# Atrial Septal Defect and Atrial Fibrillation: The Known and Unknown

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## Abstract

Atrial fibrillation (AF) is a common complication in patients with atrial septal defects (ASDs). The link between AF and ASD is fairly complex and entails modifications in electrophysiologic, contractile and structural properties, at the cellular and tissue level, of both atria, mainly due to chronic atrial stretch and dilation. Surgical repair or percutaneous closure of ASDs are equally effective in reducing mortality and symptoms but limited in preventing or curbing AF, unless combined with an arrhythmia-specific procedure. Transesophageal echocardiography (TEE) and intracardiac echocardiography (ICE) have improved the safety and success of the above procedures. Finally, clearer understanding of the pathophysiology of AF in patients with ASD (and CHF, in general) has led to target-specific advances in medical management.

## Introduction

AF is the most common sustained arrhythmia in clinical practice currently affecting approximately 2.2 million people in the United States with an estimate of more than 5.6 million, 50% of which aged 80 years or older, by the year 2050. The prevalence of AF directly correlates with age, with only 0.1% of adults younger than 55 years but 9.0% of adults 80 years or older affected.[1] Age-standardized prevalence of AF is higher among men than women and among patients with essential hypertension, ischemic or valvular heart disease, left atrial (LA) enlargement, congestive heart failure and diabetes, with cardiac failure and rheumatic heart disease being the most powerful predictive precursors.[2-13] AF is a very costly disease with significant impact on public health. The number of hospitalizations for AF has dramatically increased in the recent years

with a subsequent rise in health care costs.[14-16] The development of AF places patients at significant risk for cardioembolic strokes, steadily increasing with age from 6.7% for ages 50 to 59 years to 36.2% for ages 80-89 years[5] and doubles their overall mortality.[8] In the subgroup of patients with ASD the incidence of atrial flutter (AFL) and AF has been reported to be as high as 15-40% in the 30-35 year olds and carries ominous prognosis[7,17] ASDs are quite common representing 10% of all cardiac malformations at birth, 12% in children and 15% at clinics for children and adults.[18] There are 3 major types of ASDs: ostium secundum, ostium primum and sinus venosus defects. The ostium secundum is a true defect of the atrial septum and is located in the region of the fossa ovalis. The ostium primum defect belongs to the atrioventricular (AV) septal defects (also known as endocardial cushion defects), which may include a large ventricular septal defect and a common AV valve

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in its complete form. The sinus venosus defect is usually located at the junction of the right atrium (RA) and superior vena cava and almost always associated with partial anomalous pulmonary venous return. Two less common types of ASDs include the inferior vena cava form of sinus venosus defect and the coronary sinus septal defect.[19] With any ASD, the direction and amount of flow across the defect depends on the size of the defect and the diastolic properties of the two ventricles, which at birth are approximately equal and hence there is minimal net flow across the defect. As pulmonary arterial pressure falls, the right ventricle (RV) atrophies and becomes more distensible, while the left ventricle (LV) hypertrophies and becomes less compliant, due to increased systemic vascular resistance. This is the time when shunting of blood from the LA to the RA begins overloading the RV and shifting the interventricular septum to the left, decreasing the LV preload. The renis-angiotensin-aldosterone (RAA) system is thus activated increasing the intravascular volume and further increasing the pulmonary blood flow, eventually causing RA, LA and RV dilatation, pulmonary hypertension, right heart failure and flow reversal across the interatrial defect with significant hypoxia and cyanosis (Eisenmenger syndrome).[20] The most common initial presenting symptoms of ASD are exertional dyspnea or fatigue. Patients may then develop AF, decompensated right heart failure, occasionally, paradoxical embolus or tran-

sient ischemic attack, and finally, cyanosis (especially with inferior sinus venosus defect or right-to-left shunts).[19,21-25] Roesler in 1934 was the first to describe the natural history and clinical features of the disease based on 62 post mortem cases. Mean age of death was 36 years and usually resulted from heart failure, often associated with AF.[26] Campbell noticed that the mortality rates were quite low for the first two decades of life (0.6 to 0.7% per year) but rose significantly with subsequent decades (2.7% to 4.5% to 5.4% to 7.5% per year).[18]

