Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Clinical Medicine Insights: Cardiology

Supplementary Issue: Structural Heart Disease: Research and Practice in Coronary, Structural, Adult Congenital and Peripheral Vascular Cardiology

Atrial Septal Defects – Clinical Manifestations, Echo Assessment, and Intervention

Seth S. Martin, Edward P. Shapiro and Monica Mukherjee

Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

ABSTRACT: Atrial septal defect (ASD) is a common congenital abnormality that occurs in the form of ostium secundum, ostium primum, sinus venosus, and rarely, coronary sinus defects. Pathophysiologic consequences of ASDs typically begin in adulthood, and include arrhythmia, paradoxical embolism, cerebral abscess, pulmonary hypertension, and right ventricular failure. Two-dimensional (2D) transthoracic echocardiography with Doppler is a central aspect of the evaluation. This noninvasive imaging modality often establishes the diagnosis and provides critical information guiding intervention. A comprehensive echocardiogram includes evaluation of anatomical ASD characteristics, flow direction, associated abnormalities (eg, anomalous pulmonary veins), right ventricular anatomy and function, pulmonary pressures, and the pulmonary/systemic flow ratio. The primary indication for ASD closure is right heart volume overload, whether symptoms are present or not. ASD closure may also be reasonable in other contexts, such as paradoxical embolism. ASD type and local clinical expertise guide choice of a percutaneous versus surgical approach to ASD closure.

KEYWORDS: atrial septal defect, ostium secundum defect, ostium primum defect, sinus venosus defect, coronary sinus defect, echocardiography

SUPPLEMENT: Structural Heart Disease: Research and Practice in Coronary, Structural, Adult Congenital and Peripheral Vascular Cardiology

CITATION: Martin et al. Atrial Septal Defects – Clinical Manifestations, Echo Assessment, and Intervention. *Clinical Medicine Insights: Cardiology* 2014:8(S1) 93–98 doi: 10.4137/CMC.S15715.

RECEIVED: August 18, 2014. **RESUBMITTED:** October 29, 2014. **ACCEPTED FOR PUBLICATION:** November 09, 2014.

ACADEMIC EDITOR: Thomas E. Vanhecke, Editor in Chief

TYPE: Review

FUNDING: SSM is supported by the Pollin Cardiovascular Prevention Fellowship, Marie-Josée and Henry R Kravis endowed fellowship and a National Institutes of Health training grant (T32HL07024). The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE:

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Introduction

An atrial septal defect (ASD) is a persistent interatrial communication. It is distinct from a patent foramen ovale wherein there is a flap with intermittent communication. ASD types strictly include ostium secundum (~75% of cases), ostium primum (15–20%), and sinus venosus (5–10%), while rare coronary sinus defects are closely related.[1] Secundum ASDs are positioned by the fossa ovalis, primum ASDs inferiorly as part of the spectrum of endocardial cushion defects, and sinus venosus ASDs near the superior or inferior vena caval entry.[1,2] ASDs are highly relevant to echocardiographers and clinicians as one of the most common congenital abnormalities. The overall prevalence of diagnosed ASDs has been estimated at 3.89 per 1000 children and 0.88 per 1000 adults, which may be underestimates due to clinically silent and unidentified cases.[3] The exact genetic underpinning of ASD is uncertain in most cases, but novel insights are emerging,[4] and may influence clinical evaluation and management in the future.

In this review, we cover the clinical manifestations of ASDs, discuss the central role of echocardiography in ASD evaluation, and provide clinical practice guidelines for intervention.

Clinical Manifestations

The 2008 American College of Cardiology and American Heart Association (ACC/AHA) adult congenital heart disease guidelines provide detailed clinical guidance on ASDs.[1] The clinical course is variable.[1,5] Very small ASDs (diameter <5 mm) may not have significant clinical consequences, while a defect of 5–10 mm may lead to symptoms in the fourth or fifth decade of life. Larger defects (generally >10 mm) typically present with symptoms in the third decade of life. Normal

aging is associated with increased left ventricular stiffness and concomitant impairments in diastolic filling,[6,7] leading to an increase in left to right shunting across the ASD and right ventricular volume overload.

