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STATE OF THE ART REVIEW
Congenital heart disease

Atrial septal defect in adulthood: a new paradigm for congenital heart disease

Margarita Brida [1,2,3]*, Massimo Chessa [4,5], David Celermajer[6], Wei Li [1], Tal Geva[7,8], Paul Khairy [9], Massimo Griselli[10], Helmut Baumgartner [11], and Michael A. Gatzoulis[1]

[1]Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton & Harefield Hospitals, National Heart and Lung Institute, Imperial College, Sydney Street, London SW3 6NP, UK; [2]Division of Adult Congenital Heart Disease, Department of Cardiovascular Medicine, University Hospital Centre Zagreb, Kispaticeva ul. 12, Zagreb 10000, Croatia; [3]Department of Medical Rehabilitation, Medical Faculty, University of Rijeka, Ul. Braće Branchetta 20/1, Rijeka 51000, Croatia; [4]ACHD Unit - Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato, Piazza Edmondo Malan, 2, Milan 20097, Italy; [5]UniSR - Vita Salute San Raffaele University, Via Olgettina, 58, Milan 20132, Italy; [6]Heart Research Institute, University of Sydney, Camperdown, NSW 2050, Australia; [7]Department of Cardiology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA; [8]Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA; [9]Department of Medicine, Montreal Heart Institute, Université de Montréal, 5000 Rue Bélanger, Montréal, QC H1T 1C8, Canada; [10]Division of Pediatric Cardiovascular Surgery, Masonic Children's Hospital, University of Minnesota, 2450 Riverside Ave, Minneapolis, MN 55454, USA; and [11]Department of Cardiology III: Adult Congenital and Valvular Heart Disease, University Hospital Muenster, Albert-Schweitzer-Campus 1, Muenster 48149, Germany

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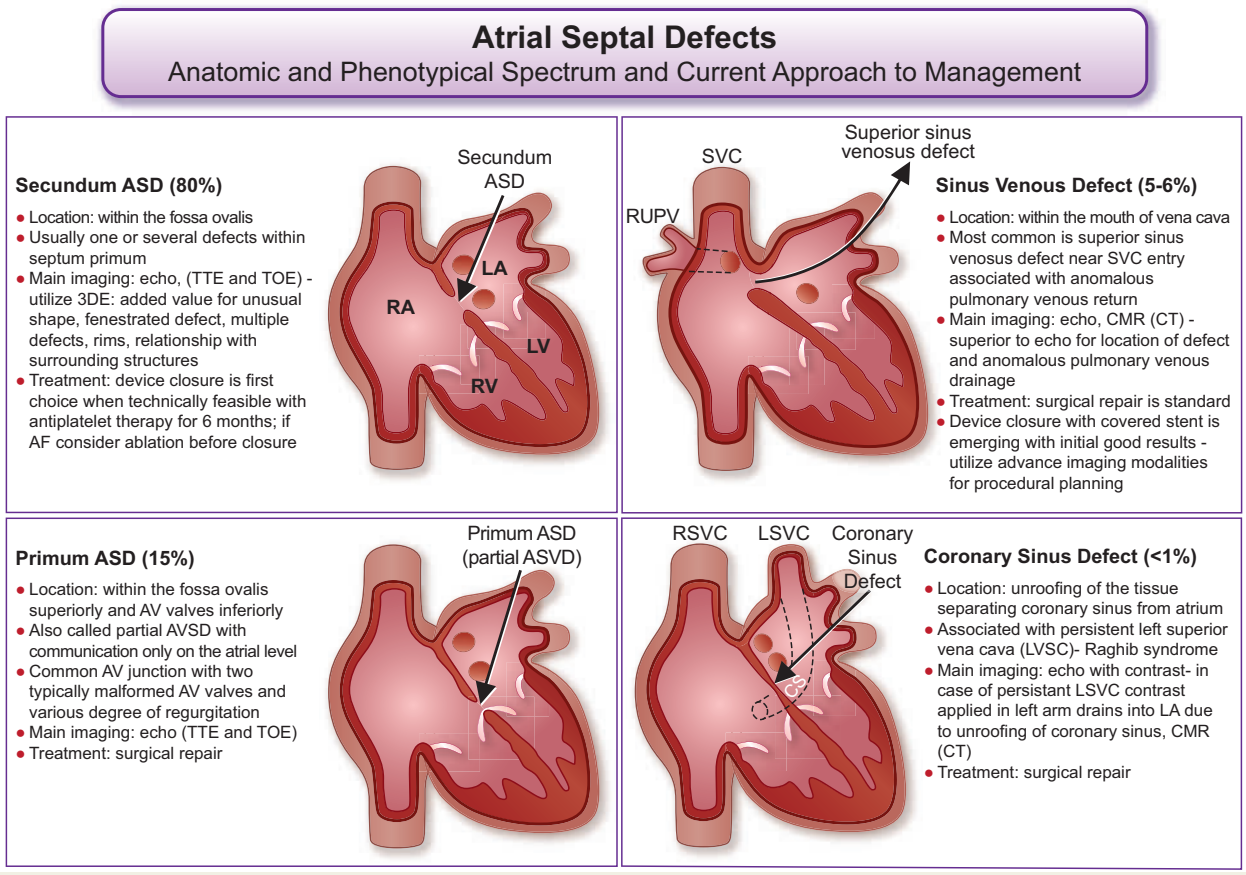
Atrial septal defects (ASDs) represent the most common congenital heart defect diagnosed in adulthood. Although considered a simple defect, challenges in optimal diagnostic and treatment options still exist due to great heterogeneity in terms of anatomy and time-related complications primarily arrhythmias, thromboembolism, right heart failure and, in a subset of patients, pulmonary arterial hypertension (PAH). Atrial septal defects call for tertiary expertise where all options may be considered, namely catheter vs. surgical closure, consideration of pre-closure ablation for patients with atrial tachycardia and suitability for closure or/and targeted therapy for patients with PAH. This review serves to update the clinician on the latest evidence, the nuances of optimal diagnostics, treatment options, and long-term follow-up care for patients with an ASD.

* Corresponding author. Tel: +385983527110, Email: margarita.brida@icloud.com

Graphical Abstract



Spectrum of atrial septal defectsASD, atrial septal defect; AF, atrial fibrillation; AVSD, atrioventricular septal defect; CMR, cardiac magnetic resonance; CT, computed tomography; LSVC, left superior vena cava; RSVC, right superior vena cava; RUPV, right upper pulmonary vein; SVC, superior vena cava; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; 3DE, three-dimensional echocardiography.

Keywords Atrial septal defect • Sinus venosus defect • Device closure • Atrial septal defect surgery • Advanced imaging • Pulmonary arterial hypertension

Introduction

Atrial septal defect (ASD) represents a direct communication between atrial chambers, allowing shunting of blood between the systemic and pulmonary circulation. A unique feature of ASD is its slow clinical progression with most children and young adults being free of symptoms, contributing to late diagnosis; hence, ASD represents the most common congenital heart disease (CHD) diagnosed in adulthood, accounting for 25–30% of new diagnoses.[1]

Traditionally, it is considered a right heart lesion, owing to the time-related complications namely arrhythmias, right heart failure, thromboembolism, and in a subset of patients, pulmonary arterial hypertension (PAH). At the same time, the pathophysiology of atrial-level shunts also impacts the left heart due to volume unloading and adverse ventricular–ventricular interaction. In most patients, ASD closure leads to reverse right ventricular remodelling inversely related to the patient age, improved functional class, improved cardiac output, and exercise capacity, irrespective of age.[2]

Although considered a more simple defect within the spectrum of CHD, challenges in optimal diagnostic and treatment options still exist, especially in patients presenting with signs of PAH and right or left ventricular dysfunction, requiring tertiary expertise and in some patients, targeted PAH pharmacological therapies. Management of ASD has considerably advanced in recent years with improved diagnostic modalities and procedural planning, timely closure following early diagnosis, mode of intervention, and clinical outcomes/overall prognosis.