### AF Induction and Maintenance in ASD Patients

The link between AF and ASD is relatively complex. Changes in atrial size and pressures have been shown to induce and maintain atrial tachyarrhythmias by various mechanisms. The effects of acute atrial stretch on atrial electrophysiology are widely divergent. Sideris et al found that an increase in right atrial pressure by acute volume overload significantly prolonged right atrial effective refractory period (AERP), interatrial conduction time and increased the propensity of the atria to fibrillate by rapid atrial pacing (RAP).[27] Other investigators, however, concluded that acute atrial stretch highly correlated with shortening of AERP and increased vulnerability for AF by single premature stimuli.[28-29] Chronic atrial stretch and/or enlargement on the other hand (as in patients with

**Figure 1:** Cross section interatrial septum showing the transseptal sheath inferior and posterior to the closure device (courtesy of Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract])
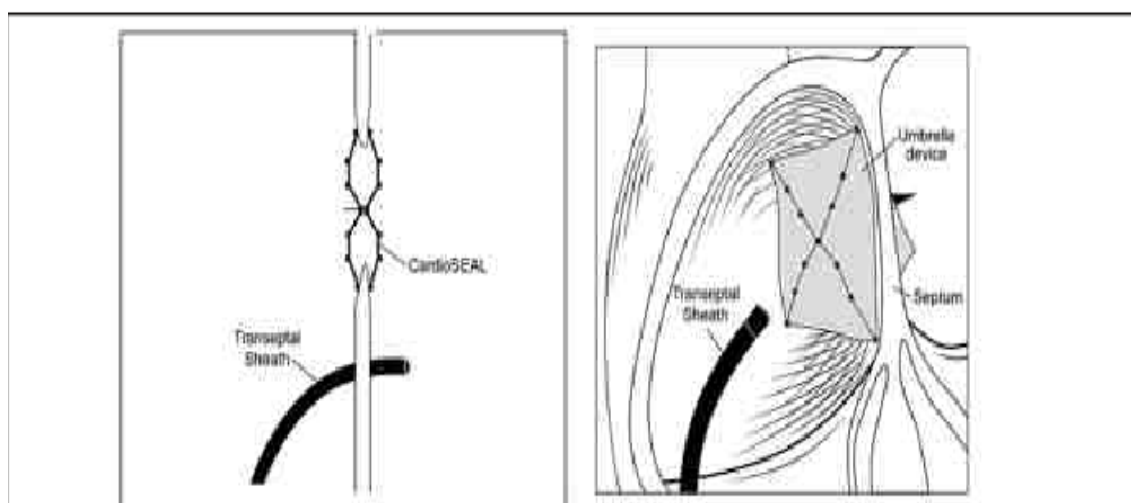
ASD), have consistently been associated with a significant increase in AERP and susceptibility to AF with single extrastimulus. A number of studies have shown that significant (at least 40%, by some[30]) atrial enlargement is associated with AERP prolongation, increased p-wave duration and extended sinus node recovery time (SNRT).[31-35] Biatrial enlargement due to AV dysynchrony by long-term VVI pacing has similarly been associated with prolongation of the AERP[36-37]

Electrical remodeling due to atrial enlargement contrasts the type of remodeling observed after RAP or AF. For the first time in an animal model, Wijffels et al[38] discovered that (artificially-induced and maintained) AF produced significant electrophysiologic changes in the atrial myocytes, namely a decrease in AERP, which caused AF to become sustained and unable to terminate spontaneously (hence, "AF begets AF").[38] Subsequent studies have confirmed the association of AF (and RAP) with marked decrease in AERP, as well as with significantly increased atrial impulse wavelength, loss of rate adaptation of the refractory period, sinus node dysfunction and accelerated conduction velocity, thus supporting the clinical experience that the success rate of chemical or electrical cardioversion of AF is higher when AF has lasted only a short time.[39-51]

Changes in atrial refractoriness has been explained at the atrial myocyte level by the concept of "ionic current remodeling" in the presence of congestive heart failure (CHF) and RAP. More specifically, with chronic atrial enlargement, there is a modest decrease in both L-type Ca2+ currents and transient outward (Ito) and slow delayed-rectifier (IKs) K+-currents, no change in inward rectifier, ultrarapid and rapid delayed rectifier, and T-type Ca2+ currents, and an increase in the Na+, Ca2+-exchanger (NCX) current. The net result is an increase in action potential duration (APD) at faster rates, paralleling AERP prolongation noted in vivo.[52-53] RAP on the other hand, has been associated with a significant reduction in the densities of Ito and Ica with subsequent reductions in APD and APD adaptation to rate and shorter atrial refractoriness.[54-56]

