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HYPERTROPHIC CARDIOMYOPATHY

Updated Meta-Analysis of Septal Alcohol Ablation Versus Myectomy for Hypertrophic Cardiomyopathy

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Objectives The purpose of this study was to perform a systematic review and meta-analysis of comparative studies to compare outcomes of septal ablation (SA) with septal myectomy (SM) for treatment of hypertrophic obstructive cardiomyopathy (HOCM).

Background SM is considered the gold standard for treatment of HOCM. However, SA has emerged as an attractive therapeutic alternative.

Methods A Medline search using standard terms was conducted to determine eligible studies. Due to a lack of randomized control trials, we included observational studies for review.

Results Twelve studies were found eligible for review. No significant differences between short-term (risk difference [RD]: 0.01; 95% confidence interval [CI]: −0.01 to 0.03) and long-term mortality (RD: 0.02; 95% CI: −0.05 to 0.09) were found between the SA and SM groups. In addition, no significant differences could be found in terms of post-intervention functional status as well as improvement in New York Heart Association functional class, ventricular arrhythmia occurrence, re-interventions performed, and post-procedure mitral regurgitation. However, SA was found to increase the risk of right bundle branch block (RBBB) (pooled odds ratio [OR]: 56.3; 95% CI: 11.6 to 273.9) along with need for permanent pacemaker implantation post-procedure (pooled OR: 2.6; 95% CI: 1.7 to 3.9). Although the efficacy of both SA and SM in left ventricular outflow tract gradient (LVOTG) reduction seems comparable, there is a small yet significantly higher residual LVOTG amongst the SA group patients as compared with the SM group patients.

Conclusion SA does seem to show promise in treatment of HOCM owing to similar mortality rates as well as functional status compared with SM; however, the caveat is increased conduction abnormalities and a higher post-intervention LVOTG. The choice of treatment strategy should be made after a thorough discussion of the procedures with the individual patient. (J Am Coll Cardiol 2010;55:823–34) © 2010 by the American College of Cardiology Foundation

Septal myectomy (SM) has been regarded as the gold standard for treatment of hypertrophic obstructive cardiomyopathy (HOCM). The less-invasive septal ablation (SA) is rapidly emerging as an attractive alternative for treatment of HOCM. The number of SAs performed worldwide since its introduction in 1995 has now reached over 5,000 (1,2), surpassing the number of SM performed over the last 45 years. It is estimated that SA procedures are 15 to 20 times more common than SM for HOCM (2). At some centers, the frequency of SM has been reduced by over 90% in favor of performing SA as definitive treatment strategy (1).

Septal myectomy has been shown to be effective in eliminating left ventricular outflow tract (LVOT) obstruction, resulting in reduction in sudden death and improvement in functional status (3). The technique has low post-operative morbidity and mortality (3). The short-term and medium-term data for SA have been encouraging as well. However, long-term data are scarce and are the subject of further research.

We aimed to carry out a systematic review and meta-analysis of the available evidence to compare the outcomes after SA and SM. Due to the conspicuous absence of randomized trials, observational studies have been used to synthesize evidence.

Methods

Search strategy. Medline search was conducted with terms like "septal ablation," "septal myocardial ablation," "non surgical septal reduction," "transcoronary ablation of septal hypertrophy," "percutaneous transluminal septal

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Abbreviations and Acronyms

CHB = complete heart block
CI = confidence interval
HOCM = hypertrophic obstructive cardiomyopathy
ICD = implantable cardioverter-defibrillator
IVS = interventricular septum
LBBB = left bundle branch block
LVOT = left ventricular outflow tract
LVOTG = left ventricular outflow tract gradient
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
OR = odds ratio
RBBB = right bundle branch block
RD = risk difference
SA = septal ablation
SAM = systolic anterior motion (of mitral valve)
SM = septal myectomy
SMD = standardized mean difference

myocardial ablation," and "alcohol ablation" in association with "cardiomyopathy, obstructive," "cardiomyopathy, familial," or "cardiomyopathy, hypertrophic."

Study characteristics. We included all observational studies (prospective/retrospective cohort and case control studies) comparing the outcome of SA with SM in adult patients with refractory HOCM. Case series and case reports were excluded from the review.

Outcome measures. Primary outcome was defined as 30-day all-cause mortality. Secondary outcomes included functional status, reinterventions, pacemaker insertions, ventricular arrhythmias, cardiac dimensions, mitral regurgitation (MR), systolic anterior motion (SAM) of mitral valve (MV), length of hospital stay, and exercise tolerance.

Meta-analysis. Meta-analysis was conducted with "metan" function in Stata version 10.0 (StataCorp, College Station, Texas). Unless significant heterogeneity was encountered, fixed-effects modeling was used. Odds ratios (ORs), risk differences (RDs), and standardized mean differences (SMDs) were used to report pooled estimates. Assessment of heterogeneity ($I^2 > 50\%$; $p < 0.05$) was achieved by comparing baseline characteristics and methodology differences across studies. In cases of significant heterogeneity, random effects meta-analysis was conducted. The random effects model was explored with meta-regression techniques incorporating covariates, namely country of study and follow-up duration, to evaluate the reasons for heterogeneity.

Two strategies were adopted for analysis of left ventricular outflow tract gradient (LVOTG) and New York Heart Association (NYHA) functional class. We first compared the post-procedure measurement between the 2 groups to assess the equivalence of the end point. The second strategy involved determination of the change occurring after procedure compared with pre-intervention time for both the groups. This change was subsequently compared between the 2 groups. To obtain mean change and SD of the difference, variances were imputed with the p values mentioned. In circumstances where the difference was reported as $p < 0.05$, $p < 0.001$, and so forth, the upper level of the p value was considered, because this resulted in a conservative estimate and down-weighting of the studies in the meta-analysis, which failed to provide accurate p values. In case of absence of meaningful p values, the variance was imputed with calculated correlation coefficients per strategies well-described elsewhere (4,5).

Results

The search strategy retrieved 288 title-abstracts for review. Of these, 177 lacked a control/comparison group; 39 were case reports or case series; and 60 were reviews, consensus articles, or expert opinion on the subject. Twelve retrospective cohort studies (6–17) were included for data extraction and analysis. Studies from the Mayo clinic (6,7,12) were derived from the same database. Hence, the study encompassing the larger time frame (1998 to 2006) was included (7). In the Cleveland Clinic experience, conduction abnormalities and mortality outcomes were derived from follow-up studies (15,16). Other clinical and echocardiographic end points were derived from the original study (14).

