Atrial septal defect repair in the age of transcatheter devices

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Abstract

The aim of this review is to discuss the management of atrial septal defects (ASD) in the adult patient paying special attention to the elderly population and the most recent transcatheter advancements. ASDs are characterized by the following categories: ostium secundum, ostium primum, sinus venosus, and coronary sinus defects; though multiple defects may exist concurrently. Intervention for closure of ASDs are indicated with the development of right ventricular volume overload, or in the clinical context of paradoxical embolic stroke. Previously, there was significant disagreement regarding the timing of ASD closure in adult patients, but there is now general consensus that adult patients with clinical evidence of right ventricular overload should undergo closure of ASDs at the time of presentation. The present review describes the typical presentation of patients with symptomatic ASD’s, medical management, and whether surgical or percutaneous approach should be pursued. We will also discuss other important considerations for patient selection and potential early and late complications of transcatheter ASD closure such as congestive heart failure, device embolization, and tissue erosion. At the time of this writing, there are currently three FDA-approved devices for percutaneous VSD closure including the Amplatzer™ Septal Occluder (ASO, St. Jude Medical, St. Paul, MN), Gore HELEX™ Septal Occluder (W.L. Gore and Associates, Newark, NJ), and Gore CARDIOFORM™ Septal occluder (GCSO, W.L. Gore and Associates, Newark, NJ) devices. Many premarket approvals were granted for devices that never went to market due to poor investigational study performance. Likewise, the HELEX device has since been discontinued upon bringing the GCSO device to market. We will focus primarily on the ASO device with a brief review of current investigations into the GCSO device, both of which carry an indication for closure small to medium sized ASDs in the ostium secundum position. Additionally, this review covers the safety of transcatheter closure of ASDs with currently available devices, review studies associated with devices available outside the United States, and perioperative considerations for transcatheter...
intervention. Obstacles to device employment and countermeasures to overcome operational challenges will also be discussed. To this end, variations or similarities of currently approved devices will be emphasized throughout this discussion where possible. Lastly, we will offer insights into device evolution trends with the expectation of new device developments on the horizon. We will briefly discuss up and coming areas of active research, including the emerging fields of novel biomaterials and gene therapy.

**Keywords:** Atrial septal defect repair, transcatheter, endovascular, elderly, current methods

**INTRODUCTION**

Atrial septal defects (ASD) are one of the most common congenital cardiac abnormalities reported both in adolescent and adult populations. The incidence of newly diagnosed atrial septal defects are second only to bicuspid aortic valves as the most common congenital heart disease in children, with ASDs accounting for the majority of congenital malformations diagnosed in adults. ASDs may be detected in asymptomatic patients, though physical findings may be subtle at best making detection prior to associated symptoms difficult in most clinical settings. Though patients with ASDs may remain asymptomatic well into adulthood, undetected ASDs may lead to potentially irreversible complications such as arrhythmias, pulmonary hypertension, stroke or their associated sequelae. The true incidence of ASD may be significantly underestimated due to the nature of their relatively silent clinical course. One study estimates 941 per one million live births have an ASD based on the metanalysis of 43 studies, which accounts for an estimated 30%-40% of adult congenital cardiac abnormalities. Ostium secundum defects are the most commonly reported ASD as compared to defects associated with the septum primum, sinus venosus, or unroofed coronary sinus which occur in descending frequency respectively.

Although surgical repair is considered as the standard method of treatment for all but secundum type defects, case reports are exist describing multiple ASDs and coronary sinus defects which transcatheter closure was successful without significant valvular impairment or conduction disturbance.

**MORPHOLOGY AND CLINICAL FEATURES OF ASDS**

**Location, Morphology, and suitability for surgery vs. transcatheter intervention**

It is important to note that morphological variations of different types of ASDs, which determines whether a particular defect is amenable for transcatheter closure. Briefly, ASDs fit into four major classes: ostium secundum, ostium primum, sinus venosus, and unroofed coronary sinus. Ostium secundum defects are characterized by enlarged foramen ovale with insufficient septem secondum development, causing incomplete closure and fusion of the atrial septum. Secundum type defects are the most common atrial septal malformation accounting for up to 80% of ASDs. Secundum type defects are considered ideal for transcatheter ASD closure due to their size and surrounding tissue for device fixture. Ostium primum defects, also known as endocardial cushion defects, are defects at the level left or right atrioventricular valves. Sinus venosus defects are located in proximity to either the superior or inferior vena cava. Lastly, coronary sinus septal defects are characterized as an “unroofing” of the coronary sinus in which allows communication between the coronary sinus and the LA. Mixed defects, or those involving multiple defect types are also possible, though less commonly reported are also typically repaired with open surgery. Although, surgical repair is considered as the standard method of treatment for all but secundum type defects, case reports are exist describing multiple ASDs and coronary sinus defects which transcatheter closure was successful without significant valvular impairment or conduction disturbance.

