Three Achilles' heels of alcohol septal ablation

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This manuscript looks at basic limitations of alcohol septal ablation in obstructive hypertrophic cardiomyopathy. They include high-grade atrioventricular blockages, residual obstructions of the left ventricular outflow tract and the so-called proarrhythmic effects of alcohol septal ablation procedure. All these weaknesses are reviewed in the context of incidence, etiology, and prevention.

Keywords: hypertrophic cardiomyopathy; obstruction; left ventricle outflow tract; alcohol septal ablation; atrioventricular blockages; proarrhythmic effects

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Introduction

Modern medical literature is flooded with data on mainly positive results of various interventions, particularly alcohol septal ablation (ASA), when treating obstructive hypertrophic cardiomyopathy (HCM). However, a limited number of papers shed light on the limitations of this procedure, which we dare to call "three Achilles' heels." ASA is a relatively common procedure in Europe, but in the Russian Federation, just a few centers perform this kind of endovascular treatment (three clinics carry out a bit more than 20 ASAs per year) [1]. Bearing in mind a relatively high incidence of HCM (according to the population-based CARDIA study it accounts for one per 500 patients) [2], it seems to be logical that the level of care for these patients is inadequate. Nowadays, there are two options for treatment of dynamic obstruction of the left ventricle outflow tract (LVOT): surgical myectomy (SM) and ASA. Surgical myectomy, which history goes back more than 50 years, is a gold standard of care in medically refractory patients. The latter, apparently, requires high technical skills of a cardiac surgeon and appropriate hands-on experience (more than 20 procedures per year) [3].

The introduction of alcohol septal ablation in clinical practice in 1995 by Ulrich Sigward contributed to its quick adaptation at many hospitals in Europe. In as little as 7 years since its introduction, the number of ASA procedures performed by interventional cardiologists exceeded that of myectomies done by cardiac surgeons over a period of 45 years. Obviously, the use of ASA in clinical practice makes care for patients with obstructive hypertrophic cardiomyopathy more available [4]. An undeniable advantage of ASA is its better reproducibility. This technology might provide better care for patients with such pathology in Russia.

At the same time, as a minimally invasive method, ASA has certain limitations. They include: 1) higher incidence of high-grade atrioventricular blocks requiring permanent pacemaker implantation; 2) more common residual LVOT obstruction; and 3) "probability" of arrhythmic events in periprocedural and long-term periods.

Atrioventricular block

The atrioventricular node is known to be supplied with blood from the eponymous artery, originating from the right coronary artery, while the His bundle with the relevant branches is mainly fed from septal branches of the left anterior descending artery [51]. Myocardial damage during ethanol injection in a target septal artery can induce conductional disturbances, predominantly in the His-Purkinje system. They can be classified as temporary (periprocedural) disturbances and permanent ones.

Periprocedural disturbances of atrioventricular conduction

Periprocedural disturbances of atrioventricular conduction present a relatively common phenomenon. According to L. Faber et al, the frequency of transient periprocedural complete block accounts for 46%. Intraoperative complete atrioventricular block (AV-block) is a sign of poor prognosis [15]. The latest data from Euro-ASA registry showed 37% periprocedural heart blocks [5].

Permanent disturbances of atrioventricular conduction

The largest European registry (including more than 1 000 patients) demonstrated a 12% frequency of implanted permanent pacemakers (PP) after ASA [5]. Also, the Northern American registry showed 8.9% patients with implanted PP [6]. Three meta-analyses (comparing ASA and SM) demonstrated a 2–5 times more frequent need in pacemaker implantation in ASA cases against SM cases [7–9]. Recent real-world data form US Nationwide Inpatient Database showed a slight difference of implanted PP after SM and ASA (9.8% vs 11.9%) [73].

Just a few publications in current literature are devoted to clarifying the causes of a huge number of high atrioventricular blocks. Most relevant articles are presented below.

S.S. El-Jack et al. described 50 patients on whom ASA was done. Nine patients (18%) underwent PP implantation. The most significant predictor of complete AV-block was identified in the preoperative complete left bundle block [10]. But the cohort was not large enough to draw fundamental conclusions.

T. Lawrenz et al. performed an electrophysiological study during ASA and assessed AV-conduction in 172 patients. Intraoperative complete AV-blocks were observed in 36 cases (20.1%). PPs were implanted in 20 patients (11.6%). Predictors of III grade AV-block were identified, they included a preoperative block in one of His bundle branches ($p = 0.010$) and an elderly age ($p = 0.023$). The most significant finding of this study was a clinical significance of retrograde AV-conduction assessment. No complete AV-block after ASA developed in patients with normal retrograde AV-conduction (negative predictive value 100%) [11].