When symptoms occur, patients often first notice dyspnea, fatigue, exercise intolerance, or palpitations.[1] Some patients may present with syncope or even with peripheral edema from overt right heart failure and others may develop recurrent pulmonary infections. Although uncommon, dyspnea in patients with ASD may be triggered by an upright position in orthodeoxia–platypnea syndrome and linked to arterial desaturation.

Atrial tachyarrhythmias, including atrial fibrillation and flutter, are present preoperatively in about one-fifth of adults with ASDs.[8] Consistent with age as a well-established risk factor for atrial arrhythmias, patients with versus without preoperative atrial fibrillation or flutter had a mean ± SD age of 59 ± 11 years versus 37 ± 13 years, respectively. Late postoperative atrial fibrillation or flutter tends to occur in those who undergo closure after the age of 40 years.[2] In older age groups, the extent of the contribution from the ASD to the arrhythmia could be difficult to discern in the presence of other contributing factors such as obesity and hypertension. Sick sinus syndrome may also develop in ASD patients due to longstanding right heart overload.[1]

In patients who have a stroke, transient ischemic attack, or peripheral arterial embolization, the clinical question commonly arises about paradoxical embolization as the underlying pathophysiologic mechanism.[9,10] A right to left shunt across the interatrial septum could allow a mobile venous thrombus or air embolus to gain access into the arterial system. The thrombus may originate from the left atrial appendage in the setting of atrial fibrillation, from a peripheral or pelvic vein, or indwelling venous catheter, while an air embolus may originate from an unfiltered intravenous infusion. Right to left shunting may occur at rest or only transiently with an increase in right-sided pressure due to coughing for instance. The presence of severe pulmonary hypertension can promote persistent net right to left shunting. In a series of 103 patients with a mean age of 52 years thought to have suffered paradoxical embolization, an ASD was present in 12%.[11] A patent foramen ovale was much more common and present in 81%.

If fixed pulmonary hypertension develops, this may mark a late disease stage and decreased survival. Pulmonary hypertension may also be idiopathic, particularly in women. The prevalence of pulmonary hypertension was 16% in a sample of 295 Belgian patients (69% women, age 46 ± 21 years) with isolated secundum ASD.[12] In those who had undergone ASD closure, age at the time of repair was the strongest predictor of development of pulmonary hypertension. Those in the highest tertile of age (>55 years) had the highest prevalence (34%) of pulmonary hypertension subsequently. Pulmonary hypertension, in turn, was associated with mortality, atrial arrhythmia, and right heart failure. Eisenmenger syndrome, a combination of pulmonary hypertension and right to left shunting, carries several clinical concerns, including thrombosis, bleeding, and increased pregnancy complications.[13]

On physical examination, a patient with an ASD may have a right ventricular heave, systolic flow murmur in the pulmonary valve region due to increased pulmonary flow, a fixed split second heart sound, or a diastolic flow rumble across the tricuspid valve.[1] An interesting association of ASD with Klippel–Feil syndrome was recently reported, which has the major physical examination features of a short neck, limited range of motion in the neck, and low hairline at the back of the head.[14] Electrocardiographic signs of a secundum ASD include a right axis, right atrial enlargement, voltage evidence of right ventricular hypertrophy, and incomplete right bundle branch block.[1,2] A superior left axis may be seen with primum ASDs, while sinus venosus ASDs are associated with an inferior P-wave axis. Severe right axis deviation, right ventricular hypertrophy, and extensive repolarization abnormalities may be seen in the presence of an ASD with Eisenmenger syndrome. Complete heart block is characteristic of familial ASD.[15] Chest x-ray findings that are compatible with an ASD include cardiomegaly, pulmonary artery enlargement, or increased pulmonary vascularity.

Echo Assessment

The guidelines recommend diagnosing an ASD by demonstration of shunting across the interatrial septum, with evaluation of the right heart and for associated abnormalities.[1] Two-dimensional transthoracic echocardiography (2D TTE) often serves this need, providing the necessary imaging information to establish the diagnosis of ASD and make informed clinical decisions.[1,16,17] The components of a comprehensive echocardiographic evaluation are shown in Table 1.