**ASD variation with age**

Clinical characteristics of ASDs differ significantly in pediatric populations as compared to adults. ASDs are detected in asymptomatic children with increasing frequency due to non-invasive screening modalities such as echocardiography, routine ECG, and even prior to birth during routine obstetric
wellness sonograms\textsuperscript{[13]}. Furthermore, studies show referral to specialty services occurs at an earlier age if subtle findings are detected on physical examination despite lack of symptoms. One such single center retrospective study indicated the median age of diagnosis was 5 months of age\textsuperscript{[14]}. Areas of increasing interest in pediatric management include predictors of spontaneous ASD closure. Many predictors of spontaneous closure have been proposed; the longest held predictor appears to be size of the ASD at time of detection with small defects (3-5 mm) having up to 87\% closure rates and large defects (> 8 mm) conferring much lower closure rates (0\%-8\%)\textsuperscript{[14-16]}. Others suggest the use of patient age at time of detection or normal weight gain after detection as clinical predictors for spontaneous ASD closure\textsuperscript{[17]}.

Adult populations with ASDs are typically asymptomatic with great variability in the onset of symptoms. More common symptoms appear to be early onset atrial flutter or atrial fibrillation due to atrial stretch, and less commonly decompensated right heart failure in patients under 40 years of age\textsuperscript{[18]}. The natural history and subsequent prognosis were reported by Campbell\textsuperscript{[19]} with progressive worsening mortality approaching 90\% by the 6th decade in patients with uncorrected defects.

**Untreated atrial septal defect in the elderly**

Elderly patients with hemodynamically significant defects more frequently encounter complications with long-term adverse consequences such atrial arrhythmia, pulmonary hypertension, and atrioventricular valvular insufficiencies related to chronic ventricular volume overload\textsuperscript{[20]}. These patients have comparatively higher prevalence of co-morbid diseases including diabetes mellitus, stroke, systemic hypertension, chronic lung diseases atherosclerosis and coronary heart diseases\textsuperscript{[21-23]}. Longstanding left to right shunt at the atrial level further results in a progressive atrial stretch and right ventricular dilatation which in turn eventually leads to tricuspid insufficiency\textsuperscript{[24]}. The left heart may also be influenced by way of increased atrial pressure, chronic volume under load, and co-morbid diseases like systemic hypertension or coronary heart disease\textsuperscript{[6]}. Furthermore, chronic LV unloading due to the left to right shunt, and diastolic compression of left ventricle...
by the dilated right ventricle may further reduce the LV end-diastolic volume in the chronic state. This so-called “masked LV restriction” may lead to development of pulmonary edema secondary to LV dysfunction and left atrium (LA) pressure increase after ASD closure\textsuperscript{[22,25]}. Due to the chronic nature of the condition, patients usually adjust their activity level to adapt to their relative disabilities, and invasive interventions are placed under increasing scrutiny due to the paucity of evidence for survival benefit. Prospective studies evaluating quality of life improvements, or elucidating risk vs. objective benefit are called for to establish the role of ASD closure in the elderly.

**IMAGING MODALITIES FOR ASD EVALUATION**

**Echocardiography**

Conventional transthoracic echocardiography (TTE) is capable of identifying the presence of ASDs, characterizing chamber dilatation, estimated pulmonary artery pressure, shunt ratio, and other coexisting cardiac conditions. Figure 2 demonstrates doppler imaging of an unrepaired ASD. Tissue doppler imaging may be of particular use in elderly patients who suffer pronounced LV diastolic dysfunction. One recent study suggests patients at risk for post ASD closure congestive heart failure by measuring early mitral annular velocity to help direct volume management during and after ASD closure\textsuperscript{[26]}. In regard to assessment of ASD morphology, including maximum defect dimensions and characterization of the surrounding tissue rim, 2D TTE is somewhat limited. These limitations are surmounted with the adjunct of transesophageal echocardiography (TEE) which offers a stepwise enhancement in characterizing the size, location, and tissue rim surrounding ASDs to determine suitability for transcatheter repair. TEE is considered a semi-invasive procedure so is undertaken only after initial evaluation with TTE\textsuperscript{[27,28]}.

