Long-term follow-up of patients with hypertrophic obstructive cardiomyopathy treated with percutaneous alcohol septal ablation

Odległe wyniki ablacji alkoholowej przegrody międzykomorowej u chorych z kardiomiopatią przerostową

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Abstract

Background and aim: Alcohol septal ablation (ASA) is a well-established method of treatment of hypertrophic obstructive cardiomyopathy (HOCM). The ASA was introduced in 1995 and long-term results have not been sufficiently stuided so far. Therefore the aim of the study was to perform a long-term assessment of ASA.

Methods: Study included 57 patients who underwent ASA in the Institute of Cardiology, Warsaw, Poland between November 1997 and December 2002. Evaluation consisted of clinical status assessment, echocardiographic test and symptom limited cardiopulmonary exercise treadmill test before the procedure, after 3 months (short-term follow-up) and after median 8 years (long-term follow-up).

Results: Mean maximal pressure gradient in the left ventricular outflow tract (LVOTG) before ASA was 85 $\pm$ 27 mm Hg and mean NYHA functional class was 2.56 $\pm$ 0.71. ASA led to a reduction of LVOTG to 39 $\pm$ 29 mm Hg ($p < 0.0001$) and improvement of heart failure symptoms (mean NYHA class 1.23 $\pm$ 0.47, $p < 0.0001$) at short-term follow-up. Three patients died during first five years from ablation (5.4%). There were two extracardiac deaths and one sudden cardiac death (SCD). In two other patients 2 equivalents of SCD (one appropriate cardioverter-defibrillator discharge and one resuscitated cardiac arrest) have been disclosed. All cardiac events occured in patients with LVOTG $\geq$ 50 mm Hg after ASA. Long-term follow-up revealed continuous decrease of LVOTG ($p < 0.0001$) and increase of percent predicted peak VO_2 consumption ($p < 0.03$) despite deterioration of mean NYHA class ($p = 0.0001$) in comparison to short-term follow-up.

Conclusions: Alcohol septal ablation is an effective method of LVOTG reduction which progresses in time. Despite worsening of subjectively assessed heart failure class over time, objective assessment of exercise capacity shows continuous improvement. Persistent LVOTG $\geq$ 50 mm Hg after ASA may increase the risk of sudden cardiac death.

Key words: hypertrophic cardiomyopathy, left ventricular outflow tract obstruction, alcohol ablation, exercise capacity, long-term follow-up

Streszczenie

Wstęp: Alkoholowa ablacja przegrody międzykomorowej (ang. *alcohol septal ablation*, ASA) jest udokumentowaną metodą leczenia kardiomiopatii przerostowej z zawężeniem drogi odpływu lewej komory (HOCM). Procedura ta została wprowadzona dopiero w 1995 r. i jak dotąd opublikowano pojedyncze opracowania dotyczące wyników odległych. Celem badania była zatem długoterminowa ocena wyników ASA.

Metody: Badaniem objęto 57 pacjentów, którzy przebyli ASA w Instytucie Kardiologii w Warszawie między listopadem 1997 a grudniem 2002 r. Ocena składała się z analizy stanu klinicznego, badania echokardiograficznego

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oraz badania ergospirometrycznego na bieżni przed zabiegiem, po 3 miesiącach od zabiegu (obserwacja krótkoterminowa) oraz średnio 8 latach (obserwacja odległa).

Wyniki: Średni maksymalny gradient w drodze odpływu lewej komory (LVOTG) wynosił 85 ± 27 mm Hg, a średnia klasa wg NYHA 2,56 ± 0,71. Zabieg ASA spowodował spadek średniej wartości maksymalnego LVOTG do 39 ± 29 mm Hg ($p < 0,0001$) oraz zmniejszenie objawów niewydolności serca (średnia klasa wg NYHA 1,23 ± 0,47, $p < 0,0001$) w obserwacji krótkoterminowej. Trzech pacjentów zmarło przed upływem 5 lat od zabiegu (5,4%). Stwierdzono 2 zgony pozasercowe i jeden nagły zgon sercowy (NZS). Wystąpiły też 2 ekwiwalenty NZS (jedno adekwatne wyładowanie kardiowertera-defibrylatora i jedno zatrzymanie krążenia, po którym chorego skutecznie reanimowano). Wszystkie zdarzenia sercowe wystąpiły u chorych z maksymalnym LVOTG po ASA ≥ 50 mm Hg. Obserwacja długoterminowa wykazała postępujący spadek LVOTG ($p < 0,0001$) oraz wzrost odsetka przewidywalnego szczytowego pochłaniania tlenu ($p < 0,03$), mimo pogorszenia średniej klasy wg NYHA ($p = 0,0001$) w porównaniu z obserwacją krótkoterminową.