Table 1 depicts the baseline characteristics of included studies. It also provides an insight into potential biases in each study impacting our inferences. Tables 2 and 3 demonstrate the estimated effect sizes for comparisons between SA and SM groups in terms of clinical and echocardiographic parameters, respectively. None of the studies reported differences in short-term mortality, arrhythmias, and re-interventions. Jiang et al. (13) reported a significantly higher long-term mortality in the SM group than the SA group. On the contrary, Ralph-Edwards et al. (9) reported higher long-term mortality in the SA group. No significant difference in adjusted 4-year survival rates was observed in the Mayo clinic experience (7). However, survival free of death and severe symptoms was lower among patients age <65 years undergoing SA than those undergoing SM.

Two studies (9,14) reported higher mean NYHA functional class after SA than after SM. These studies also reported higher LVOTG after ablation than after myectomy. However, no significant differences were discernible in NYHA functional class reduction or LVOTG reduction after the procedure in any study. Table 4 presents pooled estimates for all outcomes. No significant short-term or long-term mortality benefit was apparent, yet a significantly higher rate of pacemaker implantation and a higher LVOTG were observed after ablation than after myectomy.

Mortality. No study reported a significant difference in short-term mortality between the 2 groups (Fig. 1). On pooled analysis, the RD for short-term mortality between SA and SM groups was insignificant (RD: 0.01; 95% confidence interval [CI]: 0.01 to 0.03, $p = 0.35$).

A random effects meta-analysis was performed to compare long-term mortality, due to significant heterogeneity. No statistical difference was observed (RD: 0.02; 95% CI: −0.05 to 0.09). Baseline demographic and clinical differences (Table 1) between the 2 groups likely accounted for

Table 1 Baseline Characteristics

First Author/ Year (Ref. #)	Center/Country Study Period	Inclusion Criteria	SA/SM,n	Characteristic Differences Between Study Groups	Matching	SA/SM			Outcomes Reported
						Age, yrs Mean (SD)	% Men	Follow-Up	
Sorajja 2008 (7)	Mayo Clinic, U.S. 1998–2006	NYHA III–IV or CCS III–IV refractory to medical treatment; resting gradient ≥30 mm or ≥50 mm with provocation; IVS ≥15 mm, no MV disease	138/123	More hypertension and CAD in SA; higher LVOTG among SA group	Age and sex	61 (19)/ 60 (19)	39/39	4 yrs/4 yrs	Mortality, pacemaker insertions, heart blocks, ventricular arrhythmias, tamponade, functional status, reinterventions, cardiac dimensions
Nagueh 2001 (8)	Baylor and Mayo, U.S., NR	Resting LVOTG ≥40 mm, IVS of at least 15 mm	41/41	None that were measured	Age LVOTG	49 (17)/ 49 (16)	NR	1 yr/1 yr	Mortality, pacemakers, heart blocks, ICD insertions, functional class, ventricular arrhythmias, reinterventions, MR, AR, exercise tolerance, cardiac dimensions
Vural 2007 (11)	Turkey 2002–2006	LVOTG ≥50 mm, IVS of at least 17 mm	16/24	Higher clinical symptoms, lower LVOT, lower MR, lower SAM in SA	NR	25 (7.3)/ 24 (6.6)	88/83	1 yr/1 yr	Mortality, pacemaker, heart blocks, functional status, reinterventions, cardiac dimensions, hospital stay duration, MR, SAM
Ralph-Edwards 2005 (9)	Canada 1998–2003	Symptomatic adults with HOCM	54/48	Higher age, higher SBP, higher CAD, better NYHA class, decreased posterior wall thickness and IVS in SA group	NR	59 (15)/ 46 (17)	48/63	5 yrs/5 yrs	Mortality, pacemaker, functional status, cardiac dimensions, composite outcomes, hospital stay duration, MR, SAM
Firoozi 2002 (17)	United Kingdom 1990–2000	Resting LVOTG ≥50 mm, NYHA of at least II	20/24	Higher age in SA group	Clinical features, cardiac dimensions, LVOTG, exercise parameters	49 (13)/ 38 (16)	60/54	1 yr/1 yr	Mortality, pacemakers, functional status, cardiac dimensions, exercise tolerance
Jiang 2004 (13)	China 1994–2002	Resting LVOTG ≥30 mm, provocable LVOTG ≥50 mm, IVS ≥15 mm, NYHA III or CCS III or syncope >2/m	43/11	NR	NR	45 (13–74)/ 36 (11–69)*	NR	2 yrs/2 yrs	Mortality, pacemakers, heart blocks, ventricular arrhythmias, reinterventions, cardiac dimensions,
van der lee 2005 (10)	the Netherlands 1986–1999 SM 1999–2005 SA	Resting/provocable LVOTG ≥50 mm, mitral leaflet area >12 cm^2	43/29	Higher age, lower MR grade in SA	NR	52 (17)/ 44 (12)	NR	1 yr/1 yr	Mortality, pacemakers, ICD insertions, functional status, ventricular arrhythmias, reinterventions, cardiac dimensions, MR, SAM, mitral leaflet area
Qin 2001 (14)	Cleveland Clinic, U.S. 1997–1999*	Severe symptoms refractory to medical treatment with resting or provocable LVOTG ≥50 mm	25/26†	Higher SBP, comorbidities, more women, higher age in SA group	NR	63 (14)/ 48 (13)	28/62	3 months/ 3 months*	Mortality, pacemakers, heart blocks, functional status, reinterventions, cardiac dimensions, MR, SAM, hospital stay duration

*Mean (range). †Follow-up studies: Kwon et al. (16) reporting outcomes on mortality up to 2000; n = 55 (SA)/98 (SM). Mean follow up period in both groups was 8 years. Qin et al. (15) reporting outcomes on heart block and pacemakers up to 2004; n = 70 (SA)/134 (SM).
AR = aortic regurgitation; CCS = Canadian Cardiovascular Society; ICD = implantable cardioverter defibrillator; IVS = interventricular septum; LA = left atrium; LBBB = left bundle branch block; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; LVOTG = left ventricular outflow tract gradient; MR = mitral regurgitation; MV = mitral valve; NR = not reported; NYHA = New York Heart Association functional class (range: I to IV); RBBB = right bundle branch block; SA = septal ablation; SAM = systolic anterior motion; SBP = systolic blood pressure; SM = septal myectomy.