**3D echocardiography**

3D echocardiography provides better spatial visualization than conventional echocardiography. An example of a diagnostic 3D TEE visualizing an unrepaired defect can be seen in Figure 3A. 3D TEE can also depict 3D structures in great detail with high-resolution images allowing for enhanced understanding of complex valvular and congenital heart defects\textsuperscript{[27]}. Initially, 3D echocardiography was reconstructed from serial 2D
images, which is time-consuming and resource intensive. Nowadays real-time 3D echocardiography with matrix array transducer is available in TTE as well as TEE. 3D TTE is a promising technology capable of providing comprehensive en face images of ASD with the added benefits of being noninvasive, lower cost than TEE, portability, and carries better accessibility than TEE. 3D TTE has a potential to provide accurate information on ASD morphology such as size, location, and surrounding rims for treatment both in children and adult populations. Furthermore, real-time 3D TEE has utility in providing accurate real-time information about complex ASDs, especially those in patients with multiple ASDs, and allowing for real-time feedback of device deployment positioning.

Intrauterine Sonographic Detection of ASD
The International Society of Ultrasound in Obstetrics and Gynecology recently published guidelines on the detection of fetal cardiac anomalies in 2017 with the goal of improving early detection by obstetricians and family practitioners. The feasibility of ASD detection via intrauterine sonogram has been demonstrated by many isolated case reports, retrospective analysis, and prospective studies. Despite this, there are few reports on the sensitivity of intrauterine ASD detection (30%-74%), and should be relegated to pregnancies that carry high risk for cardiac abnormalities.

Transcranial doppler ultrasonography
Transcranial doppler ultrasonography (TCD) is a viable alternative to TTE or TEE for screening and follow-up evaluation of ASD. It offers a relative degree of comfort over TEE, and offers sensitivities equivalent to TTE in terms of identifying right to left shunts, but cannot detect other associated defects that echocardiography can.

Intracardiac Echocardiogram
Intracardiac echocardiography (ICE) offers superior visualization of the septal morphology during transcatheter device deployment. It is, as the name suggests, invasive and requires additional femoral vessel access for deployment. Real time 4D ICE also appears to be on the horizon with reports on its development and pilot study usage are now emerging.

MANAGEMENT OF ASD
Surgical vs. Medical management of Secundum ASD
ASDs are considered for closure in symptomatic patients where a left to right shunt is present with evidence of right heart pressure overload (right atrial or ventricular enlargement), and pulmonary to systemic blood flow ratio (Qp:Qs) is greater than 1.5:1. In addition to right heart overload and Qp:Qs > 1.5:1, in
asymptomatic patients, those whose pulmonary artery pressure is less than 50 percent systemic arterial pressure, and pulmonary vascular resistance is greater than one third the peripheral vascular resistance, without exercise induced cyanosis, are recommended for ASD closure\cite{40-42}.

Of great interest to clinicians in the age of readily available transcatheter repair of secundum type ASDs is the decision to pursue transcatheter or open surgical repair. One such study at Mayo Clinic sought to evaluate outcomes of surgically managed ASD cases as compared to medical management alone with a follow-up interval of 27 to 32 years after the index surgery. Study findings demonstrated that the survival rate was 74\% as compared to 85\% for age sex matched medically managed controls. In cases where surgical intervention occurred below the age of 24 years, survival rate reported was the same as age matched controls. Independent predictors of long-term survival were age at the time of operation and main pulmonary artery systolic Pressure (PASP)\cite{43}. The more recent study of the Danish population found that there was a significant reduction in the life expectancy and lower quality of life in patients with small ASDs that did not meet criteria for repair when compared to the general population\cite{44}. In another study, surgical vs. medical management were compared prospectively in a randomized clinical trial of 473 patients over the age of 40 years with a median follow up period of 7.3 years. Overall mortality rate was not statistically different. However, there was a higher rate of recurrent pneumonia noted in the medical arm. There was indeed a trend higher complication rates such as CHF, sudden cardiac death, and overall mortality in the medical arm, but was ultimately not statistically significance\cite{45}.