In this paper, we discuss the state-of-the-art contemporary diagnostic work-up with multimodality advanced imaging, optimal treatment options (surgical, interventional, pharmacological) with

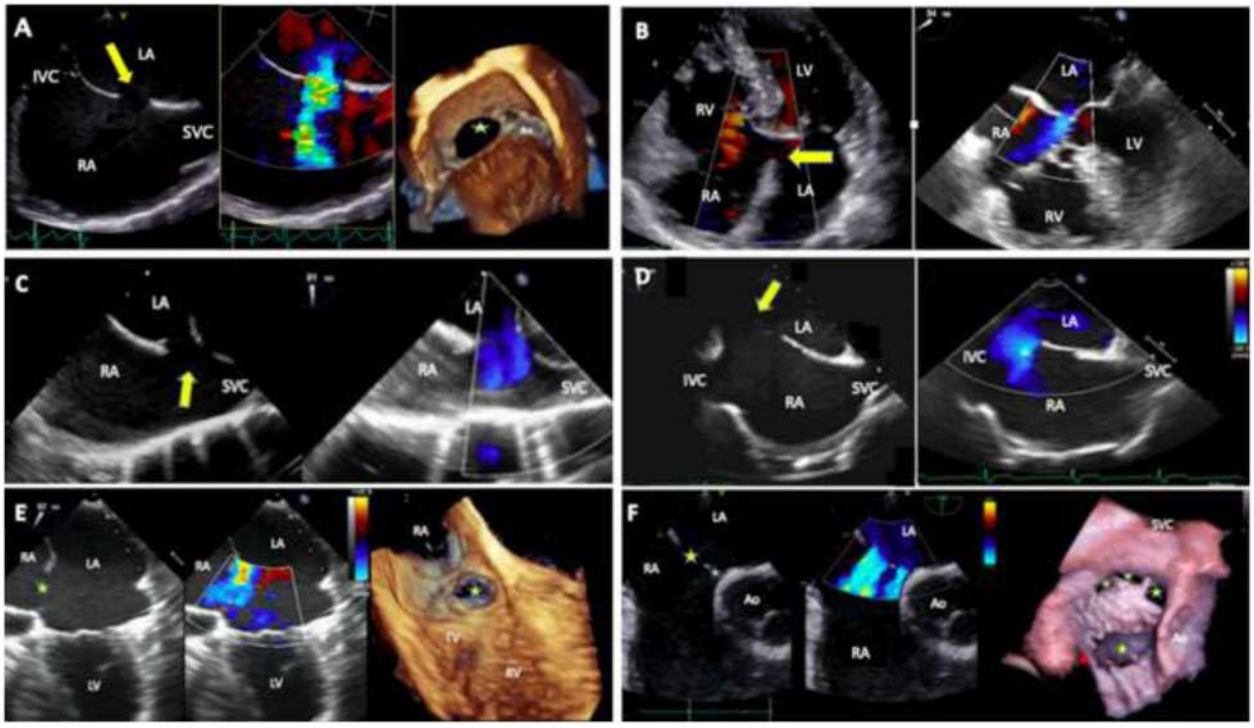


Figure 1 Types of atrial septal defects, echocardiographic presentation. (*A*) Transoesophageal echocardiography two-dimensional and three-dimensional echocardiography imaging looking on to the intra-atrial septum from left atrium, demonstrating secundum atrial septal defect (marked by *). (*B*) Transthoracic echocardiography and transoesophageal echocardiography four-chamber view colour Doppler images demonstrating primum atrial septal defect (arrow). Note common atrioventricular junction with two valve orifices. (*C*) Transoesophageal echocardiography from mid-oesophageal bicaval view demonstrating superior sinus venosus defect (arrow). (*D*) Transoesophageal echocardiography from mid-oesophageal bicaval view demonstrating inferior sinus venosus defect (arrow). (*E*) Transoesophageal echocardiography from mid-oesophageal modified left ventricle inflow two-chamber view demonstrating unroofed coronary sinus defect (marked by *) with an added value of three-dimensional echocardiography imaging looking on to the septum from right heart, the defect is shown located posteriorly at the entrance of coronary sinus, just above the tricuspid valve. (*F*) Transoesophageal echocardiography mid-oesophageal short axis aortic valve view demonstrating intra-atrial septum with two separate defects (marked by *) and added value of three-dimensional echocardiography imaging of the same patient with 'en face' view looking onto the inter-atrial septum from right atrium. Fenestrated multiple defects (marked by *) and their relation to surrounding structure are presented. Ao, aortic valve; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve.

reference to the most recent techniques, the role of cardiac catheterization for patients with PAH, and the need for long-term follow-up care.

Cause, anatomy, and pathophysiology

Cause

While most ASDs are sporadic with no identifiable cause, they can also be encountered in genetic syndromes such as Down, Holt-Oram, Ellis van Creveld, and Noonan syndrome with an approximate prevalence of 80%, 65%, 60%, and 20%, respectively.[3] Several genes have been associated with ASDs including mutations in the cardiac transcription factor gene NKX2-5, GATA4, TBX5, and others.[4] Moreover, some substances and conditions have also been associated with increased risk of having an offspring with ASD including maternal alcohol consumption, smoking, use of antidepressant drugs, and diabetes.[3,5–8]

Anatomy

Atrial septal defects are classified into secundum, primum, sinus venosus, and coronary sinus defects (*Figure 1*). Secundum ASD, the most common type of all ASDs (80%), is located within the fossa ovalis due to one or several defects within the septum primum.[3,9] Small secundum ASD needs to be distinguished from patent foramen ovale as the latter is not a true deficiency of atrial septal tissue, but rather a tunnel-like communication between the septum primum and septum secundum located in the anterosuperior portion of the atrial septum. Most secundum defects are not confluent with veins, coronary sinus, or the atrioventricular valves.

Ostium primum ASD, also called partial atrioventricular septal defect (accounting for 15% of all ASDs), is located between the inferior margin of the fossa ovalis superiorly, and the atrioventricular valves inferiorly, without a ventricular component to the defect. It is

characterized by a common atrioventricular junction with two distinct valve orifices; the atrioventricular valves in this defect are almost always abnormal.

Sinus venosus defects are typically found within the mouth of one of the venae cavae. Most common is the superior sinus venosus defect (5%) resulting from deficiency of the tissue that separates the right upper pulmonary vein from the superior vena cava; pulmonary veins from part of the right lung often connect anomalously to the superior vena cava. Inferior sinus venosus defect, on the other hand, is a rare defect (<1%) found in the mouth of the inferior vena cava involving the posterior–inferior aspect of the atrium.