JACC Vol. 55, No. 8, 2010
February 23, 2010:823–34

Table 2 Comparison Estimates of Clinical Characteristics Determined After Intervention Between SA and SM Groups

First Author/ Year (Ref. #)	Short-Term Mortality*	Long-Term Mortality*	LBBB†	RBBB†	Pacemaker Implantation†	Arrhythmias†	Re-Intervention†	NYHA Functional Class‡	NYHA Functional Class Reduction‡
Soraja 2008 (7)	0.01 (−0.02 to 0.03)	Adjusted 4-yr survival rates similar	2/138 in SA group	0/138 in SA group	10.2 (3 to 34.4)§	3.6 (0.4 to 33)	14/138 in SA group	9% in III/IV in SA group	3.0 ± 0.0 pre to 1.5 ± 1.0 post in SA group
Nagueh 2001 (8)	0.02 (−0.04 to 0.09)	0 (−0.05 to 0.05)	—	—	1.1 (0.5 to 2.7)	0.23 (0.02 to 2.2)	0/41 in SA group	−0.3 (−0.7 to 0.2)	—
Vural 2007 (11)	0 (−0.10 to 0.10)	0 (−0.10 to 0.10)	8.6 (1.5 to 49.4)§	8.5 (0.4 to 188.9)	4.7 (0.2 to 123.9)	—	3.3 (0.3 to 39.7)	0.14 (−0.5 to 0.8)	−0.08 (−0.7 to 0.6)
Ralph-Edwards 2005 (9)	0 (−0.04 to 0.04)	0.09 (0.01–0.18)§	—	—	Adjusted HR 2.98, p = 0.14	—	—	0.8 (0.4 to 1.2)§	—
Firoozi 2002 (17)	0.01 (−0.1 to 0.1)	—	—	—	4.1 (0.4 to 42.5)	—	—	0.3 (−0.3 to 0.9)	−0.6 (−1.2 to 0.03)
Jiang 2004 (13)	−0.07 (−0.2 to 0.1)	−0.4 (−0.7 to −0.1)§	0.04 (0 to 0.99)§	22 (1.2 to 396.4)§	1.4 (0.06 to 30.9)	0.5 (0.07 to 2.9)	0.8 (0.3 to 21.3)	—	—
van der lee 2005 (10)	0.05 (−0.04 to 0.1)	0 (−0.06 to 0.06)	—	—	6.7 (0.4 to 129.8)	10.2 (0.6 to 189)	2.9 (0.3 to 27.1)	0.3 (−0.1 to 0.8)	−0.3 (−0.8 to 0.2)
Qin 2001 (14)	0.02 (−0.03 to 0.06)‖	0.16 (0.03 to 0.029)§‖	0.03 (0.01 to 0.07)§¶	214.5 (12.8 to 3585.1)§¶	1.9 (1.02–3.6)§¶	—	6/25 in SA group	0.6 (0.01 to 1.1)§	−0.1 (−0.7 to 0.4)

All estimates mentioned as effect size (95% confidence interval). *Risk difference estimates. †Odds ratio estimates. ‡Standardized mean difference estimate. §Significant effect estimates; $p < 0.05$ is considered significant. ‖Mortality estimates for Cleveland Clinic experience reported by Qin et al. (14) in 2001 were derived from follow up study (16). ¶Conduction abnormality estimates for Cleveland clinic experience reported by Qin et al. (14) in 2001 were derived from follow up study (15).
HR = hazard ratio; other abbreviations as in Table 1.

the heterogeneity. Older age and more comorbidities were encountered in the SA group than the SM group in several studies (9,14), which might account for poorer outcomes in the former group. On meta-regression analysis, no significant difference was observed on the basis of the country of the study (meta-regression coefficient: −0.013, p = 0.67). However, a significant influence of follow-up duration was demonstrated (meta-regression coefficient: 0.002; p = 0.006), implying that RD for long-term mortality between SA and SM groups increased with corresponding increase in follow-up duration, partially explaining the observed heterogeneity.

Pacemaker implantation. Figure 2 demonstrates that the permanent pacemaker implantation rate was considerably higher in the SA group, compared with the SM group (pooled OR: 2.6, 95% CI: 1.7 to 3.9). Right bundle branch block (RBBB) were more commonly encountered after ablation than after myectomy (pooled OR: 56.3; 95% CI: 11.6 to 273.9). Meta-analysis of post-procedure left bundle branch block (LBBB) was limited, due to significant heterogeneity (I^2: 93.7%, p < 0.001). Two studies (13,15) reported a significantly higher LBBB after myectomy, compared with after ablation. On the contrary, Vural et al. (11) reported higher LBBB in the SA group. A pooled estimate/meta-analysis was deemed fallacious in this case.

Functional status. Meta-analysis with random effects modeling revealed no significant difference in the post-procedure NYHA functional class between the 2 study groups (SMD: 0.30; 95% CI: −0.03 to 0.63) (Fig. 3).

Figure 4 demonstrates the comparison of NYHA functional class reduction after procedure between the SA and SM groups. None of the studies showed significant differences in NYHA functional class reduction between the 2 strategies. The pooled estimate was statistically insignificant (SMD: −0.27; 95% CI: −0.54 to 0.01).

Cardiopulmonary performance status, with oxygen consumption during graded exercise protocols, was reported in few studies (8,17). Nagueh et al. (8) reported a highly significant improvement in exercise duration, peak oxygen consumption, and METS in both the SA and SM group of patients. The magnitude of improvement was similar in both groups at 1-year follow-up. However, Firoozi et al. (17) reported a superior benefit in performance status with SM during immediate post-procedure and 1-year follow-up periods.

MV abnormalities. The MR and SAM have been quantified differently across studies. No study (8,9,11) reported a significant difference in the occurrence of post-procedure moderate-severe MR between the 2 groups. The pooled OR was statistically insignificant (1.44, 95% CI: 0.6 to 3.5). van der lee et al. (10) included subjects with an increased mitral leaflet area >12 cm^2. Mean pre-procedure MR grade was significantly higher in the SM group. All SM group patients underwent a concomitant mitral leaflet extension surgery, whereas no MV correction procedure was done in the SA group patients.