More recently the 2018 ACC/AHA task force undertook a meta-analysis seeking to understand differences in outcomes of medical vs interventional management of secundum type ASDs. Their analysis found 11 studies that met criteria for inclusion, and in most instances found a protective effect with bearing on reduction of symptoms, functional capacity, and improvement of hemodynamic characteristics following either surgical or transcatheter intervention\cite{46}. Interestingly, in the same analysis, there was either insufficient data to determine relative risk of death, or a weakly positive protective effect after intervention, from the included studies. Furthermore, a nationwide study of patients with corrected and uncorrected ASDs were compared to the general population with interesting results; their findings demonstrated a relative reduction in mortality for patients who underwent repair of ASDs. But whether repaired or not, patients with ASDs patients experienced a shorter lifespan when compared to the general public\cite{47}. Taking the results of these, and similar studies, may help establish important expectations when discussing intervention; quality of life and reduction of symptoms, rather than preventing mortality, may lead discussions pertaining to goals of therapy.

**Surgical vs. transcatheter intervention**

At the time of this writing, only secundum type defects have transcatheter devices approved for intervention. Primum, Sinus Venosus, and Coronary sinus defects still carry the recommendation of open surgical intervention with only rare reports of transcatheter interventions published\cite{48-51}. In the pediatric population there are similar long term outcomes between surgical vs. transcatheter intervention, however cost analysis demonstrates a better value in terms of overall cost as well as shorter length of stay for patients undergoing transcatheter repair\cite{52}. In the adult population, mortality between transcatheter and surgical intervention are similar, but long-term reintervention rates appear to vary between the two. In a review of 718 procedures, Kotowycz et al.\cite{53} report that long term reintervention rates for transcatheter repair are more common than compared with conventional surgical approach. Other studies report similar findings - but prospective randomized studies have not been undertaken to determine true differences. Furthermore, patients more likely to undergo transcatheter repair are often higher risk than patients deemed appropriate for surgical intervention potentially skewing attempts to study differences in outcomes.

Of growing interest is the prospect of treating ASDs associated with sinus venosus defects, which are traditionally treated with open surgical repair. Presently, there are only case reports describing transcatheter
approaches. Two such case reports technical success with correcting partial anomalous pulmonary venous return of the right upper pulmonary vein by deploying a covered stent graft into the affected pulmonary vein \cite{54,55}. Abdullah et al.\cite{56} describe an approach that combines covered stent grafts and occlusion devices to correct sinus venosus defects successfully in four patients; of which two required re-intervention with an additional covered stent or PFO closure device, but all without significant complications at the 12-month follow-up point \cite{56}. Others have reported success with the immediate release patch, which has been under investigation in translational animal studies as a potential alternative to metallic devices \cite{57,58}.

Transcatheter devices available today for closure of secundum ASDs

The origins of transcatheter ASD repair can be traced back to King’s report of non-operative ASD closure during cardiac catheterization in 1976 \cite{59}. Formal development of a device for ASD, however, is attributed to the Atrial Septal Defect Occluding System (ASDOS) submitted by Babic et al in 1990 \cite{60}. Though successive iterations made the device more user friendly and showed early promise, the ASDOS was abandoned in 2001 with the development of newer generations of transcatheter devices. A history of transcatheter device evolution has been detailed by Nassif et al.\cite{61}. Today, transcatheter ASD closure is associated with low complications, short duration anesthesia, short hospital stay, and well documented long-term symptom follow up \cite{62-64}. Transcatheter ASD closure is now considered the first choice of treatment as opposed to surgical intervention. The most widely employed device worldwide, and one of two FDA approved devices for use in North America is the Amplazer device, shown in Figure 4. Echocardiography, either ICE or TEE play a considerable role in the guidance of these procedures and in further assessment of the final results. Areas of active research focus on examining other imaging modalities like magnetic resonance imaging or computed tomography to construct 3D topographical visualizations of the heart and associated defects prior to transcatheter ASD closure \cite{65-69}. A review of recent publications describing the outcomes and population size of the respective studies are listed in Table 1, including devices otherwise available outside of the United States.