Wnioski: Zabieg ASA stanowi skuteczną metodę zmniejszenia LVOTG, które postępuje w czasie. Pomimo pogorszenia objawów subiektywnie ocenianej niewydolności serca, obietywna ocena wydolności fizycznej wykazuje postępującą poprawę. Utrzymujący się po ablacji LVOTG ≥ 50 mm Hg może zwiększać ryzyko nagłego zgonu sercowego.

Słowa kluczowe: kardiomiopatia przerostowa, zawężanie drogi odpływu lewej komory, ablacja alkoholowa, wydolność fizyczna, obserwacja odległa

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder which leads to the presence of left ventricular hypertrophy [1]. In about one third of patients hypertrophy causes obstruction of the left ventricular outflow tract (LVOT) which is related to pressure gradient. Peak gradients greater then or equal to 50 mm Hg at rest or after provocation have been shown to affect prognosis [2, 3]. Initial therapy aimed at reduction of the preassure gradient consists of optimal medical therapy. If despite that gradient persists and leads to severe limiting symptoms of exertional dyspnoea [New York Heart Association (NYHA) III or IV], chest pain and presyncope or syncope patients should be considered for non-medical therapies [1]. One of the relatively new, but already established methods of pressure gradient reduction is percutaneous alcohol septal ablation (ASA) [2]. Injection of absolute alcohol into one or less often two septal perforator branches of the left anterior descending artery causes an infarction of the subaortic part of the septal wall leading to gradient decrease. Short-term and longer follow-up observations of patients undergoing ASA are well described and prove that the method is safe and effective [4-9]. Little is known about the follow-up exceeding 5 years [10]. Besides, several aspects of ASA are still a field for debate. There are concerns that extensive wall thinning may be a trigger for progression to dilated phase of the disease in a long period of time [1]. Therefore we decided to perform a long-term follow-up of patients undergoing ASA.

Material and methods

A total of 96 patients had ASA performed in the 1st Department of Coronary Artery Diesease, Institute of Cardiology, Warsaw, Poland between November 1997 and 31st October 2009. We have decided to analyse 57 patients who underwent ASA more then 5 years ago (until 31st December 2002). Alcohol septal ablation results after 6 months from the procedure in the first 25 patients from this group were reported previously [5].

Initial screening excluded 2 patients who were subjected to subsequent myectomy after failed ASA. Three patients died before 5 years from the procedure (2 extracardiac deaths due to carcinoma and pulmonary obstructive disease and 1 sudden cardiac death). One -year and 5-year mortality in analyzed population of patients were therefore 0% and 5.4%, respectively. One patient have not shown-up for follow-up visits, but was alive. Therefore a long term follow-up post ablation was performed in 51 patients (98% percent of the 52 eligible patients) (fig .1).

All patients were followed-up for median 8 years [interquatile range 8-9 years]. Clinical assessment, echocardiography testing and cardiopulmonary treadmill testing (in a subgroup of 23 patients) were performed early before ASA, after 3 months from the procedure (short-term post-ablation) and at the end of follow-up (long-term post-ablation).

The techinque of ASA procedure as well as echocardiography and cardiopulmonary treadmill testing were described in detail previously [5].

Clinical assessment consisted of heart failure class according to New York Heart Association (NYHA), episodes of angina pectoris, presyncope/syncope, history of atrial fibrillation and pharmacotherapy status.

Statistical methods

All results for continuous variables with normal distribution were expressed as mean ± standard deviation

(SD) and skewed variables as median and interquartile range (IQR). For analysis of relations between categorical variables we used Fisher exact test or χ^2 test where appropriate. Student-t test, Wilcoxon or Mann-Whitney rank sum tests for paired samples were applied to compare any paired or unpaired continuous variables, respectively. All tests were two-sided with the significance level of $p < 0.05$. All statistical analyses were performed with SAS software version 9e (SAS Institute Inc., Cary, NY).