The rarest type is the coronary sinus defect resulting from partial or complete unroofing of the tissue separating coronary sinus from the left atrium, allowing a shunt through the defect and the coronary sinus orifice. There is a common association of a coronary sinus defect with persistent left superior vena cava, termed Raghib syndrome,[10] an important aspect contributing to its diagnosis.

Pathophysiology

Atrial septal defect typically results in a left-to-right shunt with the direction and magnitude of blood flow determined by the size of the defect, relative atrial pressures related to the compliance of the both ventricles, and changes over time. Most small defects (<10 mm) are associated with a small shunt and minimum or no enlargement of the right heart structures. Larger, long-standing shunts result in right atrial and right ventricular dilatation, myocardial cellular stretch, and injury/impairment with time; increased pulmonary blood flow may trigger a pathological mechanism due to shear stress causing pulmonary endothelial cell activation and activation of growth factors, vasoconstrictors, and smooth muscle hypertrophy, thus contributing to the development of PAH. Rise in pulmonary artery pressure (PAP) with age is common, while the development of pulmonary vascular disease is relatively rare.[2,11]

Historic and current perspective

Natural history

The precise natural history of all native ASDs is difficult to ascertain, as studies that predate ASD closure in the era prior to successful open-heart surgery did not include cardiac ultrasound, the most common method to detect the full spectrum of defects. Nevertheless, there is clear evidence from historic reports that untreated significant defects are associated with a reduced lifespan. Mortality rates were low for the first two decades of life (<1%) but rose progressively thereafter, with three quarters of patients dying by age of 50. The outcome was worse for ostium primum ASDs, with high death rates, particularly over the age of 30 years.[12,13]

Introduction of atrial septal defect closure

With the introduction of surgical closure, initially without direct defect visualization (Murry in 1948), subsequently under direct vision using hypothermia (Lewis in 1952), and contemporary, with cardiopulmonary bypass, there has been accumulating evidence on safety, efficacy, and benefits of closure. Management evolved further with the introduction of catheter device closure of a secundum defect by King in 1974.[14] With constant improvement in device technology and deployment methods and the obvious advantage over surgery, avoidance of sternotomy with shorter hospital stay and quicker recovery, device closure has become the method of choice, when feasible. Generally, adult patients without closure fared significantly worse in functional capacity, arrhythmia, heart failure, and overall survival.[15–17]

Current prospects

Defect closure during early adulthood, optimally before age 25 years, is associated with excellent long-term prospects and normal survival.[18] Morbidity increases with advancing age at closure. However, symptomatic benefits and improved quality of life are observed in all age groups.[2,19,20] Survival in contemporary cohort also improved across age groups, including the elderly after closure (surgical or catheter) resembling the general population in mid to longer term follow-up.[21–23] Such superior outcomes may reflect not only improved and earlier diagnostics with defect closure at the time of diagnosis, before overt symptoms ensue, but also avoidance of closure in patients with important co-morbidities (pre-capillary pulmonary hypertension (PH) or post-capillary PH associated with left heart disease), better myocardial protection during surgical closure, or avoidance of sternotomy and cardiopulmonary bypass altogether with catheter closure, and finally arrhythmia management (pre- and post-closure) and thromboprophylaxis.[21]

Diagnostic work-up

Most young adults with ASD present with a heart murmur, or an abnormal electrocardiogram (ECG) or chest radiograph. Later on in adulthood, patients develop breathlessness and/or palpitations; clinical examination reveals a right ventricular lift with fixed splitting of the second heart sound and a flow murmur in the pulmonary area. ECG shows incomplete right bundle branch block, a tall P-wave indicative of right atrial enlargement, and a superior axis in patients with ostium primum ASD. Right heart enlargement and plethora are evident on chest radiography. With advancing age, exercise capacity and peak oxygen consumption decrease, whereas atrial tachyarrhythmias increase.

Echocardiography

Transthoracic echocardiography (TTE) using two-dimensional (2D) and colour Doppler imaging remains the first line imaging modality in assessing patients with ASD.[9,24] It provides essential information regarding defect size, location, shunt direction, right heart dilatation, and reversed inter-ventricular septal motion during diastole suggestive of haemodynamic significance. Spectral Doppler allows for estimating systolic PAP from peak tricuspid regurgitation velocity or mean and end-diastolic pressure from early and end-diastolic pulmonary regurgitation velocities, respectively. Quantification of left-to-right shunting is calculated using time-velocity integral of pulmonary and aortic flow and their relevant cross-sectional flow areas. There are, however, discrepancies between echocardiographic and cardiac catheterization shunt calculations. Therefore, right ventricular enlargement with normal or hyperdynamic function is accepted as a sign of a significant ASD that merits closure.[25] Contrast echocardiography using mixed saline and blood can be useful in identifying

intracardiac shunts in patients with restricted acoustic windows. Furthermore, contrast echocardiography in patient with coronary sinus defect and persistent left superior vena cava entering the left atrium shows contrast first appearing in the left atrium after been injected via a peripheral vein in the left arm, thus establishing the diagnosis.

Transoesophageal echocardiography (TOE) represents a complementary imaging method, almost uniformly performed following TTE. Transoesophageal echocardiography is especially helpful in patients with suboptimal transthoracic window and/or sinus venosus defect associated with anomalous pulmonary venous drainage[9] (*Figure 1*). It allows clear imaging of the fossa ovale, sinus venosus septum, drainage of the pulmonary veins, and coronary sinus. Transoesophageal echocardiography also provides essential intraprocedural imaging and guidance in the cardiac catheter laboratory for catheter closure of secundum ASD and more recently also for assisting stent closure of sinus venosus defects as well as unique imaging in the operating theatre.

Three-dimensional echocardiography (3DE) has become a well-established complementary modality in assessing patients with ASD.[26] Particular advantages of a 3DE approach include right or left 'en face' views with clear defect visualization especially if of unusual shape, fenestrated defect, and/or multiple defects, delineation of the rims of surrounding tissue, and relationship with surrounding structures (*Figure 1*). Live 3DE guidance during defect closure allows imaging of catheter delivery process, especially so if more than one device is being deployed (optimal device positioning and preventing complications). Furthermore, 3DE can provide more accurate measurement of defect size with better correlation against balloon sizing.[27]

More recently, fusion imaging, TOE and fluoroscopy, has emerged as an additional tool for more efficient navigation during catheter interventions.[28] Since TOE and fluoroscopy are displayed in different visual perspectives, the interventional cardiologist must mentally reregister the images from the two modalities. This technology overlies the two imaging modalities on one screen in real time potentially allowing for enhanced team communication and improved visual guidance in challenging cases.[29]

Intracardiac echocardiography (ICE) in some centres has largely replaced TOE as the imaging modality for ASD closure. In contrast to TOE, ICE can be performed by the primary operator of the interventional procedure under conscious sedation without the need for a second operator or general anaesthesia including endotracheal intubation, and it eliminates the risk of oesophageal trauma. Most recently, a 3D-volumetric ICE system was developed, with potential for greater anatomic information.[30]