Table 3 Comparison Estimates of Echocardiographic Characteristics Determined After Intervention Between SA and SM Groups

First Author/ Year (Ref. #)	MR*	SAM*	LVOTG†	LVOTG Reduction†	IVS†	IVS Reduction†	LVEDD†	LVESD†	LVEF†	LA Size†
Sorajja 2008 (7)	—	—	10 ± 19 mm in SA group	84 ± 60 mm pre-SA to 10 ± 19 mm post-SA	—	16 ± 7 g in SA; 6 ± 4 g in SM‡	—	—	—	—
Nagueh 2001 (8)	0.3 (0.01 to 8.2)	—	0.3 (−0.09 to 0.8)	−0.04 (−0.5 to 0.4)	−0.1 (−0.5 to 0.3)	0.1 (−0.4 to 0.5)	0.3 (−0.1 to 0.7)	−0.6 (−1.0 to −0.1)§	0.2 (−0.2 to 0.6)	—
Vural 2007 (11)	3.7 (0.6 to 23)	1.4 (0.3 to 5.6)	−0.5 (−1.1 to 0.2)	−0.12 (−0.8 to 0.5)	—	—	0.1 (−0.5 to 0.7)	−1.2 (−1.9 to −0.5)§	—	—
Ralph-Edwards 2005 (9)	1.2 (0.4 to 3.9)	4.8 (2.0 to 11.9)§	0.7 (0.3 to 1.1)§	0 (−0.4 to 0.4)	—	—	—	—	—	—
Firoozi 2002 (17)	—	—	0.6 (−0.06 to 1.2)	0.05 (−0.5 to 0.7)	−0.2 (−0.8 to 0.4)	—	0.5 (−0.1 to 1.1)	3.2 (2.3 to 4.1)§	40 ± 7% in SA group 44 ± 9% in SM group‖	−0.1 (−0.7 to 0.5)
Jiang 2004 (13)	—	—	0.4 (−0.2 to 1.1)	−0.4 (−1.1 to 0.3)	14 ± 3 mm in SA group	24 ± 2 mm pre to 14 ± 3 mm post in SA group	—	—	—	38 ± 2 mm in SA group
van der lee 2005 (10)	0.8 ± 0.8 in SA group 0.6 ± 0.6 in SM group¶	1.3 ± 0.9 in SA group 0.5 ± 0.7 in SM group#	0.4 (−0.1 to 0.8)	−0.03 (−0.5 to 0.4)	−0.3 (−0.8 to 0.2)	−0.1 (−0.6 to 0.4)	0 (−0.5 to 0.5)	0.3 (−0.2 to 0.7)	−0.1 (−0.6 to 0.3)	−0.1 (−0.6 to 0.4)
Qin 2001, 2004 (14,15)	9 ± 3 ml in SA group 8 ± 5 ml in SM group**	0.6 ± 0.8 in SA group 0.6 ± 0.5 in SM group#	1.2 (0.6 to 1.8)§	−0.1 (−0.3 to 0.1)	0.6 (0.1 to 1.2)§	−0.5 (−1.1 to 0.02)	−0.1 (−0.7 to 0.4)	—	0.4 (−0.2 to 0.9)	−0.1 (−0.7 to 0.4)

All estimates mentioned as effect size (95% confidence interval). *Odds ratio estimates. †Standardized mean difference estimate. ‡Estimate of weight of myocardial ablation from Sorajja et al. (7) on a smaller subset of patients. §Significant effect estimates; $p < 0.05$ is considered significant. ‖Fractional shortening %. ¶Mean MR grade. #Mean SAM grade. **Mean MR volume.

Abbreviations as in Table 1.

Table 4 Pooled Effect Estimates for Outcomes Comparing SA With SM

Characteristic	Pooled Studies (Ref. #s)	Estimate Used	Fixed/Random Effects	Heterogeneity Estimate		Pooled Estimate	95% Confidence Interval	p Value
				I^2 (%)	p Value			
Short-term mortality	(7–13,16,17)	RD	Fixed	0	0.95	0.01	−0.01 to 0.03	0.35
Long-term mortality	(8–13,16)	RD	Random	75	<0.01	0.02	−0.05 to 0.09	0.55*
LBBB	(11,13,15)	OR	Random	94	<0.01	0.22	0.002 to 13.28	0.48*
RBBB	(8,10,16)	OR	Fixed	26	0.26	56.33	11.59 to 273.88	<0.001
Pacemaker implantation	(7,8,10,11,13,15,17)	OR	Fixed	41	0.12	2.57	1.68 to 3.93	<0.001
Ventricular arrhythmias	(7,8,10,13)	OR	Fixed	52	0.10	1.34	0.54 to 3.32	0.52
Re-interventions	(8,9,11)	OR	Fixed	0	0.78	2.37	0.54 to 10.51	0.26
MR	(8,9,11)	OR	Fixed	0	0.39	1.44	0.59 to 3.52	0.49
Post-intervention NYHA class	(8–11,14,17)	SMD	Random	62	0.02	0.30	−0.03 to 0.63	0.08
Post-intervention change in NYHA class	(10,11,14,17)	SMD	Fixed	0	0.67	−0.27	−0.54 to 0.01	0.06
Post-intervention LVOTG	(8–11,13,14,17)	SMD	Random	61	0.02	0.45	0.13 to 0.77	<0.01*
Post-intervention change in LVOTG	(8–11,13,14,17)	SMD	Fixed	0	0.91	−0.09	−0.28 to 0.10	0.35
Post-intervention IVS	(8,10,14,17)	SMD	Random	58	0.07	−0.01	−0.41 to 0.38	0.95
Post-intervention IVS reduction	(8,10,14)	SMD	Fixed	30	0.23	−0.07	−0.32 to 0.18	0.59
LVEDD	(8,10,11,14,17)	SMD	Fixed	0	0.52	0.15	−0.09 to 0.38	0.22
LVESD	(8,10,11,17)	SMD	Random	96	<0.001	0.39	−0.99 to 1.76	0.58*
LVEF	(8,10,14)	SMD	Fixed	0.1	0.37	0.13	−0.15 to 0.40	0.37
LA size	(10,14,17)	SMD	Fixed	0	1.0	−0.12	−0.43 to 0.18	0.43

$p < 0.05$ is considered significant. *Questionable validity of interpretation due to high heterogeneity.
OR = odds ratio; RD = risk difference; SMD = standardized mean difference; other abbreviations as in Table 1.

