Late In-Hospital Pressure Gradient Measurements Improve Prediction of Long-Term Outcome of Alcohol Septal Ablation in Hypertrophic Cardiomyopathy

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Abstract

Background: Left ventricular outflow gradient is associated with increased morbidity and mortality in hypertrophic cardiomyopathy. Alcohol septal ablation is the alternative to surgery in cases refractory to drug therapy. The implication of LVOG measured 1 week post-ASA for prediction of outcome is unknown.

Objective: To observe the pattern of LVOG course and prediction of long-term clinical and hemodynamic outcome of ASA.

Methods: Baseline clinical and echocardiographic parameters were prospectively recorded in 14 consecutive patients with a first ASA, at the time of ASA, 3 and 7 days after ASA (in-hospital), and 3 and ≥ 12 months after ASA (last follow-up).

Results: There was improvement in NYHA class, exercise parameters and LVOG in 11 of 14 patients ($P < 0.005$ in all). Maximal creatine kinase level was lower than 500 U/L in those without such improvement and 850 U/L or higher in successful cases. LVOG dropped from 79 ± 30 to 19 ± 6 mmHg after the ASA. LVOG was 50 ± 21 mmHg on day 3, 39 ± 26 on day 7, 32 ± 26 at 3 months and 24 ± 20 mmHg at last follow-up. LVOG identified 27% sustained procedural successes on day 3 and 73% on day 7. The overall predictive accuracy of the test for sustained success and failure was 36% on day 3 and 71% on day 7. Combination of maximal CK and LVOG on day 7 showed four distinct outcome patterns: "early success" with low LVOG and high CK (73% of successful cases), "late success" with high LVOG and high CK, and "early failure" and "late failure" with both low CK and high or low LVOG, respectively

Conclusion: LVOG measurement 7 days post-ASA combined with maximal CK levels predicts late procedural outcome in the majority of patients.

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Left ventricular outflow gradient is associated with increased morbidity and mortality in hypertrophic cardiomyopathy [1,2]. For decades surgical myectomy had been the treatment of choice for severely symptomatic patients unresponsive to drug therapy. Recently, alcohol septal ablation emerged as an alternative intervention for relief of LVOG [3-16]. ASA is usually followed by an initial drop in gradient which is thought to be induced by ischemia, necrosis and myocardial stunning [3-13]. Then, one expects an increase in LVOG during the ensuing days, probably due to recovery of function by the stunned myocardium and resolution of edema associated with myocardial necrosis [17,18]. Shrinkage and remodeling of the septum occurs over weeks and months, with a reduction in LVOG [4-13,17,18]. Yoerger et al. [19] found that 40% of the patients with successful long-term results had similar gradients to patients with long-term procedural failures when measured in the few days after ASA. The difference between the two groups became evident 3 months after ASA when the gradients normalized in the success group and remained elevated in the failure group [19]. In most reports gradients were evaluated 3 months post-procedure [7-11,13,14]. However, the decrease in the LVOG might begin earlier than previously demonstrated [5].

In this study we evaluated the hypothesis that, following effective myocardial ablation, early remodeling of the left ventricular outflow tract might lead to a decrease in LVOG during the late hospitalization period after ASA. If so, LVOG measured 1 week after the ASA procedure might have better prognostic significance than early measurements.

Patients and Methods

The study population included 15 consecutive patients with severe symptoms despite medical therapy (New York Heart Association functional class III–IV). All had dynamic systolic anterior motion of the mitral valve-related LVOG of at least 50 mmHg at rest. The interventricular septal wall thickness was ≥ 15 mm, there was no primary mitral valve disease or significant mid-ventricular obstruction, and no associated conditions for which cardiac surgery was indicated. All patients had 1 year or more post-procedure clinical and echocardiographic follow-up and adhered to the predefined protocol of the clinical echocardiographic evaluation. Associated diseases included previous coronary angioplasty in four patients, chronic renal failure in three, chronic lung disease in three and previous aortic valve replacement, atrioventricular canal repair or mitral stenosis in one patient each. One patient had a pacemaker and one had an implantable cardioverter defibrillator implanted prior to ASA. All patients gave informed consent for the ASA procedure.