Results

Studied patients had a mean age of 48 ± 16 years and 28 of them were male (57.1%). During the intervention, a mean of 1.06 ± 0.4 (range 1 to 2) septal branches of the left descending artery were occluded by injection of mean 2.9 ± 1.3 ml (range 1 to 6) of alcohol. Dual chamber pacemaker was implanted in six patients (11.8%) after the procedure beacuse of the high degree atrio-ventricular block. Clinical and echocardiographic parameters assesed at different time points from ASA are presented in table 1.

Short-term follow-up

Alcohol septal ablation led to a significant reduction of mean maximal LVOTG (85 ± 27 vs. 39 ± 29 mm Hg, $p = 0.0001$), systolic anterior movement (86 vs. 20%, $p = 0.0001$) and moderate or severe mitral regurgitation (44 vs. 10%, $p = 0.0002$). Maximal LVOTG was reduced < 50 mm Hg in 69% of patients and < 30 mm Hg in 57% of patients. At the same time there was an

Table 1. Baseline characteristics of the study group (n = 51) before ablation and at different time points after the procedure
Tabela 1. *Charakterystyka podstawowa badanej grupy (n = 51) przed ablacją oraz w różnych okresach po zabiegu*

Parameter	Pre-ablation	Short term post-ablation	p*	Long term post-ablation	p**
Clinical					
Mean NYHA class ± SD	2.56 ± 0.71	1.23 ± 0.47	0.0001	1.98 ± 0.68	0.0001
Angina pectoris, n (%)	32 (63)	4 (8)	0.0001	6 (12)	NS
Presyncope/syncope, n (%)	18 (35)	0	0.0001	1 (2)	NS
AF, n (%)	3 (6)	3 (6)	NS	4 (8)	NS
Drugs					
beta-blockers, n (%)	26 (51)	30 (58)	NS	33 (64)	NS
verapamil, n (%)	12 (23)	10 (20)	NS	8 (16)	NS
disopyramide, n (%)	5 (10)	3 (6)		0	
amiodarone, n (%)	8 (16)	8 (16)	NS	10 (20)	NS
Echocardiographic					
Maximal LVOTG [mm Hg] ± SD	85 ± 27	39 ± 29	0.0001	20 ± 18	0.0001
Maximal LVOTG < 30 mm Hg, n (%)	0	29 (57)	0.0001	40 (78)	0.03
Maximal LVOTG ≥ 50 mm Hg, n (%)	48 (94)	15 (29)	0.0001	7 (14)	0.09
LVEDD [mm] ± SD	44 ± 4	44 ± 5	NS	47 ± 6	0.001
LVESD [mm] ± SD	24 ± 4	25 ± 5	0.03	30 ± 7	0.0005
IVSD [mm] ± SD	21 ± 5	19 ± 6	0.03	18 ± 5	NS
PWD [mm] ± SD	13 ± 3	13 ± 2.5	NS	13 ± 3	NS
LVEF [%] ± SD	75 ± 11	72 ± 10	NS	65 ± 8	0.001
LA [mm] ± SD	46 ± 6	43 ± 7	0.01	45 ± 8	NS
SAM, n (%)	44 (86)	10 (20)	0.0001	1 (2)	0.01
Moderate or severe MR, n (%)	22 (43)	5 (10)	0.0002	1 (2)	NS

AF – atrial fibrillation, IVSD – interventricular septal diameter, LA – left atrium, 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, NYHA – New York Heart Association, PWD – posterior wall diameter, SAM – systolic anterior movement
* for comparison between pre-ablation and short term post-ablation
** for comparison between short term and long term post-ablation

AF – migotanie przedsionków, IVSD – grubość przegrody międzykomorowej, LA – lewy przedsionek, LVEDD – wymiar końcoworozkurczowy lewej komory, LVEF – frakcja wyrzutowa lewej komory, LVESD – wymiar końcowo-skurczowy lewej komory, LVOTG – gradient w drodze odpływu lewej komory, MR – niedomykalność zastawki mitralnej, NYHA – New York Heart Association, PWD – grubość ściany tylnej, SAM – skurczowy ruch płatka przedniego zastawki mitralnej
** porównanie stanu przed ablacją i w krótkim okresie po ablacji*
*** porównanie stanu w krótkim i długim okresie po ablacji*