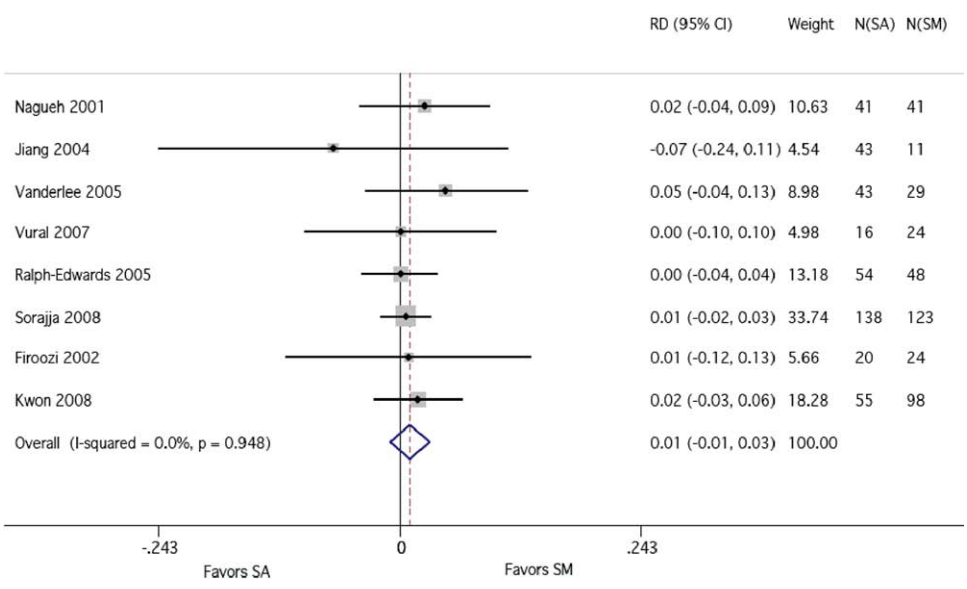

Figure 1 **Short-Term Mortality**

Risk difference (RD) estimates between the septal ablation (SA) and septal myectomy (SM) groups. CI = confidence interval.

Nevertheless, the post-procedure MR grade was similar in the 2 groups.

Ralph-Edwards et al. (9) reported a significantly higher post-procedure SAM in patients undergoing SA than those undergoing SM (OR: 4.8; 95% CI: 2.0 to 11.9). No significant differences in SAM occurrence were encountered in other studies (10,11,14).

Ventricular arrhythmias. None of the studies (7,8,10,13) observed a significant difference in post-procedure ventricular arrhythmia occurrence between the 2 groups. The pooled OR was also statistically insignificant (pooled OR: 1.34; 95% CI: 0.5 to 3.3).

Although the need for implantable cardioverter-defibrillators (ICDs) is usually independent of the choice of therapy, Nagueh et

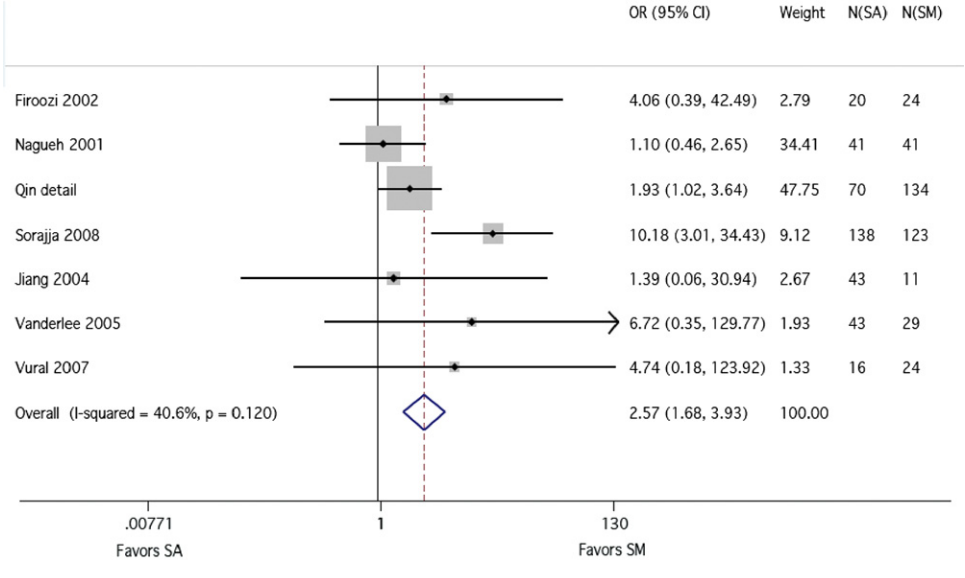

Figure 2 **Post-Intervention Pacemaker Implantation**

Odds ratio (OR) estimates between the SA and SM groups. Abbreviations as in Figure 1.

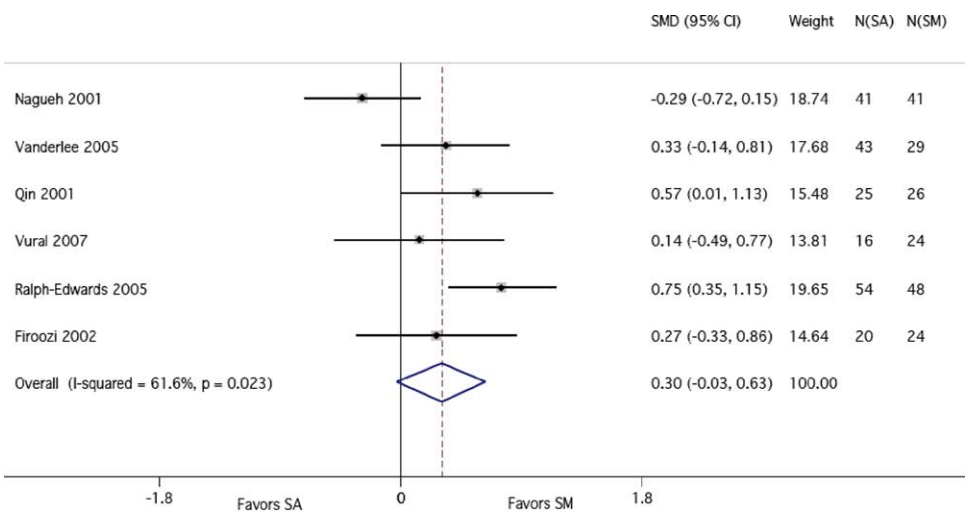

Figure 3 Post-Procedure Mean NYHA Functional Class

Standardized mean difference (SMD) estimates between the SA and SM groups. NYHA = New York Heart Association; other abbreviations as in Figure 1.