While shortening of the AERP has clearly been shown to predispose and sustain AF, lengthening of the AERP (as present in ASD patients with chronic atrial enlargement) may still increase atrial susceptibility to fibrillate by a different mechanism. Atrial refractoriness appears to be heterogeneously dispersed across key anatomic areas of

**Figure 2:** Interatrial septum with surgical closure patch through which a transseptal sheath was placed. Note an additional sheath that was placed at a more posterior and inferior location. (courtesy of Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract])
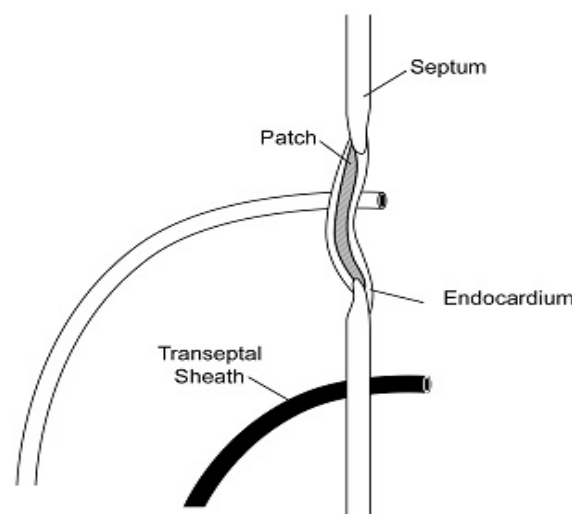
the right and left atrium, most notably the crista terminalis (CT) and the posterior wall of the left atrium (PLA), respectively.[57] Ultrastructural analysis of the CT reveals a simple end-to-end communication between the myocytes with numerous gap junctions in intercalated disks and minimal connections between laterally apposed cells, hence the propagation velocity in the CT is approximately 10 times greater in the longitudinal than in the transverse direction leading to anisotropic conduction preferentially along the anatomic LoB.[58] The increase in atrial refractoriness observed with atrial dilatation is unequally distributed across the RA (anisotropic dispersion of AERP), with AERP significantly prolonged along the thin free wall compared to the thick CT (functional LoB).[32-33] The combination of both anatomical and functional LoB's predisposes the RA to re-entrant tachyarrhythmias presenting as atrial flutter or atrial fibrillation, depending on the length of the overall LoB. A shorter LoB is more likely to "short-circuit" and become unstable, degenerating into AF. RAP and spontaneous atrial tachyarrhythmias have already been shown to produce a functional LoB between the vena cavae and its length was found to be critical for the maintenance of AFL and in preventing its degradation into AF.[59-61] The PLA is another key site where a line of anatomic LoB can be drawn perpendicularly between the superior and inferior pulmonary veins, correlating well with a region of change in subendocardial fiber orientation. This line is responsible for the breakup of wave fronts into multiple wavelets during the initiation of AF from the pulmonary vein foci.[62] In the presence of chronic LA dilation, conduction along the anatomic LoB of the PLA becomes more anisotropic due to heterogeneous dispersion of atrial refractoriness (functional LoB) creating a favorable substrate for re-entry and fibrillatory activity.[57,63]

However, even after prolonged periods of AF (months or years), electrical remodeling appears to be completely reversible and atrial refractoriness becomes normal within a few days of sinus rhythm. Allessie et al[46] suggested that a "second factor" was responsible for persistent AF. Good candidates included "atrial stunnig" (loss of atrial contractility, contractile remodeling) and atrial interstitial fibrosis (structural remodeling). Downregulation of ICaL, pronounced reduction of Ca2+ -transient current and Ca overload intracellularly were shown experimentally to cause atrial stun-

