflow tract (LVOT). Informed consent was obtained from the parents for every interventional procedure. Institutional review board approval was also obtained from the hospital ethics committees at both institutions for the use of RFCA procedure as nonstandard medical care.

Procedure. Procedures were performed under general anesthesia. Radiolucent defibrillator pads were routinely placed for remote defibrillation. Following placement of the femoral venous and arterial sheaths, all patients were routinely heparinized (100 U/kg bolus dose, up to a maximum dose of 5,000 U), and dosage was adjusted to maintain activated clotting time between 250 and 300 s.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY. A detailed assessment of the LVOT was performed by transesophageal echocardiography (TEE), which also helped to direct manipulation of the ablation catheter to the desired anatomic site. The desired anatomic site was the most prominent septal bulge producing narrowing of the LVOT; this was also the most frequent (but not invariably) point of contact of the mitral valve apparatus to the septum in systole.

PACING. Via the femoral vein, temporary pacing electrodes were placed in the right atrium and ventricle. In the initial 12 procedures, baseline pacing was carried out using different atrioventricular (AV) delays (with 10 ms decrements from baseline), while simultaneously measuring the pullback gradient across the LVOT using a 4-F Multitrack catheter (NuMed, Best, the Netherlands). If there was a substantial decrease (>50% from the baseline gradient) in the measured gradient, this was interpreted to mean that the patient might eventually benefit from permanent dual-chamber pacing. This information was obtained with a view to considering permanent pacing as a future option, in the event of nonimprovement of gradient following the RFCA procedure.

ANGIOGRAPHY. Biplane left ventricular angiography was performed, in the 30° right anterior oblique and 60° left anterior oblique projections, to show the level and extent of obstruction (Fig. 1A). In patients presenting with angina, selective left coronary angiograms were obtained to exclude myocardial bridging.

MAPPING THE CONDUCTION SYSTEM. The proximal His bundle was routinely mapped, and its anatomic relation to the LVOTO noted. The LocaLisa mapping system (Medtronic, Minneapolis, Minnesota) was routinely used for this purpose at 1 of the centers. In previous studies, we and others have demonstrated that this system is extremely accurate for continuous localization of standard intracardiac electrodes and, in particular, the His bundle over prolonged periods (25–28). Individual RF lesions were also marked on the LocaLisa image (Fig. 1B). The CARTO (Biosense Webster, Diamond Bar, California) electroanatomic mapping system was used in 2 patients to obtain similar information.

ABLATION. Via a 7-F introducer placed in the femoral artery, a 4-mm cool-tip ablation catheter (Sprinklr, Medtronic; or Thermocool, Biosense Webster, Johnson & Johnson Medical, Waterloo, Belgium) or a catheter with an 8-mm ablation electrode (n = 2; Celsius, Biosense Web-
ster) was introduced into the left ventricle. During catheter manipulation and mapping, a normal saline infusion was run through the catheter at 0.5 to 3 ml/min, increasing to 10 to 20 ml/min during application of each radiofrequency lesion. Smaller patients received lower flow rates to avoid fluid overload, and they also received a single dose of intravenous furosemide (2 mg/kg) during the procedure.

Radiofrequency ablation was commenced at the most apical part of the obstruction. Individual lesions were timed for between 60 and 120 s, with a power setting of 60 W. Catheter tip temperature and impedance were continuously monitored. Linear applications of RF lesions were carried out from this location, working toward the aortic valve. The distance of each lesion from the His bundle was continuously monitored in patients in whom LocaLisa or CARTO was used. Local electrograms recorded from the ablation catheter were checked for His bundle potentials, and if His bundle potentials were present, no energy was delivered at these sites. If such a site was considered a potential target for RF ablation for anatomical reasons, an attempt was made to distinguish a fascicular potential from a proximal His bundle electrogram, by pacing at this site and measuring the paced QRS duration. The RF lesions were applied along different planes of the ventricular septum (to achieve at least 3 lines of lesions between the most apical part of the obstruction and the region under the aortic valve (Fig. 1). Occasionally, and usually in older patients, additional maneuvers were required: for example, curving the catheter on itself within the left ventricular cavity, and then gradually releasing the curve when approaching the target area, to allow the ablation electrode to contact the septal myocardium, (Figs. 2A to 2D). In selected patients, a long sheath was used to maintain stable catheter position during RFCA. The number of lesions was determined purely on anatomical considerations, to cover the target area adequately (the septal bulge producing anatomic obstruction in the LVOT).