Magnetic resonance imaging and computed tomography

Advances in cardiac magnetic resonance (CMR) and computed tomography (CT) imaging techniques allow comprehensive imaging of all forms of atrial communications. These imaging techniques usually follow echocardiographic evaluation that leaves unanswered questions about the presence, location, size, or physiology of a pre-tricuspid communication between the systemic and pulmonary circulations.[31,32] Specifically, cine steady-state free precession (SSFP) imaging is the gold standard technique for measurements of ventricular volumes and function, whereas phase velocity flow mapping allows accurate quantification of the pulmonary-to-systemic flow ratio (Qp/Qs).[33] ECG- and respiratory-gated 3D SSFP provides high-resolution isotropic imaging of intracardiac anatomy without administration of a contrast agent. Using 2D or 3D cine or 3D SSFP MR angiography, the different components of the atrial septum and the adjacent systemic and pulmonary veins and the atrioventricular valves are clearly imaged. Two-dimensional or 3D cine phase contrast imaging allows quantification of blood flow inside and outside the heart, thus allowing for visualization of direction and velocity of blood flow and measurements of the Qp/Qs (*Figure 2*). In general, confirmation of the haemodynamic relevance of the defect and pulmonary venous drainage are the most frequent indications for CMR (*Figure 3*). Moreover, CMR is an important diagnostic tool in sinus venosus defects, primarily inferior defects.[34,35] The posterior location of these defects and the associated anomalous pulmonary venous drainage frequently hamper the ability of echocardiography to adequately evaluate these defects especially in adults.

Recent technological advances have allowed high-resolution delineation of intracardiac anatomy, including ASDs, by cardiac CT at acceptable levels of ionizing radiation exposure below 1 mSv. Despite the greatly reduced levels of ionizing radiation afforded by the latest generation of CT scanners, clinicians should note that radiation exposure should be avoided whenever an alternative approach to diagnosis is available.[36]

Advanced imaging modalities of three-dimensional printing, computational modelling and holograms

Advanced imaging modalities are increasingly utilized primarily in the context of evaluating sinus venosus defect closure. There is great heterogeneity of these defects in terms of anatomy; 3D printing technology allows its delineation and most importantly permits therapeutic simulation on the printed model, albeit without portraying post-procedural haemodynamics. To overcome this, computational models were developed to examine haemodynamic conditions and device designs by combining imaging (and processing) with fluid dynamics analyses and individual patient data on anatomy/function, thus improving understanding of cardiac physiology and pathology, facilitating personalized and precision medicine, and enabling the development of novel interventions and treatments.[37] A 3D reconstruction requires data from CMR or cardiac CT; the 3D model built, i.e. of sinus venosus defect and anomalous pulmonary vein/s, may be printed allowing for direct inspection or viewed virtually and analysed with dedicated software. Further advance on quality of the 3D model analysis can be achieved with holographically augmented reality reconstruction, allowing the physician to navigate the model using dedicated tools (Microsoft HoloLens, Redmond, Washington), examining procedural feasibility on the created model, post-device deployment anatomic relationships, and overall result (*Figure 4*). While further assessment of these novel techniques is required, they are increasingly applied in complex defects, assisting better delineation of anatomy and relationships with surrounding structures, optimizing and guiding personalized therapy.[37–39]

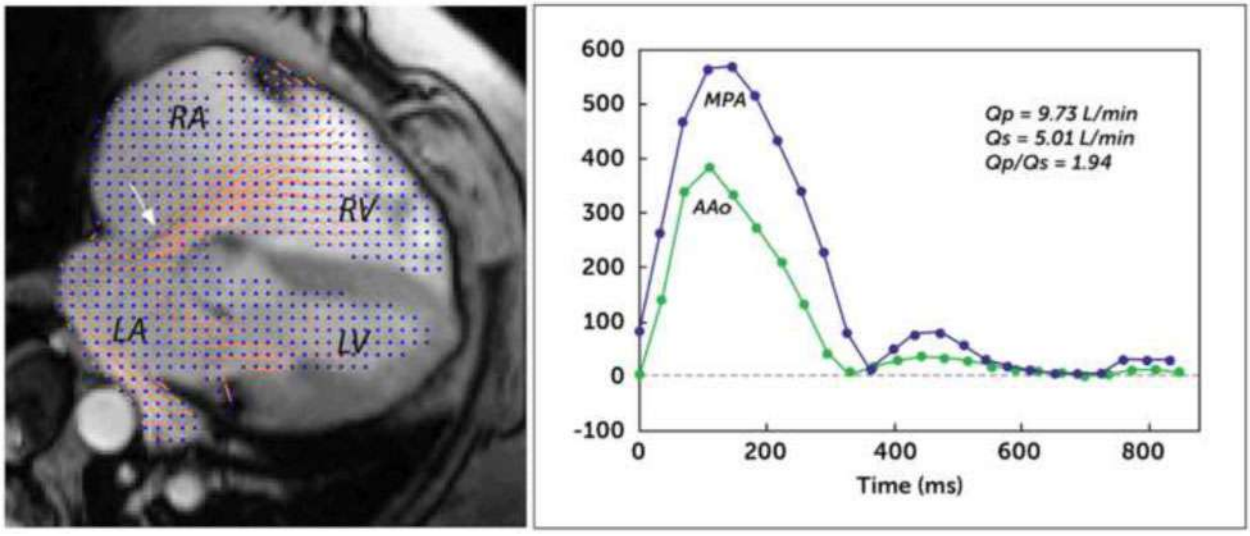


Figure 2 Cardiac magnetic resonance phase contrast four-dimensional flow velocity mapping in a patient with secundum atrial septal defect (arrow) and measurement of the pulmonary-to-systemic flow ratio (Qp/Qs). The pink colour vectors depict the direction of the flow and their lengths correspond to instantaneous velocity. Flow rate (*Y*-axis) vs. time (*X*-axis) curves of flow measurements in the proximal ascending aorta and main pulmonary artery allow measurement of Qp/Qs. AAo, ascending aorta; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