al. (8) reported increased requirement of ICD for ventricular dysrhythmias in patients undergoing SM (4 in SM; 1 in SA). These were based on risk-factor profiles and not necessarily on clinical events. van der lee et al. (10) reported ICD placement in 2 patients in the SA group and none in the SM group.

LVOTG reduction. The comparison of post-procedure LVOTG between the 2 groups was limited by significant heterogeneity (I^2: 60.7%; p = 0.02). A random effects analysis yielded a significantly higher LVOTG after ablation, compared with after myectomy (pooled SMD: 0.45; 95% CI: 0.1 to 0.8) (Fig. 5). Comparison of the net LVOTG reduction from the pre-procedure value failed to show any significant difference between the 2 strategies (pooled SMD: −0.09; 95% CI: −0.3 to 0.1) (Fig. 6).

Other cardiac dimensions. The post-procedure interventricular septum (IVS) thickness was similar between the 2 groups (pooled SMD: −0.01; 95% CI: −0.41 to 0.38). No significant differences in net reduction in IVS thickness after procedure were apparent between the 2 groups (pooled SMD: −0.07; 95% CI: −0.32 to 0.18). Besides this, no significant difference was observed between the 2 groups in terms of post procedure left ventricular end diastolic diameter, ejection fraction, and left atrial size. Data on left ventricular end systolic diameter were more heterogeneous (I^2: 95.5%; p < 0.001), limiting the validity of meta-analysis.

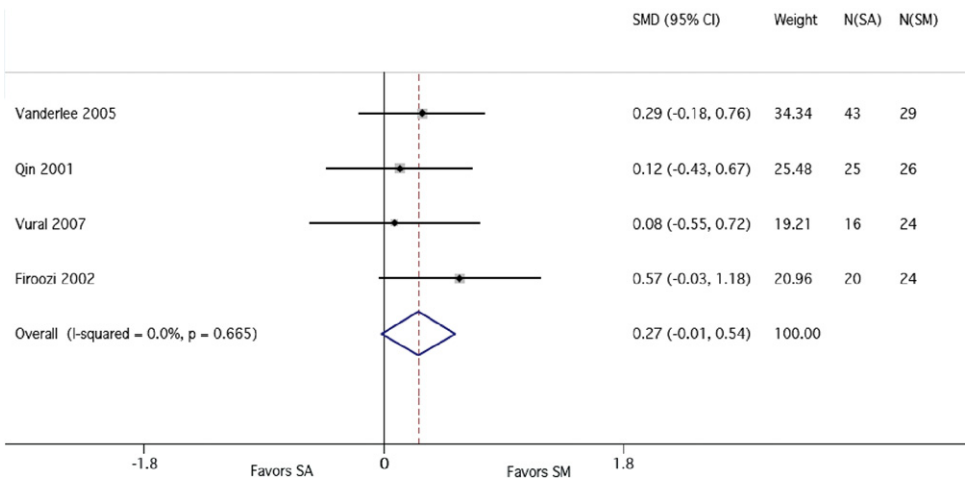

Figure 4 Post-Procedure NYHA Functional Class Reduction Compared With the Pre-Procedure NYHA Functional Class

The SMD estimates between the SA and SM groups. Abbreviations as in Figures 1 and 3.

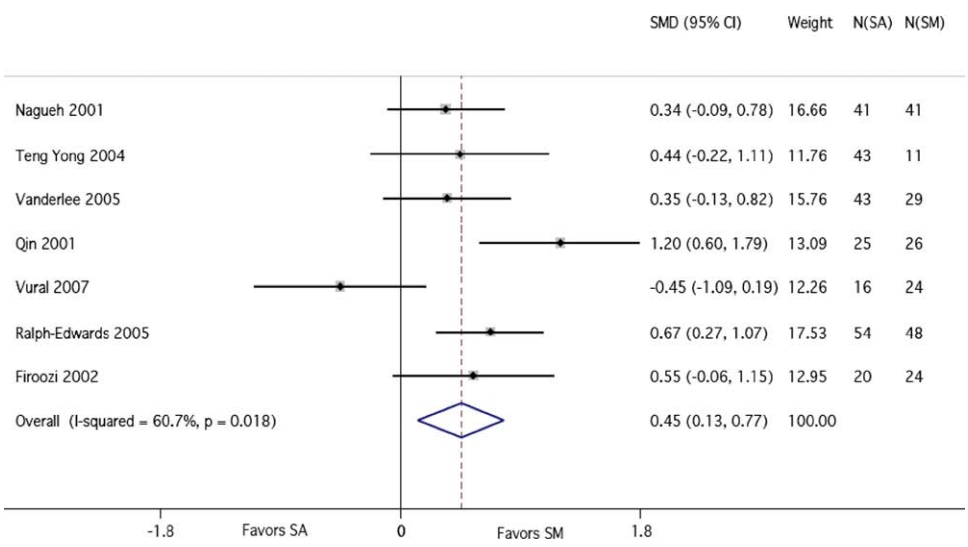

Figure 5 Post-Procedure Left Ventricular Outflow Tract

The SMD estimates between the SA and SM groups. Abbreviations as in Figures 1 and 3.