ECHOCARDIOGRAPHY. TEE during the procedure and transthoracic echocardiography at the end of the procedure were used to measure the acute change in Doppler gradient, assess aortic and mitral valve function, and to exclude a pericardial effusion.

CARDIAC ENZYMES. In the majority of patients, serum samples for measurement of cardiac troponin T were ob-

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**Figure 2** Different RF Catheter Approaches to the Hypertrophied Septum

In A and B, the hypertrophied septum is directly approached, with the ablation catheter being stabilized by the use of a long sheath (right anterior oblique [RAO] and left anterior oblique [LAO] projections, respectively). In C and D (RAO and LAO projections), the ablation catheter is curved within the left ventricle to facilitate contact with the target tissue. RF = radiofrequency.
Table 1  Demographic Data, Procedural Details and Outcomes for Children Undergoing RFCA for Septal Hypertrophy

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<th>Lesions</th>
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<th>Troponin T (Maximum) μg/L</th>
<th>Pullback Gradient mm Hg (Pre-)</th>
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AV = atrioventricular; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; ECMO = extracorporeal membrane oxygenator; ICD = implantable cardioverter-defibrillator; ICU = intensive care unit; LDH = low-dose heparin; LV = left ventricle; LVOTO = left ventricular outflow tract obstruction; MB = myocardial band; MR = mitral regurgitation; RFA = radiofrequency ablation; RFCA = radiofrequency catheter ablation; VF = ventricular fibrillation; VT = ventricular tachycardia.
tained at baseline, immediately following the ablation procedure, and at 6-h intervals thereafter for up to 24 h after the procedure, to allow for a semiquantitative estimation of myocardial necrosis. In some patients, creatine kinase-myocardial band or lactate dehydrogenase (LDH) values were also obtained.

**Statistical analysis.** Statistical analysis was performed using IBM-SPSS (version 19.0, SPSS Inc., Chicago, Illinois). Gradients before and after were not normally distributed and are presented as median and range. Additionally, we also calculated mean values for pre- and post-pullback and Doppler gradients. To compare the gradients before and after intervention, we used the Wilcoxon matched-pairs signed-rank test. p values <0.01 were considered to be significant. Freedom from reintervention during follow-up was drawn with the Kaplan-Meier method.

**Results**

**Patients.** Thirty-two of the 33 patients underwent RF ablation. One child with Friedreich ataxia had aberrant mitral valve papillary muscle attachments to the ventricular septum on pre-procedural TEE, and no RFCA was performed.

**ABLATION.** The number of RF lesions ranged between 10 and 63 (median 27), and fluoroscopy time between 12 and 60 min (median 24 min). Routine use of a mapping system reduced fluoroscopy time and ensured the application of closely spaced lesions. TEE was useful in monitoring catheter position, and the effect of the lesion, with the ablated area being characterized by irrigation fluid bubble formation followed by increased echodensity.

**COMPlications.** There was 1 procedure-related death in a 4-year-old girl, with a pre-procedure pullback gradient of 130 mm Hg. At the end of the procedure, prior to removal of all the vascular sheaths, the patient developed acute left ventricular dysfunction (left ventricular end-diastolic pressure of 34 mm Hg). TEE demonstrated a paradoxical increase in the degree of LVOTO due to tissue edema at the ablation sites. Following cardiopulmonary resuscitation, she was put on an extracorporeal membrane oxygenator for 3 days, during which there was no improvement in left ventricular function, and treatment was discontinued. Autopsy was not performed. Two patients had complete AV block and required implantation of a dual-chamber pacemaker. In one of them, AV block resolved within 1 week of the procedure. Two patients developed ventricular fibrillation related to catheter manipulation in the left ventricle and required direct current cardioversion. Minor complications included a groin hematoma (n = 1) and superficial burn at the site of the earthing electrode (n = 1, with no residual scarring).