Clues to an ASD on 2D TTE include a hypermobile interatrial septum, abrupt septal irregularity, right atrial and ventricular volume overload, and pulmonary artery dilatation. If a satisfactory subcostal view can be obtained, this is the preferred window because the interatrial septum is approximately perpendicular to the echo signal. The apical four-chamber view can also be especially useful in evaluation of the right

Table 1. Elements of a comprehensive echocardiographic evaluation for ASD.

Visualization of ASD and characterization of its size
Determination of the direction of flow
Evaluation for associated abnormalities*
Examination of right heart
Quantification of pulmonary artery pressure
Estimation of the pulmonary/systemic flow ratio

Notes: *Including mitral valve prolapse, partial anomalous right pulmonary veins (characteristic of sinus venosus ASDs and present in some secundum ASDs) and cleft anterior mitral valve leaflet (characteristic of primum ASDs).

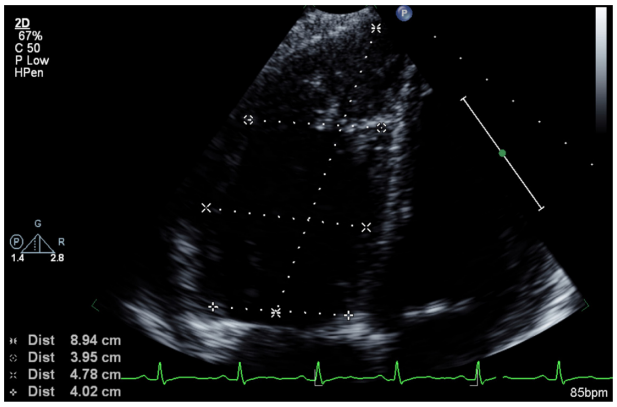

Figure 1. Demonstration of right ventricular enlargement in a patient with a secundum atrial septal defect in the apical four-chamber view by 2D transthoracic echocardiography.

heart (Fig. 1). However, the parallel orientation of the atrial septum to the echo signal in this view may lead to artifactual dropout and can be misleading. Complementary views may be obtained from the parasternal short axis and other non-standard views.

Using 2D TTE in patients with a satisfactory subcostal window, the ASD is reported to be visualized in 100% of primum ASDs, 89% of secundum ASDs, and 44% of sinus venosus ASDs.[18] However, as with other diagnoses, the sensitivity of echocardiography depends on the echo machine, acoustic windows, ultrasonographer, and echo reader. The first step may be to repeat a transthoracic echo if it is felt that one or more of these factors may be improved upon.

Applying color flow Doppler (Fig. 2) can confirm the ASD diagnosis, show directionality of flow, and help to better appreciate the ASD size; a larger width of the color flow jet across the interatrial septum indicates a larger ASD and predicts a higher shunt ratio. Pulse wave Doppler allows assessment of lower velocity flows across the interatrial septum and can be useful in estimation of the pulmonary flow to systemic flow ratio. Continuous-wave Doppler, useful for higher velocity flows, may be used to assess the gradient across the interatrial septum in patients with left atrial hypertension and restrictive ASDs, or obstruction to pulmonary venous return.[19]

If a full 2D TTE with Doppler does not establish the diagnosis of ASD, then an agitated saline contrast study can be performed to detect an ASD and/or confirm diagnosis.[1] It is expected that essentially 100% of ASDs will be detected with a high-quality agitated saline study that includes maneuvers (Valsalva, cough) to promote transient right to left shunting.[18]

A transesophageal echocardiogram (TEE) provides higher definition visualization of the interatrial septum. It may be reasonable when findings on transthoracic imaging are indeterminate or technically limited. TEE is also particularly helpful in visualizing sinus venosus ASDs and, therefore, is indicated to rule out a sinus venosus ASD in the setting of right ventricular enlargement and volume overload of unknown etiology. Furthermore, a TEE may help to detect anomalous pulmonary venous connections. Finally, the TEE can more precisely assess the size of an ASD and guide procedural planning (Fig. 3).