Reintervention rate and length of hospital stay. No significant difference was observed in the reintervention rate between the 2 strategies (pooled OR: 2.37; 95% CI: 0.54 to 10.5; p = 0.3). Pooled estimates were not calculated for length of hospital stay, due to differences in quantification of length of hospital stay across studies (9,11,14). Two studies reported shorter hospital stay in the SA group, compared with the SM group (11,14). However, Ralph-Edwards et al. (9) reported that mean hospital stay was 4.1 days longer among the SA group patients, compared with SM group patients. The authors attributed this longer post-intervention hospital stay to "caution in undertaking a new procedure" and to confirm the absence of post-intervention complications.

Discussion

This detailed review quantifies definitive risks and benefits of SA versus SM for treatment of refractory HOCM, to facilitate the choice of treatment strategy in an objective manner. We observed comparable short-term and long-

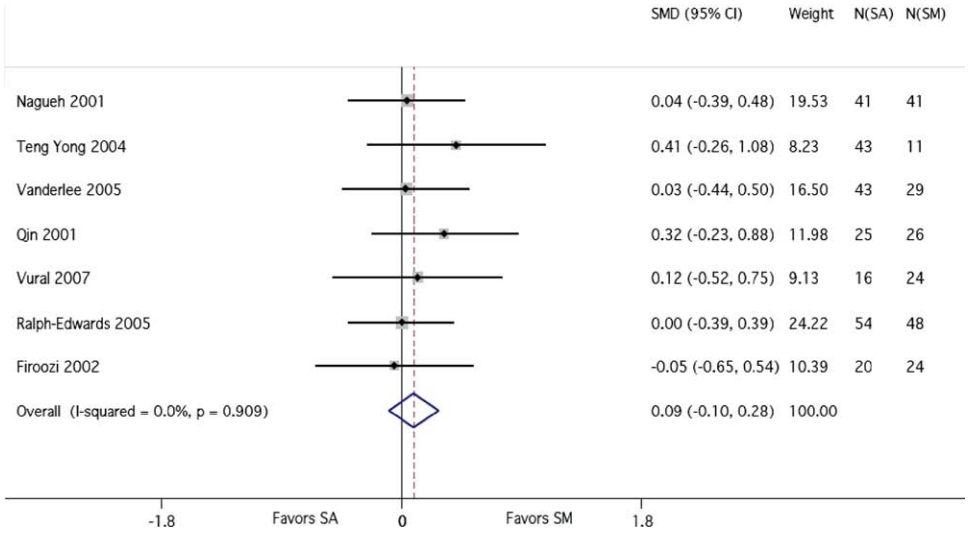

Figure 6 Post-Procedure Reduction in Left Ventricular Outflow Tract Gradient From Pre-Procedure Value

The SMD estimates between the SA and SM groups. Abbreviations as in Figures 1 and 3.

term outcomes between the SA and SM groups. Although long-term mortality estimate was limited by significant heterogeneity, the post-adjustment estimates also indicate that the difference in mortality between SA and SM groups on long-term follow-up is unlikely.

Our meta-analysis is contemporary to a similar study published recently (18). However, this study fails to include at least 4 key observational studies (7,11,13,16), indicating the potential weaknesses of the search strategy. Inclusion of additional studies in our meta-analysis resulted in comparison of 410 patients undergoing SA and 398 patients undergoing SM for short-term mortality versus comparison of 183 patients undergoing SA and 168 patients undergoing SM for the same outcome in the earlier published review. The estimates provided in our review for long-term mortality are more robust due to inclusion of follow-up studies in addition to initial published studies. We have included ancillary outcomes like MR, reintervention rate, and echocardiographic parameters as a part of our review. To overcome the baseline differences between the 2 study groups, we have described a novel method to compare the changes in NYHA functional class and LVOTG after procedure.

No significant difference was observed between the 2 groups in terms of post-procedure functional status as well as the efficacy of intervention determined by the improvement in the functional class (Figs. 3 and 4). A trend toward a better functional outcome after myectomy compared with ablation is apparent. However, the results were statistically insignificant. In addition, the prevalence of MR, ventricular arrhythmias, reintervention rate, and echocardiographic cardiac dimensions were found to be similar between the 2 groups.

The caveat to the widespread use of SA lies in the increased conduction abnormalities observed after ablation. Our meta-analysis demonstrated increased risk of complete heart block (CHB) requiring pacemaker implantation after ablation, compared with after myectomy. In addition, a significantly higher post-procedure LVOTG was seen in the SA group than the SM group; even though the amount of reduction of LVOTG from baseline values was observed to be similar between the 2 groups.

Mortality. The direct procedure-related mortality ranges between 1% and 4% for SA. A large German HOCM registry has reported a procedure-related mortality rate of 1.2% (19), which is comparable to mortality after myectomy at experienced surgical centers (20). However, in this particular registry, 12% of ablation patients had recurrent disabling symptoms (NYHA functional class III/IV) (19). Several unpredictable events like sudden cardiac death (21) and coronary artery dissections (22) have been reported after SA. The incidence of coronary artery dissections after ablation has been reported as high as 4.4% (6 of 130) (22). Septal ablation is reported to have a significant impact on quality of life parameters (23). Patients undergoing SA reported a significant reduction in psychological distress and an improvement in overall well-being.

LVOT obstruction. The LVOT obstruction in HOCM is dynamic obstruction contributed by both disproportionately thick septum and its inappropriate excursions along with the SAM of MV toward the septum. Abnormal papillary muscles have also been implicated in LVOT obstruction (24). High LVOTG has been shown to be an independent predictor of clinical outcomes, including mortality (25). Both SA and SM are effective in reducing LVOTG, although each works through completely different mechanisms. The LVOTG reduction after ablation follows a triphasic response and might take up to 3 months to completely manifest itself (26). On the contrary, SM entails removal of the "culprit" myocardium surgically, leading to an immediate LVOT widening and an instantaneous reduction in LVOTG. The differences in temporal progression of LVOTG between the 2 groups require further research.

Our meta-analysis revealed a significantly higher LVOTG after ablation in comparison with the SM group. It has been suggested that the maximal provocable gradient after ablation might be higher than that observed after myectomy (14,21). It was initially proposed that HOCM was predominantly a nonobstructive disease, with the majority of the patients devoid of a sizable resting LVOTG (20). However, recent studies have shown that approximately 37% of the HOCM patients have significant resting LVOTG, and others demonstrate sizable provocable gradients during exercise (27). It remains unknown whether higher resultant resting and provocable LVOTG amounts to a greater long-term risk of morbidity and mortality.