**ASD characteristics amenable for percutaneous closure**

Two crucial parameters should be evaluated in patients with secundum septal defect prior to intervention: maximal ASD and surrounding rim dimensions. Presently, the Amplatzer device is capable of closing
defects with a maximum defect diameter less than 38 mm[64]. An example of balloon sizing as assessed intraoperatively with balloon sizing as compared to real time TEE sizing can be seen in Figure 5. ASDs typically give the appearance of with ellipsoidal geometry that varies throughout the cardiac cycle[94,95]. Selection of optimal device size, particularly in patients undergoing the procedure without balloon sizing or multiple defects, involves measuring the major axis diameter of the defect during ventricular end systole. More recently, real time 3D TEE is challenging the need for balloon sizing with stop-flow technique as an adjunct to prevent underestimation of defect size or tissue rims[96,97].

<table>
<thead>
<tr>
<th>Device name</th>
<th>Manufacturer</th>
<th>Approval</th>
<th>Recent/ongoing studies</th>
<th>n</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocoon</td>
<td>Vascular Concepts</td>
<td>CE Mark</td>
<td>Lairakdomrong et al.[70], 2013 - retrospective</td>
<td>63</td>
<td>100% closure at 12 mo, 3 early embolization requiring surgical removal</td>
</tr>
<tr>
<td>Ultrasert II</td>
<td>Cardia</td>
<td>CE Mark</td>
<td>Thanoopoulos et al.[71], 2014 - prospective observational</td>
<td>92</td>
<td>100% closure at 6 mo, no adverse events</td>
</tr>
<tr>
<td>Eagan, MN, USA</td>
<td>Mijangos-Vázquez et al.[72], 2018 - retrospective</td>
<td>Bartel et al.[73], 2010 - case series</td>
<td>30</td>
<td>100% closure at 6 mo, no adverse events</td>
<td></td>
</tr>
<tr>
<td>Nit Occlude ASD-R</td>
<td>PFM Medical Mepro</td>
<td>CE Mark</td>
<td>Peirone et al.[77], 2014 - prospective observational</td>
<td>73</td>
<td>98.6% closure at 11 mo, no adverse events</td>
</tr>
<tr>
<td>Köln, Germany</td>
<td>Bulut et al.[78], 2016 - prospective observational</td>
<td>30</td>
<td>98% closure at 10 mo, 1 erosion requiring surgical removal</td>
<td></td>
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</tr>
<tr>
<td>Ceraflex ASD</td>
<td>CE Mark</td>
<td>Astarcigliglu et al.[79], 2015 - non-randomized</td>
<td>58</td>
<td>100% closure at 6 mo, no adverse events</td>
<td></td>
</tr>
<tr>
<td>Jena, Germany</td>
<td>Apostolopoulou et al.[82], 2018 - retrospective</td>
<td>183</td>
<td>100% closure at 22 mo, no adverse events</td>
<td></td>
<td></td>
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<tr>
<td>Figulla Flex II</td>
<td>Occlutech</td>
<td>CE Mark</td>
<td>Kenny et al.[85], 2018 - prospective randomized</td>
<td>107</td>
<td>94.4% closure at 6 mo, 1 device embolization</td>
</tr>
<tr>
<td>Jena, Germany</td>
<td>Haas et al.[90], 2016 - retrospective</td>
<td>1315</td>
<td>97.3% closure at 12 mo, 5 device embolization, 3 AV block</td>
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<td></td>
</tr>
<tr>
<td>Cardioform</td>
<td>WL Gore</td>
<td>CE Mark</td>
<td>Godart et al.[91], 2014 - retrospective</td>
<td>31</td>
<td>90.3% closure at 36 mo, 1 device embolization, 1 AV block</td>
</tr>
<tr>
<td>Flagstaff, AZ, USA</td>
<td>Roymamee et al.[92], 2015 - retrospective</td>
<td>77</td>
<td>97.4% closure at 43 year, 2 device embolization, non-inferiority to ASO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplatzer</td>
<td>St. Jude Medical</td>
<td>CE Mark</td>
<td>Aytemir et al.[93], 2013 - retrospective</td>
<td>58</td>
<td>99.3% closure at 12 mo, 2 device embolization, 4 embolic events, 2 device thrombosis</td>
</tr>
<tr>
<td>St. Paul, MN, USA</td>
<td>Kim et al.[94], 2019 - retrospective GORE Assured Study, ongoing[86]</td>
<td>152</td>
<td>100% closure at 25 mo</td>
<td></td>
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<tr>
<td>Flagstaff, AZ, USA</td>
<td>Hemptinne et al.[87], 2017 - prospective</td>
<td>522</td>
<td>Clinical Trial NCT02985684, enrollment complete, final results by 2022</td>
<td></td>
<td></td>
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<tr>
<td>Grohmann et al.[88], 2016 - prospective</td>
<td>26</td>
<td>100% closure at 6 mo, 5 wire frame fractures</td>
<td></td>
<td></td>
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<tr>
<td>Amplatzer</td>
<td>St. Jude Medical</td>
<td>CE Mark</td>
<td>Turner et al.[96], 2017 - prospective</td>
<td>1000</td>
<td>97.9% closure at 24 mo, 1 embolization, 3 cardiac erosion</td>
</tr>
<tr>
<td>St. Paul, MN, USA</td>
<td>Spies et al.[97], 2007 - retrospective</td>
<td>170</td>
<td>100% closure at 12 mo, 4 embolization, 1 TIA,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA</td>
<td>Tomar et al.[98], 2011 - retrospective</td>
<td>529</td>
<td>100% closure at 56 mo, 96.7% symptom free, 1 stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al.[99], 2019 - retrospective Post Market Surveillance (ASO S22)[100]</td>
<td>98</td>
<td>100% closure at 29 mo, 1 embolization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>602</td>
<td>Clinical Trial NCT02353351, study terminated, results not published yet</td>
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</table>
Transcatheter closure of ASDs with a maximal native diameter > 30 mm can be quiet challenging, and alternative techniques for deployment may be required, which will be discussed later. In regard to classification of surrounding rims, although there are some differences noted among studies, distances from ASD to aorta, superior vena cava, right upper pulmonary vein, inferior vena cava, coronary sinus, and atroioventricular valve are evaluated. Adequate tissue rim is defined by at least 5mm from the defect edge to the surrounding structures so as not to impinge on the vena cava, pulmonary vein, coronary sinus, tricuspid or mitral valve. Figure 6 depicts areas of interest in measuring surrounding tissue rim dimensions.