With TEE (as well as TTE), three-dimensional echocardiography may be considered to better determine the size and shape of an ASD and its anatomical relationships. Roberson et al reported their experience with three-dimensional TEE in 65 ASD patients aged 5–64 years with a body weight of 20–114 kg.[20] The echocardiographic examinations utilized live, zoom, and full-volume modes during catheter-based intervention or surgery. The investigators reported that the studies were of diagnostic quality in all 65 patients, 50 with a secundum ASD and 15 with other types. Live mode demonstrated the highest volume rate, provided superior transgastric views, and was ideal during device deployment, but carried the downside of small vector

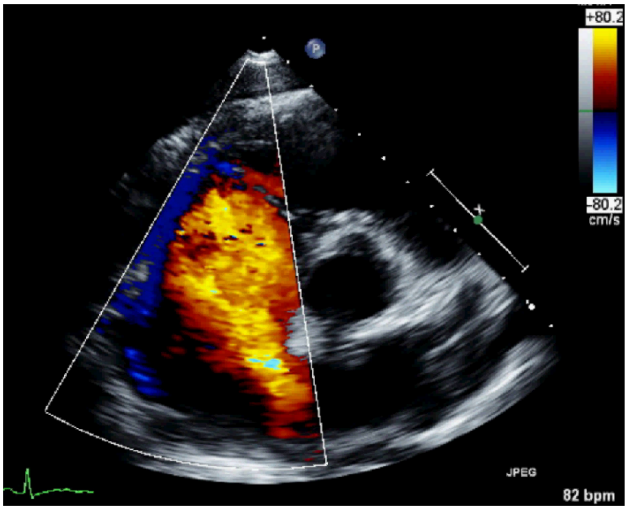

Figure 2. Left to right flow across a secundum atrial septal defect in the parasternal short axis view by 2D transthoracic echocardiography with color Doppler.

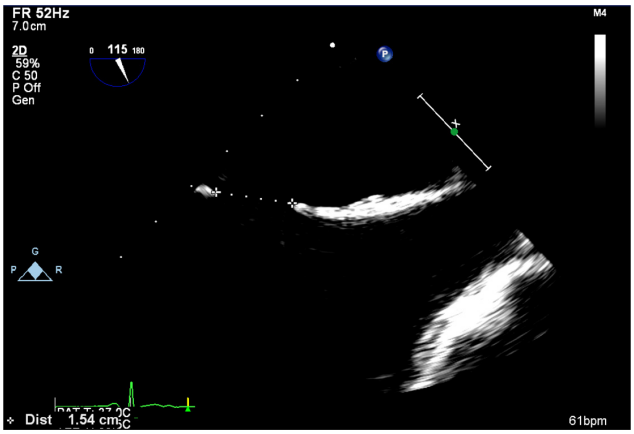

Figure 3. Sizing of secundum atrial septal defect by transesophageal echocardiography.

size. Zoom mode permitted pre-cropped live images, but had the limitation of slow volume rate. Full-volume mode had an advantage in visualizing large defects and surrounding anatomy, but was limited by stitch artifact and the need for post-acquisition cropping. Therefore, overall, three-dimensional echocardiography appears to be feasible and accurate, with complementary strengths and limitations to different views.

In patients diagnosed with an ASD, the right heart should be carefully assessed on echocardiogram. Right ventricular enlargement and interventricular septal flattening during diastole indicate a state of volume overload. Guidelines define right ventricular enlargement as a right ventricle that is larger than the left ventricle or greater than 4.2 cm in its basal diameter.[21] Accompanying right atrial and pulmonary artery enlargement may be present. Pressure in the pulmonary artery should also be estimated by Doppler interrogation of tricuspid regurgitation and right atrial pressure estimation. Specifically, pulmonary artery pressure may be estimated as the square of the velocity of the tricuspid regurgitation jet multiplied by four (modified Bernoulli equation) plus the right atrial pressure estimate. In addition, right ventricular pressure overload is suggested by systolic flattening of the interventricular septum. Invasive cardiac catheterization may be indicated after echocardiography for direct measurement of right-sided pressures.