LVOG = left ventricular outflow gradient
ASA = alcohol septal ablation
CK = creatine kinase
NYHA = New York Heart Association

The ASA procedure

A pacing electrode was inserted through the left femoral vein into the right ventricle for backup temporary pacing and induction of ventricular premature beats at predetermined (350–370 msec) coupling intervals for provocable LVOG measurement. The LVOG was continuously monitored between a pigtail catheter located in the LV apex and a guiding catheter placed in the ostium of the left main coronary artery [Figure 1]. Heparin 70 units/kg was intravenously administered. The candidate septal branch was occluded using a 1.5–2.0 mm over the wire balloon catheter. The proper septal branch for alcohol ablation was chosen using hemodynamic information of a decrease in LVOG following balloon inflation [5,6,14] as well as myocardial contrast echocardiography (Levovist, Schering, Germany) [8]. Angiographic contrast was injected through the balloon catheter to visualize the myocardial ablation area, exclude retrograde leakage to the left anterior descending coronary or fistulas to other vessels and heart cavities. Alcohol (97%) was then slowly injected (0.9–3.5 ml) following sedation of the patient. The short and long-term procedural success was defined as > 50% reduction in baseline peak gradient and a < 30 mmHg final resting peak gradient [5]. Following the ASA procedure patients were monitored in the intensive cardiac care unit for 2–3 days and the temporary pacing electrode was usually removed within 48 hours. Creatine kinase values were recorded four times daily during the first 48 hours, and then once a day until the values returned to normal. Patients were discharged from the hospital 7–8 days after ASA, following a predischarge Holter test.

Echocardiographic evaluation

Standard transthoracic echocardiographic and Doppler studies were performed. Pre-interventional transesophageal studies were performed when indicated for further evaluation of gradient mechanism and mitral valve morphology. Additional echocardiograms were performed according to the following protocol: during and at the end of the ASA procedure, 3 and 7 days after ASA, after 3 months and at last follow-up which had to be at least 12 months after the ASA. LVOG was measured at rest and following provocation with the Valsalva maneuver or following an exercise test. Severity of mitral regurgitation was graded on a 0–5 scale: 0 = none, 1 = mild, 2 = mild/moderate, 3 = moderate, 4 = moderate/severe, 5 = severe.

A treadmill exercise test was performed prior to ASA in 11 of the 14 patients, in association with echocardiographic recording (in 9 patients) for evaluation of blood pressure response to exercise and of exercise-related provocable gradient. Normal blood pressure response to exercise was defined as an increase of at least 25 mmHg in systolic pressure at peak exercise. An abnormal test was defined as a blood pressure increase < 25 mmHg (flat) or a decrease in systolic pressure during exercise. The blood pressure response was scored as normal = 0, flat = 1 and hypotensive = 2 points.

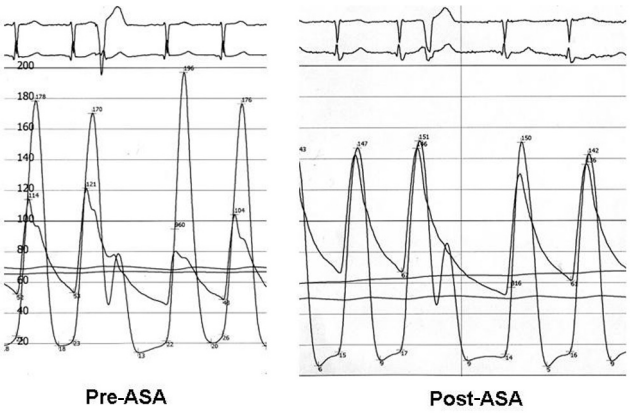

Figure 1. Left ventricular outflow gradients before and after ASA. Following injection of alcohol note change in resting and post-extrasystolic gradients, disappearance of bisferiens pulse and changed morphology of QRS due to appearance of right bundle branch block.

Statistical analysis

Data were expressed as mean ± SD. Continuous variables were compared by paired Student *t*-test and the chi-square test was used for categorical variables. A P value of < 0.05 was considered statistically significant.

Results

Clinical data prior to and following ASA

ASA was attempted in all 15 patients and was performed in 14 because we failed to cannulate a proper septal branch for ablation in one patient. Patients' age was 61 ± 13 years (range 34–75) and 8 were males. The major clinical and hemodynamic findings are summarized in Table 1. All patients were severely symptomatic in NYHA functional class III–IV. Chest pain was found in 10 patients prior to, and in 5 following the procedure. Syncope was diagnosed in two patients prior to and in one patient after ASA. The blood pressure response to exercise was abnormal in all 11 patients in whom the test was performed prior to ASA and improved or normalized in 10 of these 11 after the procedure ($P < 0.001$). Mitral regurgitation of moderate to severe degree was present in 10 patients prior to, and 2 patients after ASA ($P < 0.001$) [Table 1].

Maximal CK rise after ASA ranged from 350 to 3,000 U/L. It was < 500 U/L (411 ± 73) in all cases with long-term failure and

Table 1. Major clinical and hemodynamic parameters before and after alcohol septal ablation.