Figure 7 illustrates the tissue rim measurements as seen via intraoperative TEE. Tissue measurements are best taken as follows: AV valve and right upper pulmonary vein tissue rim are best viewed in the 4 chamber view, SVC and IVC rims are best measured in the Bi-Caval view, and the Aortic and posterior rim measurements are best taken in the short axis view. These are recommendations, but individual body habitus and variations in heart orientation may necessitate obtaining alternate views to accurately measure tissue rims. Interestingly, Yan et al. describe generating a custom 3D model to visualize and assess device closure feasibility based on 3D TEE end systolic dimensions with 29 of 30 patients found to have deficient posterior-inferior rim size (< 3 mm), providing a proof of concept for simulated in-vivo device fitment prior to undergoing transcatheter intervention. Though, caution should be maintained regarding attempting transcatheter closure with inadequate rim size, as many studies demonstrate increased risk for device embolization with difficult retrieval or conversion to open surgery.

Special issues in the management of elderly patients with ASD

Comparative benefits from ASD closure in the elderly population have historically been underreported as compared younger populations. The paradigm of non-operative management of previous generations had, in some ways, stymied broad acceptance and given cause to thwart intervention where there was no perceived benefit. However, percutaneous management of ASD in elderly patients has gained reluctant enthusiasm, as evidenced by analyzing trends in hospitalizations captured by the National Inpatient Sample Database. The promise of shorter hospitalization time and reduced complication rates is tempered with the many difficulties faced perioperatively due to the tendency toward combined comorbidities. Realistic benefits of ASD closure include symptomatic relief, improvements of functional status as well as the overall improvement in the quality of life.
Outcomes of ASD closure in elderly Patients:
In two separate studies Swan and Khan both found that following ASD intervention, a small cohort of geriatric patients with a median age of 70 years old, saw improvement in their New York Heart Association (NYHA) class, 6 minute walk time and improvement in overall physical/mental health score in addition
to an extremely high procedural success rate (98%)\textsuperscript{[23,107]}. Furthermore, Nakagawa et al.\textsuperscript{[103]} reported that after intervention in a population composed of patients 70 years or older with hemodynamically significant ASD, percutaneous closure is efficacious and safe. The intervention led to a significant improvement of PA pressure and NYHA functional class, as well as reversal of RV enlargement\textsuperscript{[103]}.