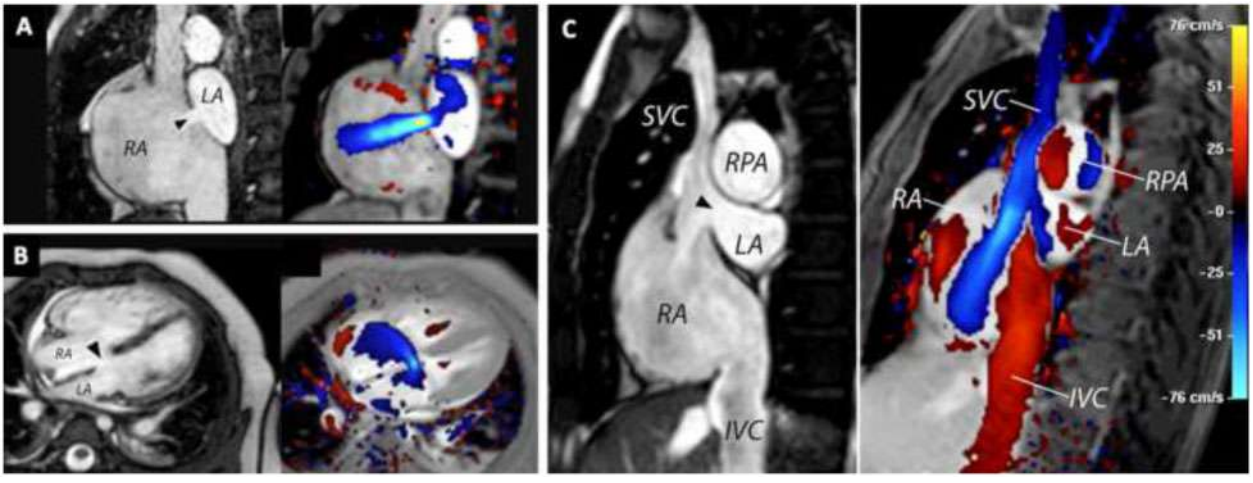


Figure 3 Cardiac magnetic resonance imaging demonstrating exact anatomy and haemodynamic burden of different types of atrial septal defects; note that anatomy is shown on the left side and colour-coded flow on the right side of each figure. (*A*) Cine steady-state free precession (left panel) and colour-coded in-plane cine phase velocity flow mapping (right panel) of left-to-right flow in a patient with secundum atrial septal defect. (*B*) Cine steady-state free precession (left panel) and colour-coded in-plane cine phase velocity flow mapping (right panel) of left-to-right flow in a patient with primum atrial septal defect. (*C*) Cine steady-state free precession (left panel) and colour-coded in-plane cine phase velocity flow mapping (right panel) in a patient with superior sinus venosus defect. Note that the defect is superior to the atrial septum (above the superior vena cava–right atrium junction), between the right upper pulmonary vein and the superior vena cava (arrow). IVC, inferior vena cava; LA, left atrium; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

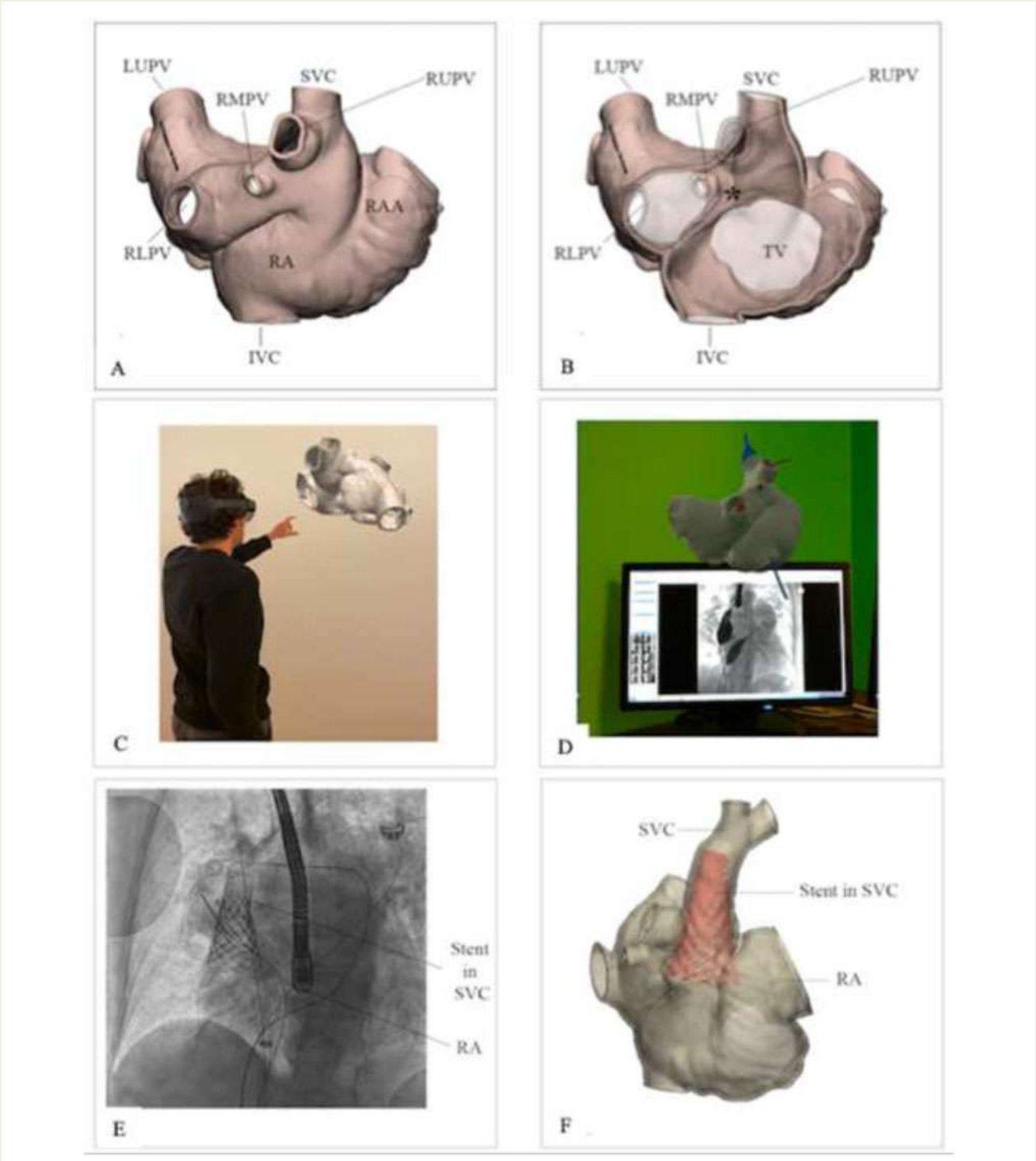


Figure 4 Advanced imaging modalities of three-dimensional printing, computational modelling and holograms in planning of superior sinus venosus catheter closure. (*A and B*) Three-dimensional anatomic model derived from cardiac-computed tomography scan dataset, showing anatomy and relations between pulmonary veins and superior sinus venosus defect (marked by *). Right upper pulmonary vein drains at superior vena cava–right atrium junction. (*C*) Holographic augmented reality prototype model created by the same cardiac computed tomography scan dataset. The holographic model can be navigated using specific Lens (in this specific case, Microsoft HoloLens II). (*D*) Holographic model used for the procedure planning with balloons into the superior vena cava (blue colour balloon) and the right mid-pulmonary vein (red colour balloon). (*E*) Angiographic outcome of the catheterization with the final result of stent implantation. (*F*) Three-dimensional model post-superior vena cava stenting. IVC, inferior vena cava; LA, left atrium; LUPV, left upper pulmonary vein; RA, right atrium; RAA, right atrial appendage; RLPV, right lower pulmonary vein; RMPV, right mid pulmonary vein; RUPV, right upper pulmonary vein; SVC, superior vena cava; TV, tricuspid valve. Courtesy of three-dimensional and Computer Simulation Laboratory of the IRCCS-Policlinico San Donato and ARTINESS srl—Milan.

Cardiac catheterization

Catheter assessment is not routinely required for the diagnosis and management of patients with ASDs as non-invasive imaging provides not only the diagnosis and morphology of the defect but also the haemodynamic consequences with regard to right ventricular volume overload, which are the basis for management decisions.[25] Direct assessment of haemodynamics, however, should be obtained in patients with PH, left heart disease, and for older patients with signs of, or risk factors for, coronary arteries disease such that coronary artery visualization and treatment should precede ASD closure.