A. Axelsson et al. reported on their study including 87 patients, 24 (28%) of which required PP due to high-grade heart block. A basic PR interval exceeding 200 ms and acute complete AV-block during the procedure were the most significant predictors [12].

S.M. Chang et al. published ASA results for 261 patients with obstructive HCM. 31 patients (14%) received PP. Such parameters as female gender, bolus ethanol injection, ablation of more than one septal branch, baseline left bundle branch block (LBBB) and first-grade baseline AV-block were determined to be independent predictors of complete AV-block [23].

D.R. Talreja et al. published an article, which compares the influence of ASA and SM procedures on the heart conduction system. 58 patients in this trial underwent ASA and 117 patients received SM. The ASA group without branch blocks on the baseline electrocardiogram (ECG) had 40% of right bundle branch blocks (RBBB) and 6% of complete heart blocks. The ASA group with baseline RBBB showed no postoperative changes on ECG. In the ASA group with baseline LBBB, a complete heart block was observed in 75% of patients. For comparison, in the SM group with normal baseline ECG, LBBB was observed in 46% of patients, while in the group with baseline RBBB a complete heart block developed in 60% of cases. No new changes on ECG after SM were identified in patients with baseline LBBB. Thus, the authors conclude that ASA is more commonly associated with RBB damage, while SM—with LBB damage. This fact allows for choosing the required management technique depending on baseline ECG to mitigate the need in PP implantation [13].

Taking into account all those factors contributing to development of a complete AV-block, it is possible to formulate two main ways to reduce the number of postoperatively implanted PP after ASA: 1) more rigorous selection of patients, with due regard for baseline changes on ECG; 2) reduction of the ethanol dose (a relatively low frequency of implanted PP due to "low" ethanol doses was demonstrated in [14]).

A "high grade" AV-block often occurs after ASA procedures and every surgeon experiences a reflection on subsequent implantation of PP, perceiving it as a complication of the procedure. It should be noted that in current literature, for example, according to J. Veselka et al., no significant differences were observed in a 5-year survival rate between patients with and without implanted PP after ASA [56]. Note that this study looks underpowered.

Residual obstruction of left ventricle outflow tract

Nowadays there are no standards for reporting ASA results in current literature; therefore, many researchers use completely different criteria of procedure efficiency. Undoubtedly, a decrease in the peak gradient in LVOT is an important indicator of efficiency. However, some authors believe that a 50% reduction of the LVOT gradient could be considered as the efficiency criterion [17, 22, 24], while others think that the procedure is effective, if the reduction of the LVOT gradient amounts to 80% [18]. It seems logical that authors use less gradient reduction values as criteria for effectiveness in order to be able to include a smaller sample in the study.

In accordance with the recommendations of ESC, AHA and ACCF, ineffectiveness of drug therapy in patients with severe symptoms of chronic heart failure and a provoked LVOT gradient of more than 50 mmHg should be considered as an indication for septal reduction therapy in patients with obstructive HCM. This value is mainly based on the expert's opinion, not on the evidence [3, 48].

What reduction of the gradient is to be accepted as the target of septal reduction therapy? This question remains unanswered. Nevertheless, M.S. Maron et al. in their 2003 publication reported that patients with residual obstruction with a LVOT gradient lower than 30 mmHg demonstrated a significantly higher long-term survival [34].

It is worth noting that the severity of LVOT obstruction after ASA changes dynamically and biphasic up to 1 year as a consequence of iatrogenic myocardial infarction. In this connection, the true size of the effect should be analyzed at least at 1-year follow up [24]. Anyway, younger patients are characterized by a slower hemodynamic response and should be followed longer [74].

How many patients show residual obstruction after alcohol septal ablation?

This issue is insufficiently covered in literature and to some extent is speculative. In a number of publications, even those based on extensive experience, the parameter of the number of patients with residual obstruction is "retouched" by the quantity of reinterventions.

According to the European ASA registry, 10% of patients underwent repeat interventions, 7% reASA and 3% SM) [5]. The Northern American registry includes 874 ASA patients, out of which 112 patients underwent reASA (12.8%) and 25 received SM because of residual LVOT obstruction [6]. The Scandinavian multi-center study showed 17% patients who underwent reinterventions during follow-up after ASA [19].

V.L. Fernandes et al. published a two-center experience of 629 ASA procedures, with 106 patients (17.1%) needing reintervention, 81 (14%) patients reASA and 25 patients SM [26]. Unfortunately, specific information about the number of patients with residual obstruction is missing.