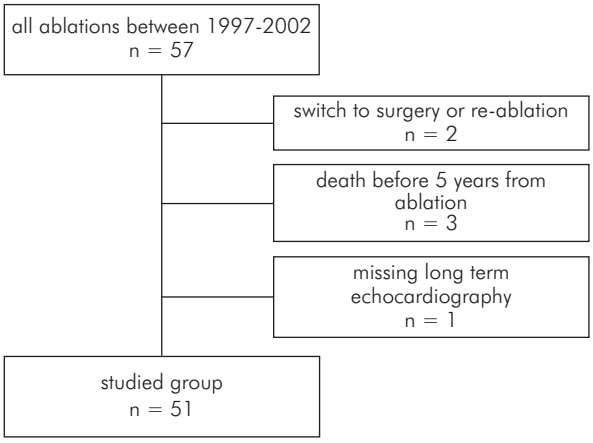

Fig. 1. Flow chart of study group
***Ryc. 1.** Schemat kwalifikacji chorych do badania*

improvement of mean functional heart failure class according to NYHA (2.56 ± 0.71 vs. 1.23 ± 0.47, p = 0.0001), reduction of angina symptoms (63 vs. 8%, p = 0.0001) and elimination of presyncope/syncope episodes (35 vs. 0%, p = 0.0001). Alcohol septal ablation resulted in significant reduction of interventricle septal diameter (IVSD 21 ± 5 vs. 19 ± 6 mm, p = 0.03) and an increase in left ventricular end-systolic diameter (LVESD 24 ± 4 vs. 25 ± 5 mm, p = 0.03).

Long-term follow-up

In comparison to short-term follow-up there was a continuous significant reduction of mean maximal LVOTG (to 20 ± 18 mm Hg, p = 0.0001) and SAM (to 2%, p = 0.01). At the same time there was a marked decrease of left ventricular ejection fraction (LVEF, 72 ± 10 vs. 65 ± 8%, p = 0.001), but the values remained above the cut-off value for systolic heart failure. During long term follow-up there were also an ongoing significant increase of the left vantricular end-systolic (to 30 ± 7 mm, p = 0.0005) and end-diastolic (44 ± 5 vs. 47 ± 6 mm, p = 0.001) diameters, but both of those parameters remained within reference ranges for the diagnosis of left ventricular dilation in all patients.

Subanalysis of exercise capacity

Subanalysis of exercise capacity performed in 23 patients from the studied group revealed that ASA leads to a significant increase of percent predicted peak VO_2 consumption for sex and age (55.8 ± 15.9 vs. 68.4 ± 19.6%, p = 0.005). Importantly, there was a continuous increase of percent predicted peak VO_2 uptake at long term follow-up (to 76.3 ± 24.0%, p = 0.03).

Events

We decided to perform an additional analysis of the patients with sudden cardiac death (one patient who died before 5 years from ablation and was excluded from the analysis) or its equivalents (one appropriate implantable cardioverter-defibrillator discharge and one resuscitated cardiac arrest in patients included in the main analysis). Their baseline characteristic as well as procedural parameters and results of ASA over time are presented in table 2. There were two patients with a higher maximal LVOT gradient at baseline and two of those patients were younger in comparison to the rest of the studied patients.

Table 2. Characteristics of patients with SCD or its equivalents (see text for details)
***Tabela 2.** Charakterystyka pacjentów z NZS lub jego ekwiwalentem (szczegóły w tekście)*

	Study period	Symptoms		Echocardiographic parameters				
		dyspnoea NYHA class	angina CCS class	LVOTG [mm Hg]	IVSD [mm]	LVEF [%]	LVESD [mm]	LVEDD [mm]
AZ	baseline	III	II	130	22	82	25	41
26-year-old	3 months	II	I	65	25	80	17	36
woman	long-term	–	–	–	–	–	–	–
ZH	baseline	III	I	110	20	84	25	53
50-year-old	3 months	I	I	72	15	73	25	43
man	long-term	I	I	42	20	57	29	41
AP	baseline	II	I	82	23	82	18	36
20-year-old	3 months	I	I	65	20	79	21	40
woman	long-term	II	I	85	35	71	27	45