Another potentially useful non-invasive Doppler estimate is the ratio of the pulmonary/systemic blood flow (Qp/Qs): [(pulmonary artery diameter)^2 × pulmonary artery velocity time integral]/[(left ventricular outflow tract diameter)^2 × left ventricular outflow tract velocity time integral]. In our experience, the best measurement of pulmonary outflow diameter comes from TEE (longitudinal pulmonary valve view), pulmonary flow from TTE (parasternal short axis), left ventricular outflow diameter from TEE (esophageal view at ~120°), and aortic flow from TTE (5 chamber view) or TEE (gastric view). In the absence of the TEE, accurate measurement of the pulmonary outflow tract diameter can be particularly challenging; guidelines recommend using the parasternal short-axis view at the base of the heart,[16] but the subcostal view may also be considered. At least in expert hands, Qp/Qs by echo agrees well with invasive cardiac catheterization, the gold standard for Qp/Qs.[22]

Adjunctive Testing

In patients in whom the diagnosis remains uncertain after echocardiographic assessment, cardiac computed tomography and magnetic resonance imaging may provide complementary information to characterize an ASD and associated abnormalities.[23,24] Particularly, when right ventricular volume overload is found, but an ASD diagnosis cannot be made in routine practice, the guidelines give a Class I recommendation to refer such a patient to an adult congenital heart disease center for additional testing.[1]

In cases wherein the symptoms are discrepant with objective clinical data, maximal exercise testing is recommended based on expert opinion.[1] Exercise testing is also recommended to evaluate a change in oxygen saturation in patients who have mild-to-moderate pulmonary arterial hypertension, but not in patients with severe pulmonary arterial hypertension. The guidelines also recommend against diagnostic cardiac catheterization in younger patients with uncomplicated ASDs,[25,26] but do advise consideration of cardiac catheterization to rule out coronary artery disease in patients who are at risk because of age or other risk factors. Given advances in cardiac computed tomography angiography, this noninvasive imaging modality could be reasonable as an alternative to cardiac catheterization.

Intervention

Counseling recommendations for patients with an ASD who have severe pulmonary arterial hypertension and Eisenmenger syndrome are centered on avoiding pregnancy and limiting activity. The guidelines advise that such women should be counseled to avoid pregnancy due to excess maternal and fetal mortality.[13,27] Regarding activity, it is advised that patients with pulmonary arterial hypertension only participate in low-intensity activity, and that those with severe pulmonary arterial hypertension with right to left shunting avoid active physical effort entirely.[1]

Medical therapy for patients with ASD is focused on management of atrial fibrillation.[1] The guidelines advise appropriate anticoagulation followed by an attempt at restoration of sinus rhythm. If sinus rhythm cannot be maintained, then the recommendation is for rate control and anticoagulation. Patients who are being conservatively managed should initially undergo repeat clinical and echocardiographic assessment every 2–3 years.

The primary indication for ASD closure is right heart volume overload, as evidenced by right atrial or ventricular enlargement.[1] Whether or not symptoms are present, guidelines recommend intervention, as impact on the right heart indicates a clinically significant shunt. In patients who suffer a paradoxical embolism, ASD closure is relatively less controversial than PFO closure and is considered reasonable, based on expert opinion. In the rare patient with orthodeoxia–platypnea, ASD closure is a reasonable approach. According to the guidelines, ASD closure may also be considered if there is documentation of net left to right shunting, a pulmonary artery pressure or pulmonary vascular resistance <2/3 systemic levels, or response to pulmonary vasodilator therapy or test ASD occlusion. Such patients should be managed in conjunction with a pulmonary hypertension specialist. A patient with severe, fixed pulmonary arterial hypertension and no left to right shunting should not undergo ASD closure.

The guidelines[1] do not provide specific guidance on a threshold for the Qp/Qs that should serve as an indication for intervention in a patient with a high-volume shunt without evidence of right heart enlargement. Unfortunately, there is no strong evidence to inform this issue. Nevertheless, the clinical

question commonly arises whether a patient with a Qp/Qs >1.5 or >2 should undergo ASD repair based on this indication alone. A standard clinical practice has been to repair ASDs with a Qp/Qs >2, while some experts have advocated for a lower threshold of 1.7[28] or 1.5.[8] Therefore, local expertise and standards of care, combined with clinical judgment, are necessary to apply the Qp/Qs in decision making about ASD repair. Recently, a group showed that plasma endothelin-1 levels were associated with right heart enlargement and were reduced following percutaneous ASD closure.[29] It was suggested that endothelin-1 might be useful as a diagnostic test when evaluating patients for ASD closure; however, further studies are needed to delineate its clinical role.