Some authors note that residual obstruction in LVOT in patients with HCM is associated with negative long-term prognosis [18, 30, 31, 35, 50].

Number of obstructions

Just a few authors declare the exact number of residual obstruction in LVOT after ASA (Table 1).

As can be seen from Table 1, according to current data the frequency of residual obstruction after ASA varies from 15% to 46%.

Predictors of residual obstruction after alcohol septal ablation

It seems that residual obstruction after ASA is relatively common, but the direct cause of this phenomenon is still unclear or not well established. Just a few scientific papers in current literature include an analysis of causes of a high gradient after alcohol septal ablation.

M. Lu et al. identified baseline septal thickness as a predictor of residual obstruction (sensitivity 86%, specificity 55%) while analyzing echocardiographic studies

Table 1. Residual left ventricle outflow tract obstruction after alcohol septal ablation

Author/year	Number of patients	Efficiency criteria	No. (%) of patients with residual LVOT obstruction
M. Lu et al., 2016 [17]	102	50% reduction of baseline LVOT gradient	29 (28%)
P. Sorajja et al., 2012 [18]	177	80% LVOT gradient reduction and final LVOT gradient lower than 10 mmHg	45(25.4%)
J. Veselka et al., 2014 [21]	178	A resting LVOT gradient lower than 30 mmHg	27 (15%)
S.M. Chang et al., 2004 [22]	173	50% reduction of baseline LVOT gradient	39 (22.5%)
L. Faber et al., 2007 [30]	312	LVOT flow velocity by echo-Doppler < 2 m/s at rest, provocative gradient of <60 mmHg	162 (46%)

No, number; LVOT, left ventricle outflow tract

and magneto-resonance tomographic data of patients who underwent ASA [17].

In a recent paper from M. Kitamura et al., it was demonstrated that involvement of two and more segments of the myocardium is a predictor of repeat interventions after ASA [29].

C. Van der Lee et al. found out that the ASA procedure in patients with obstructive HCM and elongated anterior mitral leaflet is less effective than SM [25].

According to data from Faber et al. based on the experience of 313 patients, the young age, relatively "thick" septum, high baseline LVOT gradient and high postoperative LVOT gradients were identified as predictors of inappropriate hemodynamic results [55].

Independent predictors of the obstruction after surgical myectomy

In current literature, the factors that provoke residual obstruction after SM procedures are more fully studied than after ASA. Due to more radical changes in the architectonics of the output tract of the LV after surgical excision of the obturating muscular bulge, it seems obvious that the predictors of residual obstruction after SM can be interpolated to the practice of ASA, and be used in some cases as predictors of a residual "high" gradient in the LVOT after the ASA procedure.

Y.H. Cho et al. described an experience of 52 repeat SM. Six patients (12%) had the residual LVOT obstruction due to isolated mid-ventricular obstructions. The remaining 46 patients had SAM-related residual obstruction in LVOT, which was caused by an inadequate septectomy length (31 patients, 51%) and a combination of an insufficient length and depth of septectomy (13 patients, 25%). Two patients had residual gradients due to a combination of SAM-syndrome and mid-ventricular obstruction (4%) [16].

K. Minakata et al. described the experience of 20 repeat myectomies (20/610) due to residual obstruction. Intraoperatively, they identified the following causes of residual obstruction: insufficient excision of the muscular shaft of LVOT in the first operation (13 patients), mid-ventricular obstruction (8 patients) and abnormal papillary muscles (3 patients) [68].

A couple of publications demonstrate that the excess length of the anterior valve is an independent predictor of obstruction of LVOT [27, 28].

Recently, more and more evidence has been presented to prove the leading significance of the so-called drag force in the pathophysiology of obstruction of LVOT in HCM [52]. This concept replaced the "Venturi effect," which justified the implementation of isolated septal reduction therapy [53]. However, more

Table 2. Anomalies of the mitral valve as possible causes of residual left ventricle outflow tract obstruction

Structures	Parameter	Just description / presence of evidence in clinical trials
Papillary muscles	Hypertrophy PM	Just description [64]
	"Ingrowth" of the papillary muscle directly into the anterior mitral valve	Just description [67]
	Single papillary muscle	Just description [66]
	Additional PM	Just description [65]
	Apical (anterior) displacement of PM	Proved in a trial [59]
	Bifurcation (splitting) of PM heads	Proved in a trial [59]
Mitral leaflets	Excessive length of anterior mitral valve	Proved in a trial [27, 28]
	Excessive length of posterior mitral valve	Just description [70]
Chords	Tendon chords "weakness" (excess length)	Just description [71]
	Abnormal attachment of secondary chords	Just description [69]
The obtuse angle between the axis of the left ventricle and the axis of the ascending aorta	The obtuse angle between the axis of the left ventricle and the axis of the ascending aorta	Just description [32, 57]

PM, papillary muscles

and more research groups emphasize the essential role of the mitral valve and its subvalvular apparatus in the formation of obstruction in LVOT [25, 27, 28, 72]. The anomalies of the mitral valve (up to 20%) that occur frequently in HCM are capable of affecting LVOT obstruction, independently, or in combination with, septal hypertrophy [54] (Table 2).