**RELIEF OF OBSTRUCTION.** Gradient reduction, as measured by pullback directly after the procedure, was recorded in the majority of survivors, although individual responses were variable (Table 1). The median pre-procedure pullback gradient was 80 mm Hg (range 10 to 130 mm Hg, mean 78.5 ± 26.2) and decreased to 34 mm Hg (range 10 to 90 mm Hg, mean: 36.1 ± 16.5, p < 0.01). Follow-up echocardiography, performed prior to discharge from hospital, at 6 weeks, at 3 and 6 months post-procedure, and annually thereafter, showed that there was a continuous decrease in the gradient during this interval. The Doppler echocardiographic gradient pre-procedure ranged between 30 and 144 mm Hg (median 100 mm Hg, mean 96.9 ± 27.0 mm Hg). The post-procedure Doppler gradient at the last follow-up ranged between 0 and 140 mm Hg (median 25 mm Hg, mean 32.7 ± 27.1 mm Hg, p < 0.01) (Fig. 3). Apart from the patients requiring reinterventions (surgical or redo-RFCA), who were identified within this interval, the gradient reduction has been maintained at the most recent follow-up in the remaining patients, some of whom have had further minor gradient reductions.

**CARDiac EnZymes.** Troponin T values rose from <0.1 μg/l pre-procedure to a median peak value of 11.2 μg/l (range 1.19 to 31.0 μg/l). Creatine kinase-myocardial band (baseline laboratory reference range 60 to 365 IU/l) and LDH (baseline laboratory reference range <900 IU/l) values, where measured, also showed a significant increase (Table 1).

**POST-PROCEDURAL FOLLOW-UP.** All patients, except the girl who died, were extubated directly after the catheterization procedure. One child who had a persistent sinus bradycardia was monitored on the intensive care unit for a period of 48 h. Oral aspirin (5 mg/kg/day) was commenced on the evening of the procedure and continued for 6 months. Patients were monitored for 24 to 48 h, and subsequently discharged from the hospital. One child (patient 27) (Table 1) showed an acute reduction in the severity of mitral valve regurgitation directly after the procedure. Of the remaining patients, there was a decrease in the degree of pre-existing mitral valve regurgitation in a further 11 patients, all of whom had had varying degrees of systolic anterior movement of the mitral valve. In particular, apart from the single patient who died, none of the others demonstrated an increase in the degree of mitral regurgitation.

**LATE FOLLOW-UP.** All survivors have undergone serial outpatient follow-up (median follow-up duration of 48 months; range 3 to 144 months). All but 1 of the patients had symptomatic improvement following the procedure: tiredness with exertion (28 pre- to 1 post-RFCA); dyspnea with effort (16 to 0); exertional angina (3 to 0); nonarrhythmic syncope (8 to 0). Formal exercise testing was not performed in this series for several reasons: young patient age, absence of pre-procedure exercise tests, patient referral from other countries without facilities for standardized exercise testing.

Additional procedures were undertaken in 5 patients. Patient #26 (Table 1, Fig. 4) in whom there was no change...
in LVOTO after ablation underwent surgical myectomy. Four children (Patients #1, #5, #23, and #24) underwent a second RFA procedure between 6 and 64 months after initial ablation. All had demonstrated a good acute response to the initial RFCA. TEE during RFCA demonstrated that aberrant papillary muscle attachments of the mitral valve contributed significantly to residual LVOTO in Patient #1, who underwent surgical myectomy and mitral valve replacement during the same hospital admission. In Patient #5 there was a further reduction in LVOTO following the second ablation. Patient #23 had prominent His bundle potentials recorded at the ideal ablation site during the second procedure; despite having a permanent pacemaker, it was decided not to produce iatrogenic AV block, and RF lesions were applied at adjacent LVOT sites without His potentials. Patient #24 had no improvement in LVOTO during the second RFA. Temporary AV sequential pacing, however, showed a marked improvement in LVOTO, and a permanent pacemaker was therefore implanted. At 39 months after this procedure, she underwent a third RFCA for recurrent LVOTO, with an excellent response. Figure 4 shows that there was an 87.5% freedom from reinterventions at 10 years of follow-up.

**LATE ARRHYTHMIAS.** Patient #2 with familial HCM has had implantable cardioverter-defibrillator implantation, 5 years after RFCA, for recurrent sustained monomorphic ventricular tachycardia. Patient #22 died in her sleep, 2.5 years after RF ablation. She had been noted at follow-up to have recurrent nonsustained (asymptomatic) ventricular arrhythmia and had been treated with a beta-blocker. The mechanism of death was presumed to be arrhythmic.