Available approaches to secundum ASD closure include percutaneous device closure and surgical closure. A percutaneous approach is preferred (Fig. 4) when the anatomy of the defect is suitable as it avoids the need for cardiopulmonary bypass, cardioplegia, thoracotomy, sternotomy and related bleeding, or central nervous system complications, while carrying a cosmetic advantage. Recently, Hoashi et al reported their 7-year (2007–2012) experience at a single center in Japan with percutaneous transcatheter device closure.[30] Regarding patient selection, key inclusion criteria were an ASD diameter of <34 mm, sufficient ASD rim with >5 mm margins of the defect from the mitral and tricuspid valves, inferior vena cava, right upper pulmonary vein, and coronary sinus, and body weight >8 kg. Eligible patients did not have multiple defects that could not be adequately covered by the closure device, did not have a pulmonary vascular resistance greater than 7 woods units, and were without associated congenital cardiac anomalies requiring cardiac surgery such as a partial anomalous pulmonary venous connection, unroofed coronary sinus, or cor triatriatum.

Hoashi et al overall had excellent success performing percutaneous transcatheter ASD closure in 237 men and 472 women with a mean age of 28 years (SD 20, full range 5–80) and mean ASD diameter of 15 mm (SD 5, full range 2–31). The procedure was generally safe with few complications after percutaneous transcatheter ASD closure. There were no cases complicated by atrioventricular block, infective endocarditis, or residual leaks, and no deaths occurred. However, the procedure was complicated by a case of embolization into the left atrium soon after device closure requiring emergent surgical retrieval. Another patient had late device erosion with development of fistula between the left atrium and aorta, and required surgical removal of the device and patch closure at 3 months after the percutaneous procedure.

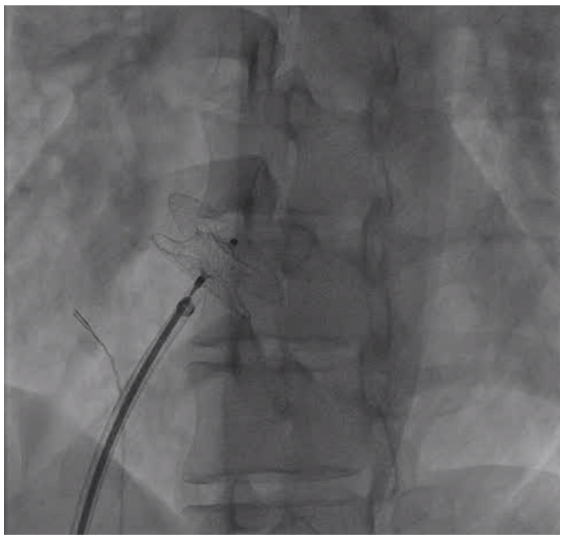

Figure 4. Fluoroscopic image of percutaneous atrial septal defect closure.

A smaller trial involving 137 patients at 13 centers in the United States, performed from 2003 to 2006, further supports the safety and efficacy of percutaneous transcatheter closure of secundum ASD.[31] The trial used closure devices with a hydrophilic coating to improve echocardiographic visualization and reported an overall success rate of 97%. Follow-up was obtained through 12 months in 122 participants and 5 years in 83 participants, with a wire frame fracture in 12% and possible leak in 27%, but none of the fractures or leaks appeared to be clinically significant. No device erosions or catastrophic complications were observed.

Surgical closure is reasonable when the anatomy of the defect is not amenable to a percutaneous approach or when concomitant tricuspid valve repair or replacement is planned. For those who have an ostium primum, sinus venosus ASD, or coronary sinus defect, surgery is the recommended technique. Minimally invasive surgical approaches to ASD closure are promising alternatives to standard median sternotomy.[32–34] In planning the surgical approach, it is crucial to identify anomalous pulmonary veins and other associated congenital abnormalities.