		LVOT gradient (mmHg)					Exercise test	
	NYHA class	Base	Valsalva	Exercise test	IVS (mm)	MR Severity	Duration (min)	BP Score
Pre-ASA	3.4±0.4	80±30	111±38	98±50	19±2.0	3.8±1.5	2.6±1.4	1.5±0.6
Follow-up	1.9±0.7	24±20	28±35	27±17	17±2.8	1.1±0.3	6.5±2.9	0.6±0.6
P	<0.00002	<0.003	<0.0004	<0.002	<0.008	<0.0007	<0.0004	<0.005

ASA = alcohol septal ablation, BP = blood pressure, IVS = interventricular septum, LVOT = left ventricular outflow tract, MR = mitral regurgitation, NYHA = New York Heart Association. For mitral regurgitation severity and blood pressure response scoring see text.

> 850 U/L (1375 ± 673) in all cases with long-term procedural success (P = 0.008). Six patients (43%) developed right bundle branch block and four patients (29%) developed first-degree atrioventricular block following ASA. DDD pacemaker was implanted for high grade AV[1] block during hospitalization for ASA in two patients and was implanted in one patient 9 months after the procedure because of syncopal episodes associated with the development of second-degree AV block. One patient developed abrupt no-flow in the left circumflex coronary artery following the ASA with localized postero-basal infarction. The complication did not influence the excellent long-term clinical and hemodynamic outcome in this patient. Another patient with severe chronic lung disease died 2.7 years after ASA because of pneumonia and septicemia.

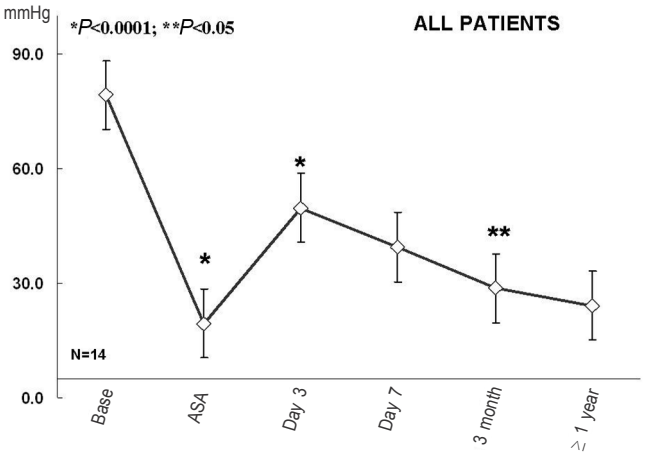

Figure 2. The course of left ventricular outflow gradient in all treated patients

The course of left ventricular pressure gradient

Immediately following ASA the echocardiographic gradient dropped to ≤30 mmHg in all cases, from 79 ± 30 to 19 ± 6 mmHg [Figures 1 and 2]. Three days after ASA the mean gradient increased to 50 ± 21 mmHg; at 7 days (pre-discharge) it was 39 ± 26 mmHg, at 3 months 33 ± 26 mmHg and at 12 or more months (last follow-up) the mean gradient measured 24 ± 20 mmHg [Figure 2]. Provocable gradients (after Valsalva or exercise) also decreased significantly after the procedure [Table 1]. Three months after ASA, based on clinical and hemodynamic parameters, 11 patients were defined as successes (LVOG < 50% of the pre-procedure value and an absolute LVOG of < 30 mmHg) and 3 patients were considered long-term failures.

Two distinct patterns of LVOG course were observed in cases of sustained success as well as in cases of failure [Figure 3]. Of the 11 successful cases, 8 (73%) had a biphasic early decrease in gradient already during hospitalization. Their LVOG decreased sharply immediately after the procedure, followed on day 3 by an increase to around 50% of pre-ASA value, but the gradient fell again by day 7 ("early success" pattern, Figure 3A). In contrast, the other three cases (27%) with long-term success had a biphasic pressure gradient course but the LVOG dropped only after hospital discharge ("late success" pattern, Figure 3B). In the three patients with criteria for long-term procedural failure (at 3 months), the initial gradients of 50–100 mmHg decreased to 15–25 mmHg immediately after the ASA. In two of the three patients the gradients returned close to pre-ablation values 3 days after the procedure, and persisted with little variability during the follow-up ("early failure" pattern, Figure 3C). In the remaining patient, however, the original gradient decreased from 100 to 25 mmHg, remained low (30 mmHg) during late hospitalization, but was approximately 80 mmHg at 3 months post-ASA ("late failure" pattern, Figure 3D). This patient underwent a second ASA procedure 1 year later without recurrence of gradient during the ensuing 2 years of additional follow-up (not shown in Figure 3).