**Discussion**

**Surgery.** Timely relief of LVOTO in the setting of HCM has been shown in adults to relieve symptoms, restore normal exercise tolerance, and improve life expectancy. In selected centers, surgical myectomy in children results in an excellent hemodynamic outcome, with very low mortality. In the series of Theodoro et al. (9) from the Mayo Clinic (n = 25, over a 20-year period), there were no operative or late deaths (although 2 patients required circulatory support with an aortic balloon pump), and 2 patients required a repeat surgical myectomy. Individual surgical series for relief of LVOTO in pediatric patients are small. The median age of the patients in the Mayo Clinic series was 14 years (range 2 months to 20 years), which is considerably older than in our series. Septal myectomy involves the resection of a relatively small amount of muscle from the proximal ventricular septum (approximately 3 to 5 g) (29). This appears to widen the LVOT sufficiently and to abolish the Venturi forces that produce systolic anterior motion of the mitral valve leaflets (30–32). This has important implications for the RFCA procedure described here, as the effective lesion size and depth required to relieve LVOTO is sufficiently circumscribed to be amenable to catheter ablation.

**RFCA.** The use of electrical energy to treat LVOTO was initially described by Armistead et al. (33) during open heart surgery.
surgery. Compared with conventional RF ablation, cool-tip ablation allows the use of longer durations and higher powers of radiofrequency current to achieve a larger lesion volume and lesion depths of 6 to 10 mm (34–38). Based on these studies and on clinical data, we aimed to achieve catheter tip temperatures between 40°C and 50°C, with a nominal power setting of 60 W. The mechanism of RF effect is most likely tissue desiccation, followed by muscle atrophy. Lawrenz et al. (39) recently demonstrated the beneficial effect of RF ablation in adult patients with LVOTO. They suggested that the mechanism of benefit might be the result of a local movement disorder, preventing the treated segment of septum from contracting effectively. This effect was also seen in some of our patients (Fig. 5). In >50% of their patients, they performed RF ablation from the right ventricle (39). Given that the septal thickness in some patients may exceed 30 mm, it is unclear how transcatheter lesions on the right ventricular septum might create adequate relief of LVOTO. If validated from further observations, however, this approach might be particularly suited to young children. **Permanent pacing.** Sequential AV pacing, which was performed in some children early in our experience, was discontinued after data from adult studies demonstrated no consistent benefit (40–42). No attempt was made during RFCA to deliberately create left bundle branch block, and none of the patients had left bundle branch block at follow-up (43).

**Assessment of outcome.** Serial echocardiographic follow-up showed further improvement in LVOTO, suggesting that there is continuing tissue remodeling following the procedure. Peak serum cardiac enzyme levels did not appear to correlate with the degree of gradient reduction and might not have any long-term prognostic value. **Are the RF lesions potentially arrhythmogenic?** ASA is associated with intramyocardial scarring, and the same applies to RFCA. At follow-up, ASA patients appear to be at a higher risk for arrhythmic events when compared with surgical my-
ectomy patients (44,45). Saul et al. (46) demonstrated in an infant lamb model that RF lesions increase in size, with loss of demarcation of the borders and fibrous tissue invasion of the surrounding normal myocardium. Two patients in our series developed a late arrhythmia (1 nonsustained) and may have had natural progression of their HCM. These data are comparable to the best pediatric surgical series (9).

**How to avoid procedural complications?** Carrying out RF ablation at a very advanced stage of disease may be associated with a higher risk of paradoxical increase in LVOTO from tissue edema, and this needs to be considered in planning therapy and the timing of RFCA. The safety of the procedure might be improved by careful anticoagulation, use of smaller fluid volumes to irrigate the catheter tip, and the judicious use of diuretics to avoid fluid overload. Two patients developed AV block (1 recovered) and required permanent pacing.

Retrospective evaluation of the local electrograms at the ablation site did not identify a clear His potential. In addition, 2 patients had transient ventricular fibrillation, which is a risk associated with prolonged catheter manipulation in the left ventricle. These risks are indeed higher, when compared with surgery. It must be stressed, however, that surgical series are small, and not all surgical series have shown results compared with the Mayo Clinic gold standard (where 1 patient required permanent pacing, and 2 patients required temporary use of an aortic balloon pump) (9). Aberrant mitral valve papillary muscle attachments might play an important role in causing LVOTO and should be identified by pre-procedural TEE.

**Conclusions**

RFCA adds to the therapeutic options available for relief of symptomatic LVOTO in young patients. The benefits include ease of application, use of standard catheter and ablation equipment, repeatability, and short hospital stay. The procedure is more controlled than ASA. Identification of the His bundle and preservation of AV conduction are also potential benefits. If the safety and efficacy of RFCA can be established in larger series, it may result in a lowering of the threshold for interventional therapy of HCM in children.

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