Similarly, in 2014 Komar et al.\textsuperscript{[108]} studied the mid-term outcome of patients over the age of 60. Interestingly, their primary outcome was focused more on quality of life indices and functional benefits rather than complications or long term survival. Metrics such as time of sustained exercise before feeling short of breath, VO\(_{2}\max\), and the SF-36 quality of life questionnaire to gauge the benefits of ASD closure. Symptomatic parameters like incidence of shortness of breath or time of exercise before shortness of breath both improved significantly; furthermore 88% of patients surveyed had a significant subjective improvement in quality of life 12 months following their index surgery\textsuperscript{[108]}.

**Obstacles in transcatheter atrial septal defect closure in elderly patients:**

The most salient issue in elderly cases is not their primary pathology, but their co-morbid systemic and cardiac diseases. This necessitates careful preoperative evaluation of the associated risk factors as an essential aspect of successful treatment. Approximately one third of the patients showed systemic hypertension and systemic diseases like diabetes mellitus, and a considerable extent of pulmonary and neurological disease conditions were also present\textsuperscript{[109]}. Among the cardiac co-morbidities pulmonary hypertension is reported in nearly 50 % of the cases, chronic atrial arrhythmia in more than 20% and ischemic heart disease in about 15% of the patients\textsuperscript{[110,111]}. Post-closure pulmonary edema developed because of “masked LV restriction” may appear in 2% to 4% of the elderly cases may be evaluated with a balloon occlusion prior to ASD closure\textsuperscript{[112]}.

Similarly, diastolic dysfunction and stiffening of the LV causes increased left to right shunting, which may explain in part why the late diagnosis is established in elderly patients who were previously asymptomatic. Careful assessment of left ventricular and left atrial pressures via left heart catheterization during defect balloon occlusion and weighing potential hemodynamic consequences vs. perceived benefits of intervention, are especially important in the elderly patient population. Miranda et al report that left ventricular end diastolic pressure may help predict left atrial pressures in those undergoing ASD repair. They found that the vast majority of patients who had a baseline left ventricular end diastolic pressure > 15 mmHg developed significantly elevated left atrial pressure during balloon occlusion of ASD\textsuperscript{[113]}.

**ASD and pulmonary arterial hypertension**

Due to chronic right ventricular volume overload, elderly patients with hemodynamically significant ASDs have a tendency to present with pulmonary hypertension. Pulmonary hypertension develops as a result of increased pulmonary blood flow due to left-to-right shunting. However, the anomalous rise in pulmonary blood flow creates secondary physiologic changes such as pulmonary vascular intimal proliferation and medial hypertrophy that affect pulmonary vascular resistance\textsuperscript{[114,115]}. The consequence of such changes has been observed to be reversible in younger patients, but may not be fully reversible in the elderly\textsuperscript{[116]}. It is well understood that the natural course of ASD and the associated effect on pulmonary hypertension is notably worse than in patients without pulmonary hypertension\textsuperscript{[117]}. Thus, pulmonary hypertension is traditionally considered an absolute contraindication to ASD intervention, especially surgical closure\textsuperscript{[118]}. The expansion of therapeutic options for treating pulmonary hypertension may offer new avenues for ASD closure. An area of active research is the role of ASD closure in combination with new pulmonary hypertension treatments such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, even if initial hemodynamic parameters are unamenable to ASD closure\textsuperscript{[119-122]}. More recent studies such as the North American Atrial Septal Defect Pulmonary Hypertension (NAAPH) Study demonstrate feasibility of ASD closure in patients with PAH with an aggressive “treat to repair” strategy.
which first addresses underlying pulmonary hypertension\textsuperscript{[123]}. Optimization of elderly patients with concomitant pulmonary hypertension prior to ASD closure remains an area of active research.

**Cardiac erosion after percutaneous ASD intervention**

In patients with superoanterior rim deficiency, the increased risk of serious complication, i.e., “cardiac erosion” may increase after implantation of the device. The exact mechanism of “cardiac erosion” is not been well understood; previous clinical experience proposed that an aortic rim deficiency and oversized occlusion device may be highly correlated with cardiac erosion\textsuperscript{[124]}. In response, updated instructions-to-user were published for the Amplatzer device with specific guidance for aorto-superior rim size specifications\textsuperscript{[125]}. One recent case series reported that absence of the aortic rim was common finding among patients who developed erosion\textsuperscript{[126]}. Subsequently, other putative risk factors were also reported as physicians modified their practices and over sizing became less common\textsuperscript{[127]}. Specifically, deficient aortic or SVC rim size, along with balloon sizing were associated with increased risk of erosion\textsuperscript{[128]}. It should be noted, however, that these studies are retrospective in nature, and prospective studies have not yet been undertaken to determine true causal relationships for erosion relating to rim size.