Patients with PH must be evaluated with particular care as haemodynamics have a major impact on management decisions. Atrial septal defect closure has been shown to be safe and associated with a decrease in PAP and improvement of symptoms when pulmonary vascular resistance (PVR) <5 WU, albeit extent of improvement and PVR are inversely related.[2,40,41] When PVR ≥5 WU, patients are unlikely to improve and may be worse off after complete defect closure.[40,42,43] Invasive measurement of PVR is therefore mandatory when signs of PH are present (estimated systolic PAP >40 mmHg from the peak tricuspid regurgitation Doppler velocity or other indirect signs of PH if PAP cannot be estimated).[25] Calculation of PVR requires pulmonary blood flow using the Fick principle, the most accurate method for measurements of oxygen consumption. Current guidelines do not recommend vasoreactivity testing (with inhaled nitric oxide) when deciding whether to close an ASD in patients with PAH (PVR ≥3 WU).[25] For patients with PVR ≥5 WU, targeted PAH pharmacological therapy with re-evaluation of haemodynamics at follow-up should be considered. If PVR drops on treatment (<5 WU) and there is a significant left-to-right shunt (Qp/Qs >1.5), fenestrated closure may have merits, although the long-term impact of this approach is unknown. For patients with PVR ≥5 WU despite PAH treatment, ASD closure is contraindicated.[25]

While PH usually develops due to shunt (pre-capillary PAH), patients may also develop PH due to concomitant left heart disease (post-capillary PH). Patients with left ventricular impairment (systolic and/or diastolic) equally require invasive haemodynamic assessment if contemplating ASD closure, as the latter in the setting of increased pulmonary arterial wedge pressure may worsen heart failure. Preconditioning with heart failure medical therapy and pre-device deployment balloon test occlusion with reassessment of haemodynamics helps guide therapy (complete, fenestrated, or no defect closure) considering that an increase in left heart filling pressure due to ASD closure may worsen symptoms and outcome.[44,45]

Treatment

The decision regarding optimal treatment for ASD should be made in a multidisciplinary CHD team environment; the best treatment in the presence of right ventricular overload is timely closure irrespective of age (excluding patients with advanced pulmonary vascular disease and/or left heart impairment).[25]

Catheter closure

Technique and devices for catheter closure of ASDs have markedly evolved and been refined. Device closure is the treatment of choice for most patients with a secundum ASD with excellent results (very low complication rates and shorter hospital stay and recovery compared to surgery).[46] The procedure is mostly performed under both fluoroscopic and TOE guidance. There is a debate on the necessity of balloon sizing for selection of device size; those in favour argue about better defect sizing and obtaining information on compliance of surrounding tissue/rims.[47,48]

Main anatomic features precluding device closure are insufficient surrounding rims, multiple defects or extremely large defect for currently available devices, and possibly excessively bulging atrial septal aneurysm.[49] Sufficient and stable rims are necessary to support device stability and avoid disc interference with atrioventricular valves and venous returns. In up to 5–10% of cases, rims are too small and/or too floppy and flimsy to allow for safe and stable device deployment. An isolated absent aortic rim may be overcome by deploying the device to embrace the atrial septum around the aortic root.[49] Multiple defects may still be suitable for device closure, with attention directed towards avoiding interference with other intracardiac structures and the conduction system while considering rim support and defects sizes.[50,51]

Various occluder-type devices based on non-degradable shape memory alloys have been used in clinical practice. They were designed around two main concepts: self-centring and waist adaptability (*Table 1*). The recent development of new material biodegradable occlusion devices has attracted increasing interest with the potential of providing a temporary scaffold for tissue endothelialization following controllable degradation over time leaving only 'native' tissue behind.[52–55] However, more data are required before these novel techniques become widely utilized.[56]

A new and promising technique of catheter ASD closure pertains to sinus venosus defects.[57] The superior sinus venosus defect associated with partial anomalous pulmonary venous drainage procedure involves balloon test inflation in the anticipated stent landing zone with echocardiographic and pulmonary venographic depiction to confirm feasibility of closure and subsequently unobstructed pulmonary venous drainage, followed by deployment of a covered stent.[58] Recently published data showed no mortality amongst patients who underwent percutaneous superior sinus venosus closure; early stent embolization, haemopericardium, and occlusion of the pulmonary vein are reported as potential complications.[58,59] Inferior sinus venosus defect device closure has also been proposed;[60] in a recently published paper, five patients underwent successful percutaneous closure of their inferior sinus venosus defect employing a PDA occlude device.[61] Advanced imaging modalities, *ex vivo* simulation of stent implantation using printed or virtual 3D models, and 3D holographic augmented reality have helped better plan this procedure.[59,62] Further studies are clearly needed; surgical closure of sinus venous defects still represents the standard treatment.

Surgical closure

Surgical closure is the treatment for sinus venosus, primum, coronary sinus defect, and secundum ASDs not amenable to device closure. Historically, these procedures were performed via a median sternotomy on cardiopulmonary bypass with smaller defects closed by direct suture and larger with patches, most commonly from homologous or heterologous pericardium, Gore-Tex, Dacron, or other artificial materials. Currently, alternative techniques are considered and utilized, with a seeming shift from conventional median

Table 1 The most frequently available atrial septal defect occlusion devices and their characteristics

Device	Company	Type	Advantages	Limits	More
Amplatzer Septal Occluder	Abbott	Double disc-self-centring	• Progenitor of device family • Largest experience • Long-term data • Flexible delivery system	• Nickel release reported • Most of the reported cases of erosion	• Wide range of sizes
Figulla Flex II ASD Occluder	Occlutech	Double disc-self-centring	• Soft and flexible braiding • Conforms better to the defect • Flexible delivery system • No hub on left atrium disc • Smaller hub on right atrium disc	• Larger delivery sheath • Less long-term data	• Fenestrated device available • Titanium oxide coated surface
Cardioforme ASD	GORE	Waist adaptable	• Softer device • Less metal exposed to blood stream • Good septum alignment	• Only five available sizes (closing up to 35 mm defect) • Larger delivery sheath • Lack of long-term data	• Thinner device profile
Cocoon Septal Occluder	Vascular Innovation	Double disc-self-centring	• Supposed nickel release reduction thanks to nano-platinum coated surface	• Stiff device-cable • Larger delivery sheath • Lack of long-term data	
CeraFlex ASD Occluder	LifeTch Innovation	Double disc-self-centring	• Titanium nitride coated surface	• Fewer available sizes • Larger delivery system • Lack long-term data	
Hyperion ASD Occluder	Comed BV	Double disc-self-centring	• Available with hub or without hub, and 'with hole' design	• Larger delivery system • Lack long-term data	

ASD, atrial septal defect.

sternotomy to a partial mini-sternotomy (limited to inferior median sternotomy through a midline incision) and a thoracotomy (right anterolateral or vertical axillary).[63] Endoscopic techniques are also employed with cardiopulmonary bypass established with peripheral cannulation (right jugular vein and right femoral artery and vein). Although a totally endoscopic approach is possible, some surgeons prefer to combine this technique with a small anterior thoracotomy (4–6 cm). Furthermore, robotically assisted ASD closure, a type of minimally invasive procedure with an endoscopic, closed chest approach, has become increasingly popular over the past decade.[64] In comparison with modern minimally invasive approaches, the traditional sternotomy remains the easiest technique with the shortest ischaemic and cardiopulmonary bypass times. Operations performed via limited skin incisions, however, are comparable to those of standard techniques in terms of morbidity and mortality, each having their specific advantages and potential drawbacks, but addressing also cosmetic and psychological concerns.[63,65,66]

Surgical outcomes of ASD closure are excellent with mortality <1% and low morbidity; major post-procedural complications occur in <7%. The most common complications represent postoperative arrhythmia.[18,67] The vast majority of ASD procedures are elective and, depending on the approach and techniques, the postoperative length of stay rarely exceeds 4–5 days. Exceptionally, immediate surgical intervention maybe required in the setting of dislodged or embolized catheter occluder device.