Postintervention, early echocardiographic follow-up is generally performed at 24 hours and 4 weeks. An early priority is monitoring for post-pericardiotomy syndrome. Suggestive symptoms including chest or abdominal pain, vomiting, fever, or fatigue, should prompt immediate evaluation with an echocardiogram. Following implantation of the septal occluder device, aspirin 81–325 mg daily is a standard therapy for at least 6 months, while clopidogrel 75 mg daily for 1 month may also be used at the discretion of the operator.[33,35] Oral anticoagulation, with warfarin for instance, is typically reserved for those with other indications for such therapy. Additionally, guidelines state that endocarditis prophylaxis is indicated for 6 months following device closure.[36]

At 6 months, 1 year, and periodically thereafter, routine follow-up for evidence of device erosion or other complications is advised. New chest pain or syncope should prompt urgent evaluation for device erosion. In addition, annual follow-up should occur for ASD patients who have undergone closure and also have pulmonary arterial hypertension, atrial arrhythmias, right or left ventricular dysfunction, coexisting valvular lesions, or other cardiac lesions.

Summary

In summary, ASDs are a common congenital abnormality that most commonly occur as an ostium secundum defect. Left to right shunting generally leads to right ventricular overload and symptoms in adulthood. Echocardiography is central to diagnosis and also informs the interventional approach. Percutaneous or surgical ASD closure may be indicated in the presence of right heart volume overload, paradoxical embolism, orthodeoxia–platypnea, or an elevated pulmonary/systemic flow ratio.

Author Contributions

Wrote the first draft of the manuscript: SSM. Contributed to the writing of the manuscript: SSM, MM, EPS. Agree with manuscript results and conclusions: SSM, MM, EPS. Jointly developed the structure and arguments for the paper: SSM, MM, EPS. Made critical revisions and approved final version: SSM, MM, EPS. All authors reviewed and approved the final manuscript.