**FUTURE DIRECTION OF TRANSCATHETER INTERVENTION FOR ASD**

The transcatheter ASD repair has evolved from employment in select patients unable to undergo open surgical repair, to applications in pediatric populations, and is now gaining traction in the elderly. Where currently secundum type ASDs and limited case-reports of closure in other varients of ASD are now being reported, we may expect future devices to address these limitations. On the other hand, complications arising from this procedure, especially cardiac erosion, are still being reported. Progress over the last several decades in terms of safety and efficacy are impressive and point to a bright future in the treatment of congenital heart defects. We conclude this review by looking to the near and long-term future in the state of the field.

**New devices for difficult ASD closure**

Several technical modifications have been introduced over the years to address difficult transcatheter ASD closure, including delivery sheath modification, position deployment, or additional material to hold the left atrial disk inside the LA. Some advocate deployment with balloon assisted placement\textsuperscript{[129]}. This technique, however, may cause injury to the pulmonary vein. The development of steerable catheters may offer improved techniques in positioning ASD devices\textsuperscript{[130]}. Use of such a steerable catheter has been described in case reports, but has not yet been implemented in commercially available devices, offering an opportunity for future development\textsuperscript{[131]}.

**Endovascular retrieval of embolized devices**

A well described early and mid-term complication of transcatheter ASD closure is device dislodgement and embolization. The rote response, if the device has been fully deployed, is to convert to open surgery for retrieval and repair. Improving techniques for endovascular retrieval are supported by case reports, case series, and retrospective reviews of experience\textsuperscript{[132-134]}. Common embolization sites are the left ventricle, abdominal aorta and femoral vessels\textsuperscript{[135,136]}. Lastly, Martins, Mendez, and Anjos provide an excellent pictorial stepwise description of various retrieval techniques and devices, and even include demonstrative videos\textsuperscript{[137]}. Protective devices to prevent embolization during surgery may be an area of future interest to prevent distal embolization periprocedurally\textsuperscript{[138]}.

**Salvage of residual shunt with device-in-device intervention**

Intracardiac devices that are malfunctioning, whether dislodged, malpositioned, or sub-optimally effective, are typically treated with open heart surgery for removal and remedy. At the present, there are only case reports describing “device-in-device” salvage to return function to such malfunctioning devices\textsuperscript{[75,139]}. The
concept of device-in-device salvage involves deploying a second device through residual defects the first device did not completely close, in order to provide an adequate seal zone the first device did not provide. These early reports may eventually become the foundational principals for guidelines to prevent conversion to open surgery, but no definitive conclusions can be drawn with such limited data. Likewise, residual shunts following surgical repair of ASDs may be of great interest in the case of secundum ASDs.

GENE THERAPY, TISSUE ENGINEERING, AND STEM CELL THERAPY FOR ASD

The goals of treatment in congenital cardiac malformations are ever shifting. Seventy-five years ago, researchers and clinicians sought to find appropriate screening criteria where risk factors for ASDs were poorly understood. With the advent of better screening methods and guidelines, the difficult decision of who should undergo surgery or medical management then became the diagnostic dilemma. With newer, safer, conventional and endovascular procedures well established, the next logical progression in the field is primary prevention of the disease process. Several reports proposing genes associated with ASD that may inform progress toward potential targets for gene therapy in genetically linked variants of ASD [140-142]. Furthermore, elucidating the temporal and spatial relationships among terminally differentiating cells during cardiogenesis may provide further insight into the precise moment in congenital defects begin [143,144].

Until primary prevention with gene therapy is technically feasible, other interventions may be on the horizon. Tissue compatibility of ASD closure devices remains an area of interest for researchers and clinicians alike. Biocompatible and bioabsorbable based devices are currently under investigation [145]. Those at the beginning of their surgical career may see 3D printed custom devices or bio inspired devices in the form of surgical glue or gels that can be deployed endovascularly emerge within their career [54,146-148].

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