Medical therapy

Advanced PAH therapy should be considered in the presence of PAH with PVR ≥5 WU, namely oral endothelin-receptor antagonist and/or phosphodiesterase type 5 inhibitor with subsequent re-evaluation of haemodynamics as discussed.[68] The evidence of long-term benefits from a treat-and-repair approach in patients with PAH and prevalent systemic to pulmonary shunts is currently lacking.[69] For patients with PVR ≥5 WU despite PAH treatment, ASD closure should be avoided and proactive advanced PAH therapy employed using initial or sequential combination treatment including prostacyclins. Subcutaneous or inhaled forms of administration are preferred over parenteral therapy to avoid the risk of paradoxical embolism and infection due to shunt lesion.[70,71]

Medical treatment for other complications, primarily arrhythmias and heart failure, depends largely on standard measures, not specific to ASD, such as antiarrhythmic drugs, anticoagulation, and diuretics.

Thromboprophylaxis in patients with atrial fibrillation (AF) may be guided by established risk scores for stroke vs. bleeding risks, e.g. CHA2DS2-VASc and HAS-BLED.[72] Direct oral anticoagulants may be considered, although evidence on their use in CHD is limited.[73]

Cardiac remodelling after defect closure

The haemodynamic response, right and left cardiac remodelling, including electrical remodelling is apparent almost immediately after closure albeit this remodelling process appears to continue for at least 1 year.[74,75] The extent of cardiac remodelling, i.e. decrease in right heart volumes with an increase in left ventricle filling, is inversely related to age at the time of closure. Persistent right heart dilation and residual functional tricuspid regurgitation are more prevalent in older patients with late ASD closure and with right ventricular end-systolic volume index (RVESVI) >75 mL/m^2 at the time of closure, and are associated with elevation of brain natriuretic peptide levels and right ventricular dysfunction.[76,77]

Follow-up care

Patients with ASD may require and benefit from adult CHD specialist care throughout adult life, particularly those with late ASD closure and incomplete reverse right ventricular remodelling and patients with primum ASDs prone to left atrioventricular valve problems.

Patients with a small defect without initial RV volume overload require close surveillance to observe RV size and shunt volumes for potential time-related changes. To ensure optimal life-long care, 'transition' from paediatric to adult CHD services is required; lapse of care may be associated with increased late morbidity and mortality.[78]

Short- and long-term morbidities

Specific post-closure complications

Catheter closure is safe and effective with rare adverse events that may include device-related arrhythmia, device embolization, pericardial effusion, cardiac tissue erosion, and thrombus formation.[79,80] Post-surgical closure complications may include pericardial effusion, rarely tamponade; primum ASDs with their specific atrioventricular valve morphology is associated with valve regurgitation and/or stenosis, progressive heart block, and/or late development of left ventricular outflow tract obstruction.[81] Obstruction to the systemic or pulmonary veins may occasionally happen after repair of sinus venosus defects, whether surgical or catheter.

Arrhythmias

Atrial flutter and AF are relatively common in ASDs; their prevalence increases steeply with age with up to 20% experiencing atrial flutter and more than 50% AF over the age of 60.[82–84] The extent of atrial structural remodelling is highly dependent on the duration of volume overload secondary to left-to-right atrial shunting.[85] Electrophysiological alterations have been described in both atria, albeit more pronounced in the right atrium, and include reduced voltages, prolonged atrial refractory periods, and spatial heterogeneity of conduction. Recent studies suggest that marked conduction disturbances in Bachmann's bundle may contribute to the substrate for AF in patients with ASDs.[86]

The impact of ASD closure on AF remains controversial. In the absence of randomized trials, no definitive evidence links ASD closure, whether percutaneous or surgical, to improved arrhythmia-free survival. A meta-analysis of 25 studies concluded that percutaneous ASD closure was not associated with a reduction in atrial arrhythmias.[87] Some studies suggest that closure at a younger age (e.g. <40 years) affords some protection against AF,[87–89] while others report neutral effects and even proarrhythmic consequences.[2,90] Atrial septal defect closure may trigger early transient arrhythmias. Persistent AF is less likely to be affected, while paroxysmal arrhythmias may potentially improve with a likelihood that decreases with age. In summary, there is no compelling rationale for AF to be considered an indication for ASD closure, an outcome substantially altered by closure, or a reason to select one approach to closure over the other.

However, for adults with AF and a newly diagnosed ASD that meets criteria for closure, catheter ablation should be performed prior to percutaneous closure whenever possible (*Figure 5*). Freedom from post-closure AF is superior in those with catheter ablation prior to ASD closure compared to those without (79% vs. 37%).[91] Moreover, closing the ASD first increases the complexity of trans-septal access, although trans-septal puncture across an adjacent portion of the native septum often remains feasible in patients with closed ASDs. For exceptional cases with exceedingly large closure devices, direct puncture through the prosthesis has been described.[92] Magnetic navigation can also be considered as an alternative approach. On the whole, the success of trans-septal access is 90–98%, with 75% of patients remaining arrhythmia-free post-AF ablation at 1 year.[92,93] Additional studies are required to determine whether prophylactic catheter ablation should be considered prior to ASD closure in adults without documented AF, and whether targeting non-pulmonary vein triggers such as Bachmann's bundle could further improve arrhythmia-free survival.

Sinus node dysfunction is more prevalent in patients with superior sinus venosus defects and atrioventricular block occurs more frequently in patients with primum defects (irrespective of surgery) in the setting of inferiorly displaced atrioventricular conduction systems.[94]

Heart failure

There are many factors that influence the development of heart failure in the setting of ASD. In general, the degree of right heart volume overload depends on the size of the defect and the relative compliance of the left vs. the right ventricle. Thus, as the left ventricle stiffens with age (especially in the presence of hypertension or ischaemic heart disease), the degree of left to right shunting and right heart volume overload increase. Atrial tachyarrhythmias may accelerate chronic heart failure and lead to decompensation, particularly in older patients. Furthermore, the development of PH, particularly with a volume-loaded right ventricle, is likely to exaggerate right ventricular dysfunction.[17] Last but not least, left atrioventricular valve regurgitation after repair of primum septal defect can be an important cofounder that should be considered for re-operation.[81]