Despite the more than 20-year history of development of the ASA method, residual LVOT obstruction remains a real downside of the procedure. Probable ways to optimize the results of ASA are a more careful selection of patients and intraoperative use of contrast echocardiography. We need more data on ASA efficiency in different patterns of mitral anomalies. The development of endovascular interventions on the mitral valve is likely to open additional options for interventional cardiologists in the treatment of patients with obstructive hypertrophic cardiomyopathy [20].

Proarrythmic effects of alcohol septal ablation procedure

The introduction of ASA in 1995 into clinical practice was marked by a debate about the ethical aspects of the intervention and the likely harm to the patient due to creating an iatrogenic infarction. Studies based on MRI data showed that ablation leads to a scar, so it does not distinguish favorably from myectomy, and may serve as a prerequisite for ventricular arrhythmia in the future [33]. The most solid position of the opponents of the ASA method was taken after the publication of a series of reports about the so-called proarrhythmic effects of the ASA procedure [41–44]. What is generally understood by the so-called proarrhythmic effect? In most cases, the proarrhythmic effect was the recording of any life-threatening arrhythmia (ventricular tachycardia, ventricular fibrillation, triggering of an implanted cardioverter-defibrillator) in the perioperative or long-term period.

In the early 2000s, several cases of recording a monomorphic ventricular tachycardia in patients with HCM (who had previously undergone ASA) were described. The nature of that tachycardia indicated a possible mechanism for the reentry, which was easily linked to the iatrogenic scar in the interventricular septum [41–44].

A.P. Noseworthy et al. investigated the incidence of sudden cardiac death and the frequency of proarrhythmic events in the long-term period in 89 patients with obstructive HCM who had underwent ASA. The mean follow-up period was 5.0 (2.3) years. During the observation period the cases of sudden cardiac death (SCD) were not observed. The secondary endpoint (ventricular tachycardia (VT), ventricular fibrillation (VF), "discharge" of the implantable defibrillator cardioverter (ICD), asystole) was evaluated in patients with implanted devices: ICD or pacemaker (42 patients in total). In 9/42 patients, a secondary endpoint was achieved (4.9% per year). In patients with an initial low risk of SCD a secondary endpoint was achieved in 4/29 cases (2.8% per year); in patients with an initial high risk of SCD—5/13 cases (13.4% per year) [35].

A team of researchers from Toraxcenter (Rotterdam, the Netherlands) investigated the effect of ASA on the long-term outcomes of patients with obstructive HCM. Long-term outcomes of 91 ASAs and 40 SMs performed in patients with similar demographic characteristics were compared. The primary endpoint was cardiac death (excluding sudden cardiac death and cases of ICD discharges), the secondary one was non-cardiac death. 1-, 5-, 8-year-old freedom from the primary endpoint was 96%, 86%, and 67% in the ASA group, 100%, 96%, and 96% in the SM group, respectively. Patients who underwent ASA were 5 times more likely to reach the primary endpoint (4.4% versus 0.9% of adverse events per year) [38].

In the study by B.J. Maron et al. ICD discharges were 4 times more frequent in patients with HCM and previous ASA (4/17 [24%], or 10.3% per year [95% CI, 2.0%–28.4%]) than those with the previous SM (6 / 50 [12%], or 2.6% per year [95% CI, 1.2%–7.2%]); p = 0.04 [39].

In 2010, R.A. Leonardi et al. published a meta-analysis comparing SM and ASA in the parameter of the frequency of sudden cardiac death and the frequency of ventricular arrhythmias in the long-term. Mortality from all causes was equally low in both groups. After patient stratification according to baseline characteristics, all-cause mortality and sudden cardiac death were even lower in the ASA group [36]. However, this study had significant limitations: on the one hand, it was statistically a significantly different observation period after ASA and SM. On the other hand, the format of meta-analysis of retrospective observational studies by itself does not allow us to draw fundamental conclusions and is often accompanied by contradictory results. Also, extremely doubtful is a very low incidence of sudden cardiac death after ASA (0.4% per year), which is inconsistent with the data of other authoritative clinics (4.9% per year) [35].