Conduction abnormalities and arrhythmias. Conduction abnormalities have been shown to be significantly higher after SA as compared with SM. Septal ablation creates a transmural septal infarct between the anterior and inferior free walls; this area commonly contains the right bundle branch, and hence there is an increased propensity toward RBBB after ablation (6). Septal myectomy entails removal of subendocardial tissue in the anterior septum containing the left bundle branch fibers, increasing the risk of LBBB in comparison with SA. Patients with pre-existing RBBB are more likely, given these considerations, to need a permanent pacemaker after SA, whereas those with LBBB are more likely to need pacing after SA (6). The frequency of CHB requiring permanent pacemaker therapy after SA has ranged between 10% and 33% across studies (6,28,29). High volume of ethanol injection, bolus ethanol injections, and injection of more than 1 artery are recognized determinants of post-ablation CHB (15); thus, targeted and slow injection with minimum ethanol quantity might help reduce CHB. Some nonrandomized studies have suggested that septal myocardial reduction by coil embolization does not induce CHB (30). Pacemaker implantation rate after myectomy was $<1\%$ in the absence of pre-existing RBBB in the hands of experienced surgeons (6). It must be pointed out that up to 36% of patients with failed SA undergoing SM have required pacemaker implantation for CHB postoperatively (7).

Our meta-analysis did not demonstrate any significant increase in the occurrence of ventricular arrhythmias after ablation. It is postulated that SA produces a "permanent arrhythmogenic substrate" in the form of an intramyocardial scar, which could increase the risk of lethal re-entrant arrhythmias (1). However, histological analysis has revealed that this is a sequestered and stabilized scar, which is very different from that produced as a result of ischemic necrosis (31). It has been recently reported that sustained ventricular arrhythmias are relatively uncommon after SA, hence suggesting that SA is not pro-arrhythmic (32). The risk of tachyarrhythmia induced by SA still remains speculative. The nonarrhythmogenicity of the scarred myocardium has not been rigorously tested and merits further evaluation.

MV abnormalities. Mitral valves are often redundant (33) and anteriorly displaced in hearts with HOCM. Mitral regurgitation might occur because of SAM and increased LVOT flow velocity or due to intrinsic MV disease. It is important to know the etiology of MR before embarking on the treatment choice. Septal ablation will not address MR if it is due to intrinsic MV abnormality. These patients are best-treated by SM in conjunction with MV repair. Combining SM with mitral leaflet extension achieved better results in patients with dilated MV annulus (10). The hemodynamic status (reduction in MR grade/SAM) was reportedly better in the SM group than the SA group. Although statistically insignificant, a trend toward higher reinterventions and higher complication rate was evident after ablation.

Influence of age on outcomes. In the Mayo Clinic experience (7), patients ≤65 years of age had better symptom resolution and a higher survival after myectomy than ablation. In Cleveland Clinic experience (16), advanced age at the time of SA was associated with higher long-term mortality in comparison with the younger patients undergoing ablation. Advanced age has been shown to be a significant and independent risk factor for intraprocedural as well as late occurrence of CHBs (34). The surgical results have to be viewed in light of possible selection bias against older individuals with multiple comorbidities and because the excellent surgical outcomes might be limited to very experienced centers. Seggewiss et al. (31) demonstrated that younger patients with thicker IVS have unsatisfactory reduction of LVOTG. Similarly, Faber et al. (19) demonstrated that suboptimal reduction in LVOTG was associated with younger age. These studies indicate that SM might be more beneficial among younger individuals due to a better relief of obstruction, which might directly translate into improved clinical outcome and significant long-term mortality benefit.

The success of SA is largely determined by perforator anatomy, most failures being attributed to unfavorable coronary anatomy with an absent appropriate septal perforator artery. (20). It is important to determine the exact mechanism of HOCM before choosing the treatment modality, because concurrent papillary muscle dysfunction, abnormal papillary muscle insertion, or MV abnormalities are unlikely to respond to SA and hence are more amenable to surgical correction. The learning curve for SA is steep, especially regarding the selection of patients and, to some extent, target perforator arteries.

Table 5 Considerations to Decide Choice of Procedure for Treatment of HOCM

Feasibility of each approach
Institutional expertise
Patient characteristics
Anatomy (septum, papillary muscles, septal perforator, mitral valve)
Different mechanism
Size and location of septal reduction
Heterogeneous disease
SAM independent
SAM related
Anterior coaptation
Positive angle between LVOT and the leaflets
Chordal slack
Informed decision after detailed discussion about both therapies

HOCM = hypertrophic obstructive cardiomyopathy; LVOT = left ventricular outflow tract; SAM = systolic anterior motion.

Study limitations. Table 1 demonstrates that the patients undergoing SA and SM are inherently different. It is presumable that there are different referral patterns for patients for the 2 procedures at various centers across the world accounting for these differences. There are small numbers of patients in all the included studies, and the follow-up period has been relatively short across the studies. The direct comparisons as drawn in meta-analysis are harder to interpret, given these baseline differences between the 2 groups. No randomized trials exist comparing the 2 strategies. It has been proposed that a randomized controlled trial to compare SA and SM is an "unrealistic consideration" due to low rates of end points in both treatment arms (35). A significant heterogeneity was encountered in several comparisons in our analysis. Careful inferences with a great deal of caution have to be drawn under these circumstances. The meta-regression technique, used to explain heterogeneity, might be fraught with biases attributable to a small number of studies.

Conclusions

Currently, the choice of SA versus SM for treatment of HOCM is guided by several considerations (Table 5). Although SM continues to be the "gold-standard" treatment for refractory HOCM, SA has emerged to be an attractive alternative. Short-term and medium-term results after SA have been encouraging. Although SA offers comparable results in terms of mortality benefit and functional improvement, it clearly increases the risk of conduction abnormalities requiring permanent pacemaker implantation. Extensive discussions must be conducted with patients to explain the risks and benefits of the 2 procedures. It is advisable that SA be performed at tertiary level centers by experienced interventional cardiologists in conjunction with imaging and clinical cardiologists with expertise in treating patients with HOCM. This

would go a long way in ensuring the safety and efficacy of this procedure, which can be very important in the armamentarium of treatments for HOCM.

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