The measurements on the third day post-ASA predicted late outcome (presence or absence of long-term success) with a 27% sensitivity, 66% specificity, 70% positive predictive value and 18% negative predictive value. Measurements on the seventh day after ASA showed a 73% sensitivity, 66% specificity, 89% positive predictive value and 40% negative predictive value. On the third day and on the seventh day post-procedure, LVOG was indicative of long-term outcome (success or failure) in 5 of 14 patients (36%) and 10 of 14 patients (71%), respectively.

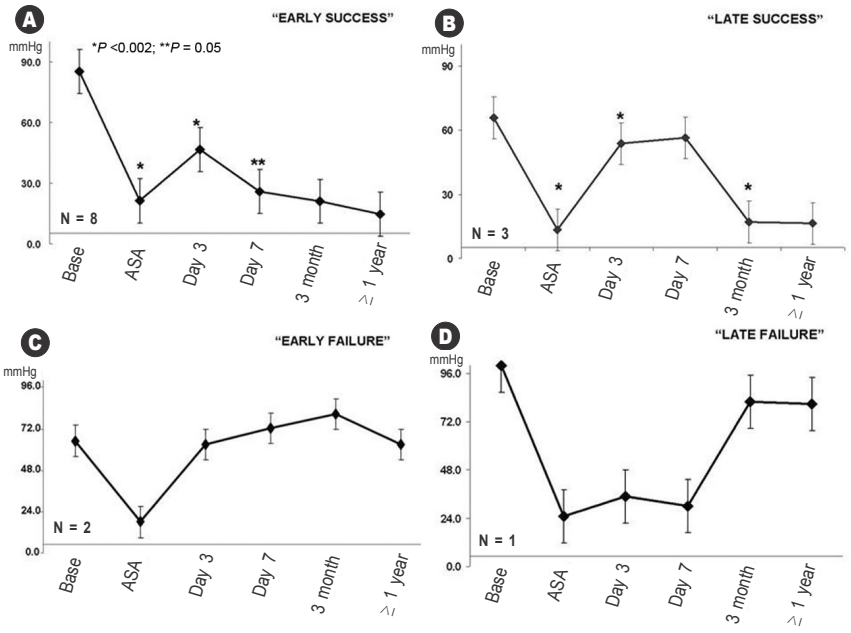

Figure 3. The four patterns of left ventricular outflow gradient course in our patients. In successful cases [**A** and **B**] a typical biphasic pattern was found "early" (during hospitalization) or "late" (at 3 months). Procedural failures [**C** and **D**] also became apparent either "early" (during hospitalization) or "late" (at 3 months).

AV = atrioventricular

Discussion

Previous studies demonstrated that the immediate post-procedural reduction in LVOG following ASA does not correlate with late outcome [12,17]. By the third day after a technically successful ASA a major increase in LVOG occurs both in patients with late success and in those with late failure. Following that homogeneous procedural drop followed by early rise, the course of the gradient becomes variable. Repeated measurements during the week after ASA in the present study showed two distinct patterns of LVOG course in patients with long-term success and in those with long-term failure. Patients with successful outcome demonstrated a biphasic LVOG course. The first decrease in LVOG occurred during the ASA and the second decline occurred either by day 7 ("early success" pattern, found in 73% of cases) or only after hospital discharge ("late success" pattern, found in 27% of cases). Similarly, in patients with long-term failure the LVOG either did not drop by day 7 ("early failure" pattern) or had a transient drop on pre-discharge evaluation, but LVOG recurred 3 months after ASA ("late failure" pattern). Interestingly, maximal post-procedural CK values had important additive value in defining long-term outcome. The maximal CK values were < 500 U/L in failures and > 850 U/L in successes. Thus, a high or low CK value post-ASA helped distinguish between "early success/late failure" and "late success/early failure" categories of patients. Chang et al. [20] reported that low serum CK values predicted failed ASA procedures. The amount of alcohol injected did not correlate with subsequent outcome in our study, as found by other investigators [14,21].

To the best of our knowledge, this is the first report in which LVOG measurements performed on days 3 and 7 after ASA were evaluated and their predictive value for late procedural outcome assessed. We found that gradients measured on day 7 after ASA are more indicative of final procedural outcome than measurements done at 3 days. Observing both parameters of pre-discharge LVOG and maximal CK values appeared to accurately predict late outcome in the majority of our patients. We hope the practical usefulness and implications of this observation will be evaluated in larger prospective series.

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