J.C. Balt et al. reported that according to the loop recorder data in the perioperative period 3/44 (7%) patients had sustained VT / VF. Subsequently, in the observation period of 3.5 years, no sustained VT / VF was observed in patients [40].

F.A. Cuoco et al. studied 123 patients with obstructive HCM after ASA who had previously received ICD (i. e., high-risk SCD patients) as a primary prevention of sudden death. The follow-up period was 2.9 years. The frequency of annual ICD discharges was 2.8%, which is much lower than previously reported [45].

In 2014, P.A. Vriesendorp et al. published the results of treatment of 690 patients with obstructive HCM, 124 of whom were medically treated, 316 were subjected to ASA, and 250 received SM. The data was obtained from three reference centers of HCM. The follow-up period was 7.6 (5.3) years. Endpoints: all deaths and cases of SCD. It is noteworthy that a comparable 10-year survival was achieved, both with drug treatment and with ASA, and with SM (84%, 82%, and 85%, respectively). The annual incidence of SCD was lower in the invasive treatment groups: 1% / year for ASA, 0.8% / year for SM, compared with 1.3 per year for medical treatment. The main feature of this study is the use of a non-composite endpoint (SCD and cardiac mortality), and a separate endpoint for SCD. The second important difference is the exclusion of hospital arrhythmic events from the final analysis. Nevertheless, the authors concluded that all three methods are characterized by a good long-term survival, with the SM method featuring the lowest SCD frequency [46].

P. Sorajja et al. compared the results of 177 procedures of ASA and 177 SM in patients stratified by age and sex with an average follow-up period of 5.7 years. They found out that the incidence of SCD (including death from an unknown cause) was 1.3% / year after ASA and 1.1% / year after surgical myectomy [18].

M.K. Jensen et al. in their work in 2013 demonstrated an 88% 10-year survival rate in 470 patients with obstructive HCM treated with ASA. At the same time, the frequency of annual SCD was 1.2%, which is comparable to that in patients with non-obstructive forms of HCM [47].

Three recently published meta-analyses based on retrospective observational data did not reveal a significant difference in survival between patients exposed to ASA and SM at least in the 5-year follow-up period [7–9]. Of course, the scar in the ventricular septum is a prerequisite for the development of the reentry of tachycardia. However, how often this phenomenon occurs and what impact it has on the survival of patients exposed to ASA, especially in a 5-year follow-up, remains an open question because of a shortage of literature on this issue.

A.P. Noseworthy et al. noted an increased risk of ventricular tachycardia in patients with high postprocedural gradients in LVOT [35], consistent with the data of M.S. Maron et al., in which the presence of LVOT obstruction in itself was a risk factor for sudden death in patients with hypertrophic cardiomyopathy [34]. In addition, a number of studies demonstrated a relationship between myocardial fibrosis and ventricular arrhythmia in patients with hypertrophic cardiomyopathy [60–63]. The initial marked fibrosis of the myocardium can probably serve as a significant confounding factor in studies evaluating long-term arrhythmic events after alcohol septal ablation and surgical myectomy.

Conclusion

Current literature demonstrates a comparable 5-year survival rate of patients with and without an implanted pacemaker. More data is needed to assess whether there is a negative impact of pacemaker implantation after the procedure of ASA on the prognosis of patients. A more careful selection of patients and a reduction in the dose of ethanol administered are likely to reduce the number of high-grade atrioventricular blocks that accompany the ASA procedure. The negative effect of the residual obstruction on the prognosis of patients has been convincingly proven [18, 30, 31, 34, 35, 50]. However, insufficient attention has been paid to identifying predictors of residual obstruction after ASA in current literature. Ventricular arrhythmia due to an "iatrogenic scar" after ASA is a well-described phenomenon. Nevertheless, the issue of the effect of this substratum on long-term survival in the observation period of more than 5 years remains controversial in current literature. Apparently, the initial expressed fibrosis of the left ventricular myocardium can have a negative effect on the results of ASA, predisposing to arrhythmic events. Despite its inherent disadvantages, alcohol septal ablation currently demonstrates a comparable long-term survival rate of patients with surgical myectomy.

We hope that the development of endovascular interventions on the mitral valve, the use of new embolization agents for alcohol septal ablation, will help eliminate the shortcomings and improve the results of this procedure.

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Conflict of interest

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Author contributions

Conception and study design: M.G. Kashtanov.

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