CCS – Canadian Cardiovascular Society, IVSD – interventricular septal diameter, 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, NYHA – New York Heart Association

CCS – Canadian Cardiovascular Society, IVSD – grubość przegrody międzykomorowej, LVEDD – wymiar końcoworozkurczowy lewej komory, LVEF – frakcja wyrzutowa lewej komory, LVESD – wymiar końcowoskurczowy lewej komory, LVOTG – gradient w drodze odpływu lewej komory, MR – niedomykalność zastawki mitralnej, NYHA – New York Heart Association

Discussion

Our results show that ASA is an effective method of left ventricular outflow

tract gradient reduction and leads to improvement of objectively measured exercise capacity in patients with hypertrophic cardiomyopathy. Importantly both of those effects progress over time.

Previous reports on shorter follow-up after ASA are concordant with our findings. Seggewiss et al. demonstrated an ongoing haemodynamic and clinical improvement over 5 years of follow-up [10]. Similarly Fernandes et al. described a series of patients observed up to 5 years from ablation and demonstrated a decrease of left ventricular outflow tract gradient, improvement of functional class and increase of the exercise duration time [8].

Importantly although in the course of time there are signs of left ventricular dilation and a mild decrease of ejection fraction all parameters remain within normal ranges. In our previous report comparing measurments performed at 3 and at 6 months after the procedure we found neither a further increase in end-systolic dimension nor contractile function deterioration [5]. Therefore worsening of those echocardiographic parameters beyond initially observed after 3 months from the procedure is probably a long lasting and ongoing process. At the same time we did not observed further decrease of interventricular septal wall diameter beyond that observed after 3 months from the procedure.

A separate important issue relates to potential higher risk of sudden cardiac death in patients after ASA with residual LVOT gradient ≥ 50 mm Hg. All events observed in our group occurred in patients with high residual gradient. Nevertheless there are a few features which distinguish those patients from the rest of the studied group.

Limitations of our study include a relatively small studied group which preclude definite conclusions especially in relation to clinical outcomes. We also did not perform an analysis of diastolic dysfunction. However a 2-year observation perfomed by Jassal et al. showed that alcohol septal ablation leads to significant and sustained improvement in echocardiographic measures of diastolic function [11]. Our study concentrated on clinical, echocardiographic and cardiopulmonary test parameters. The analysis of ambulatory ECGs for evaluation of the frequency or intensity of ventricular arrythmias in patients before and after ASA is the matter of other manuscript [submitted].

References

1. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003; 24: 1965-1991.
2. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995; 346: 211-214.
3. Sorajja P, Nishimura RA, Gersh BJ, et al. Outcome of alcohol septal ablation for obstructive HCM. Circulation 2008; 118: 131-139.
4. Knight C, Kurbaan AS, Seggewiss H, et al. Nonsurgical septal reduction for hypertrophic cardiomyopathy. Circulation 1997; 95: 2075-2081.
5. Rużyłło W, Chojnowska L, Demkow M, et al. Left ventricular outflow tract gradient decrease with non-surgical myocardial reduction improves exercise capacity in patients with hypertrophic obstructive cardiomyopathy. Eur Heart J 2000; 21: 770-777.
6. Chojnowska L, Rużyłło W, Witkowski A, et al. Early and long-term results of non-surgical septal reduction in patients with hypertrophic cardiomyopathy. Kardiol Pol 2003; 10: 269-282.
7. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003; 348: 295-303.
8. Fernandes VL, Nagueh SF, Wang W, et al. A prospective follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy – the Baylor experience (1996-2002). Clin Cardiol 2005; 28: 124-130.
9. Kuhn H, Lawrenz T, Lieder F, et al. Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008; 97: 234-243.
10. Seggewiss H, Rigopoulos A, Welge D, et al. Long-term follow-up after percutaneous septal ablation in hypertrophic obstructive cardiomyopathy. Clin Res Cardiol 2007; 96: 856-863.
11. Jassal DS, Neilan TG, Fifer MA, et al. Sustained improvement in left ventricular diastolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. Eur Heart J 2006; 27: 1805-1810.