REFERENCES

1. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52:e143–263.
2. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation*. 2006;114:1645–53.
3. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–72.
4. Perrot A, Schmitt KR, Roth EM, et al. CCN1 mutation is associated with atrial septal defect. *Pediatr Cardiol*. 2014. PMID: 25135600.
5. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation*. 1968;37:805–15.
6. Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, Lakatta EG. Left ventricular diastolic filling performance in older male athletes. *JAMA*. 1995;273:1371–5.
7. Swinne CJ, Shapiro EP, Lima SD, Fleg JL. Age-associated changes in left ventricular diastolic performance during isometric exercise in normal subjects. *Am J Cardiol*. 1992;69:823–6.
8. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med*. 1999;340:839–46.
9. Loscalzo J. Paradoxical embolism: clinical presentation, diagnostic strategies, and therapeutic options. *Am Heart J*. 1986;112:141–5.
10. Ward R, Jones D, Haponik EF. Paradoxical embolism. An underrecognized problem. *Chest*. 1995;108:549–58.
11. Khositseth A, Cabalka AK, Sweeney JP, et al. Transcatheter Amplatzer device closure of atrial septal defect and patent foramen ovale in patients with presumed paradoxical embolism. *Mayo Clin Proc*. 2004;79:35–41.
12. Gabriels C, De Meester P, Pasquet A, et al. A different view on predictors of pulmonary hypertension in secundum atrial septal defect. *Int J Cardiol*. 2014;176:833–40.
13. Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J*. 1998;19:1845–55.
14. Bejiqi R, Retkoceri R, Bejiqi H, Zeka N, Maloku A, Berisha M. Klippel-Feil syndrome associated with atrial septal defect. *Med Arch*. 2013;67:141–2.
15. Bizarro RO, Callahan JA, Feldt RH, Kurland LT, Gordon H, Brandenburg RO. Familial atrial septal defect with prolonged atrioventricular conduction. A syndrome showing the autosomal dominant pattern of inheritance. *Circulation*. 1970;41:677–83.
16. Baumgartner H, Bonhoeffer P, De Groot NM, et al. Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31:2915–57.
17. Silversides CK, Dore A, Poirier N, et al. Canadian cardiovascular society 2009 consensus conference on the management of adults with congenital heart disease: shunt lesions. *Can J Cardiol*. 2010;26:e70–9.
18. Shub C, Dimopoulos IN, Seward JB, et al. Sensitivity of two-dimensional echocardiography in the direct visualization of atrial septal defect utilizing the subcostal approach: experience with 154 patients. *J Am Coll Cardiol*. 1983;2:127–35.
19. Vick GW 3rd, Murphy DJ Jr, Ludomirsky A, et al. Pulmonary venous and systemic ventricular inflow obstruction in patients with congenital heart disease: detection by combined two-dimensional and Doppler echocardiography. *J Am Coll Cardiol*. 1987;9:580–7.
20. Roberson DA, Cui W, Patel D, et al. Three-dimensional transesophageal echocardiography of atrial septal defect: a qualitative and quantitative anatomic study. *J Am Soc Echocardiogr*. 2011;24:600–10.
21. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.
22. Dittmann H, Jacksch R, Voelker W, Karsch KR, Seipel L. Accuracy of Doppler echocardiography in quantification of left to right shunts in adult patients with atrial septal defect. *J Am Coll Cardiol*. 1988;11:338–42.
23. Taylor AM, Stables RH, Poole-Wilson PA, Pennell DJ. Definitive clinical assessment of atrial septal defect by magnetic resonance imaging. *J Cardiovasc Magn Reson*. 1999;1:43–7.
24. Boxt LM. Magnetic resonance and computed tomographic evaluation of congenital heart disease. *J Magn Reson Imaging*. 2004;19:827–47.
25. Freed MD, Nadas AS, Norwood WI, Castaneda AR. Is routine preoperative cardiac catheterization necessary before repair of secundum and sinus venosus atrial septal defects? *J Am Coll Cardiol*. 1984;4:333–6.
26. Shub C, Tajik AJ, Seward JB, Hagler DJ, Danielson GK. Surgical repair of uncomplicated atrial septal defect without "routine" preoperative cardiac catheterization. *J Am Coll Cardiol*. 1985;6:49–54.
27. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *J Am Coll Cardiol*. 1998;31:1650–7.
28. Attie F, Rosas M, Granados N, Zabal C, Buendía A, Calderón J. Surgical treatment for secundum atrial septal defects in patients >40 years old. A randomized clinical trial. *J Am Coll Cardiol*. 2001;38:2035–42.
29. Komar M, Podolec J, Plazak W, et al. Elevated level of plasma endothelin-1 in patients with atrial septal defect. *Cardiovasc Ultrasound*. 2014;12:31.
30. Hoashi T, Yazaki S, Kagisaki K, et al. Management of ostium secundum atrial septal defect in the era of percutaneous trans-catheter device closure: 7-year experience at a single institution. *J Cardiol*. 2014. PMID: 25113951.
31. Javois AJ, Rome JJ, Jones TK, et al. Results of the U.S. food and drug administration continued access clinical trial of the GORE HELEX septal occluder for secundum atrial septal defect. *JACC Cardiovas Interv*. 2014;7:905–12.
32. Nezafati MH, Nezafati P, Soltani G, Jahanbakhsh S, Hoseinikhah H. Long-term assay of off-pump atrial septal defect closure using vena caval inflow occlusion and minimally invasive approaches in 130 cases dagger. *Eur J Cardiothorac Surg*. 2014. PMID: 25326016.
33. Baharestani B, Rezaei S, Jalili Shahdashti F, Omrani G, Heidarali M. Experiences in surgical closure of atrial septal defect with anterior mini-thoracotomy approach. *J Cardiovasc Thorac Res*. 2014;6:181–4.
34. Luo H, Wang J, Qiao C, Zhang X, Zhang W, Song L. Evaluation of different minimally invasive techniques in the surgical treatment of atrial septal defect. *J Thorac Cardiovasc Surg*. 2014;148:188–93.
35. Ford MA, Reeder GS, Lennon RJ, et al. Percutaneous device closure of patent foramen ovale in patients with presumed cryptogenic stroke or transient ischemic attack: the Mayo clinic experience. *JACC Cardiovasc Interv*. 2009;2:404–11.
36. Wilson W, Taubert KA, Gewitz M, et al. American Dental Association. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–54.