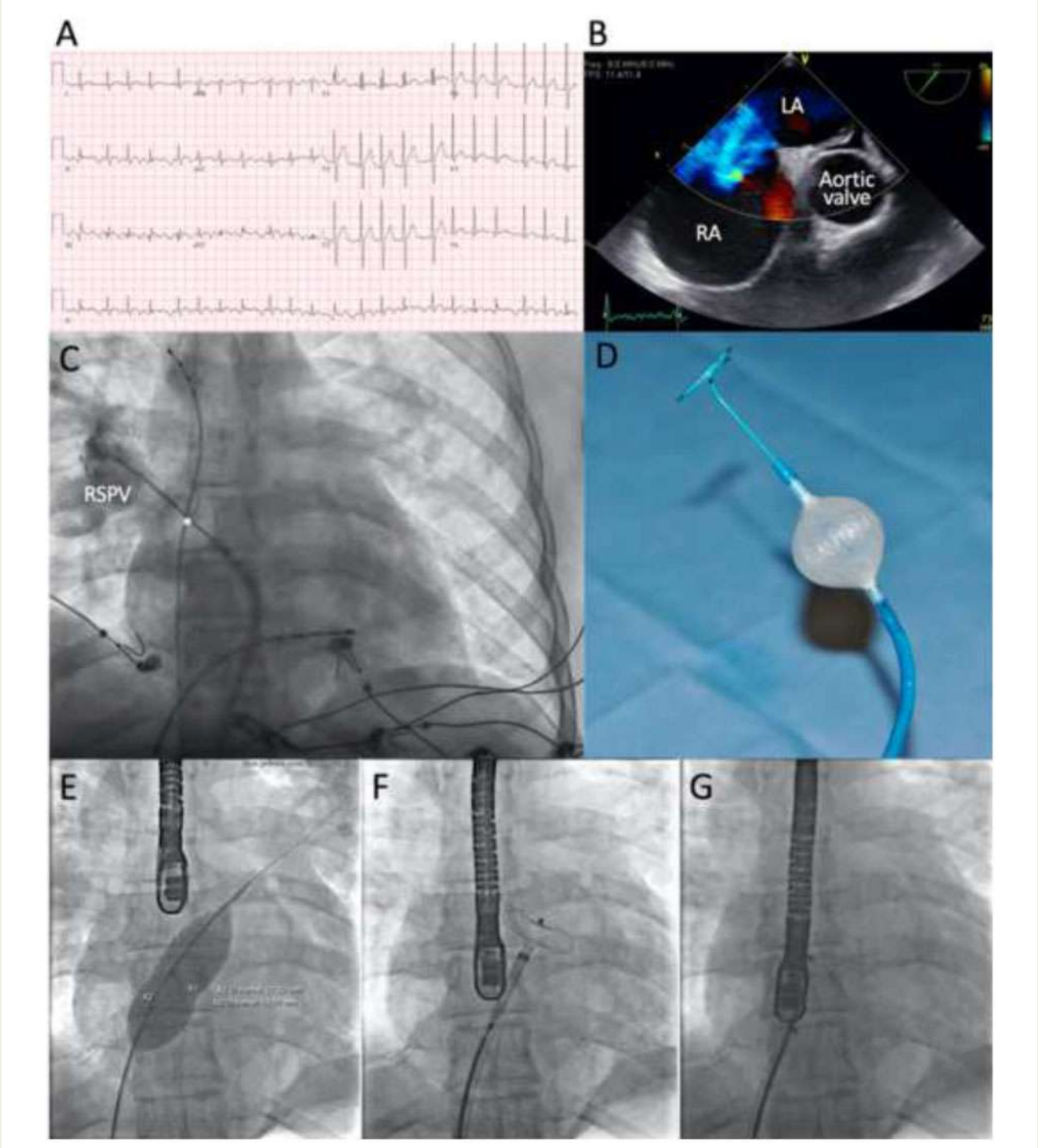


Figure 5 Catheter ablation of atrial fibrillation prior to atrial septal defect closure. (*A*) Atrial fibrillation with a ventricular response rate of 135 b.p.m. in an adult patient with no prior medical history. (*B*) Diagnostic work-up revealed a 20-mm secundum atrial septal defect. Transoesophageal echocardiography shows basal short-axis view of the atrial septal defect. Shunting from the left-to-right atrium is demonstrated by colour-flow imaging. (*C*) Catheter ablation of atrial fibrillation by electrically isolating all four pulmonary veins by means of a 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Dublin, Ireland). The cryoballoon (marked by *) is positioned at the ostium of right superior pulmonary vein. A circular mapping catheter (Achieve, Medtronic) to record pulmonary vein potentials is introduced in the central lumen of cryoballoon catheter and placed in the right superior pulmonary vein. (*D*) Similarly angled cryoballoon and Achieve catheter outside the body. (*E*–*G*) Closure of the defect is demonstrated. In the absence of recurrent atrial fibrillation, the atrial septal defect was percutaneously closed 6 months after ablation: (*E*) balloon sizing of the defect; (*F*) deployment of the left atrial portion of a 22-mm Amplatzer septal occluder (Abbott, Chicago, IL, USA); (*G*) release of the device. LA, left atrium; RA, right atrium; RSPV, right superior pulmonary vein.

Pulmonary hypertension and Eisenmenger syndrome

PH is a relatively rare complication even amongst large ASDs. Nevertheless, the risk of PH complicating ASD increases with advanced age and is more common in sinus venosus defects and loosely relates to larger defect size.[95,96] Contemporary series report lower prevalence of PH amongst patients with closed defects than in previous eras (~3%). We submit this reflects earlier diagnosis and timely closure, i.e. a proactive approach.[97] Severe pulmonary vascular disease, including Eisenmenger syndrome, has been historically reported in 5–10% of adults with untreated defects, more common in women, but rare nowadays.[40] Defect closure in patients with Eisenmenger syndrome is contraindicated.

Stroke

Patients with ASD are at increased risk of stroke, which is not completely abolished after closure. In the large ASD series on this subject, the prevalence of stroke was 4% with open defects and 1.4% with closed defects.[98] In former, paradoxical embolism is the commonly suggested mechanism, whereas in the latter, the risk of stroke relates to AF and/or pulmonary venous remodelling after ASD closure.[99] For this reason, older patients may be considered for anticoagulation for 6–12 months after ASD closure irrespective of pre-procedural AF or not.[88]

Pregnancy

Pregnancy is well tolerated in patients with uncomplicated ASDs. However, there is a small risk of paradoxical embolus and stroke; thus, women should be advised to have the defect closed, ideally before conception. If the diagnosis of uncomplicated ASD is made during pregnancy, it is safe to continue with pregnancy and plan ASD closure electively post-partum. Pregnancy outcomes for women with a repaired defect are similar to that of the general population.[100] For the occasional patient with ASD and PAH, pregnancy risks are still thought to be prohibitive; thus, timely counselling and effective contraception should be offered.[101–103] Alternatives, such as surrogacy and/or adoption, should also be discussed.

Conclusion

Why is ASD in adulthood a paradigm for CHD, if not the paradigm? Because the current proactive approach of defect closure at the time of diagnosis, before overt symptoms ensue, has led to normalization of prognosis for young adults and improved quality of life, functional class, and survival for all adult patients, irrespective of age. Although simple in anatomic terms—within the spectrum of CHD–ASDs call for tertiary expertise with all options being considered, namely catheter vs. surgical closure, pre-closure ablation for patients with atrial tachycardias and suitability for closure or/and targeted therapy for patients with ASD and PAH.[104] Many patients will benefit from lifelong follow-up, for late complications to be detected and treated promptly, while all patients should employ healthy life-style choices and adaptation to minimize cardiovascular risk factors in general and maximize the benefits from undergoing ASD closure.

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Data availability

The data underlying this article are available in the article.

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