ning.[55,64-65] The duration of contractile dysfunction correlated well with the duration of AF and could take months prior to full recovery.[66] Still, atrial fibrosis is the hallmark of AF "domestication" by maintaining an arrhythmogenic substrate. Atrial fibrosis is the convergent pathologic end point of a variety of cardiac insults, including chronic atrial stretching (such as with an ASD), and a reparative process to replace degenerating myocardial cells.[67-68] Mechanical stretch induces increased angiotensin II (AngII) and transforming growth factor (TGF) –beta 1 expression and collagen synthesis in cardiac fibroblasts. It also stimulates cardiomyocyte signaling via activation of the angiotensin II type 1 (AT1) receptors and mitogen-activated protein kinase, with direct fibroblast-activating effects.[69-73] A lower percentage of atrial cardiomyocytes (compared to the ventricles, 45% vs 76%), and thus, a larger concentration of fibroblasts, inevitably leads to pronounced atrial extracellular matrix accumulation and remodeling.[74-75] Fibrosis has significant electrophysiologic effects, namely, it creates localized areas of muscle fiber disarray and thinning causing conduction slowing, increased conduction heterogeneity, unidirectional conduction blocks and smaller and more numerous reentrant circuits, a necessary substrate for AF.[76-80] Atrial myocytes, on the other hand, assume a more fetal phenotype (dedifferentiation), which resembles the changes in ventricular myocytes due to chronic ischemia (hibernation); such changes are initially reversible and heterogeneously distributed, however, in dilated atria (especially the RA), progression to DNA cleavage, programmed cell death and replacement with fibrous tissue, have been observed.[46,81]

## ASD Repair and AF

Therefore, patients with significant ASDs should be offered elective closure once the diagnosis is made. Current indications for ASD closure include right atrial and ventricular dilation by echocardiography, MRI or CT associated with ASD minimum diameter > 10mm on echocardiography and/or Qp:Qs > 1.5:1.0 by echocardiographic or cardiac MRI flow assessment or from oxygen saturation runs, when cardiac catheterization is performed. Treatment includes surgical repair of the ostium primum and sinus venosus ASDs, as well as of the ostium secundum ASDs, which are unsuitable for percutaneous device closure (defect

> 36mm, inadequate atrial septal rims for stable device deployment, or proximity of the defect to the AV valves, the coronary sinus or the vena cavae) [19,82]. Mortality and symptoms are significantly improved after surgical repair of ASDs, regardless of age, pulmonary arterial pressure (PAP) or pre-operative functional class.[22,83-84] On the other hand, the incidence of atrial tachyarrhythmias (most notably AF and AFL) is significantly age-dependent, with a higher incidence of AF and AFL among patients undergoing surgical closure in adulthood. Multiple studies have shown that preoperative, persistent and new-onset (i.e. postsurgical) AF or AFL are significantly more common among older patients.[21,23-25,83,85-92] For instance, Gosh et al observed a lower incidence of preoperative AF (23.5% vs 43.6%, p < 0.05) among patients 35-50 years old than among patients older than 50 years and a lower incidence of new AF (7.8% vs 34%, p < 0.05) in the former than the latter group.[93] The reported incidence of AF and AFL after surgical closure of ASD at adult age was indeed comparable to the incidence of these arrhythmias in natural history studies of ASD patients, namely, 15-40% in 30-35 year-olds.[7,18] Some studies even claimed a higher incidence of new onset supraventricular arrhythmias in surgical patients than in patients receiving medical management (39% vs 14%, p=0.01).[89,94] These numbers are significantly different from the 3% incidence reported by Roos et al for ASD patients operated in childhood.[95] The etiology of persistent or new-onset atrial arrhythmias following surgical repair of ASD in adults in not completely understood, however, the extent of residual RA dilatation after ASD closure appears to play a critical role. Indexed RA area remains increased after ASD repairs in adults compared to that in control subjects (still relatively decreased over time) and the decrease in RA area is inversely proportional to the patient's age at the time of the ASD closure .[96] As shown earlier, persistent atrial dilatation is essential for the initiation and domestication of AF and AFL. In addition, surgical scars (from the ASD repair) in the RA free wall act as anatomical LoB allowing either re-entry phenomena and AFL or scattered atrial electrical activity and AF to take place depending on the length of the LoB.[59-61,97-99] Finally, parameters such as the use of cardioplegia, type of cannulation, location of the defect and the presence of abnormal pulmonary venous drainage have been associated with sinus node injury or dysfunction and atrial arrhythmias .[21-24] The unacceptably high rates of persistent or new AF and AFL after adult ASD surgery (with their associated risks of stroke and chronic drug therapy) in conjunction to the small added risk of performing an AF surgical procedure, such as the modified Cox-Maze procedure, support their combination in such high risk patients.[100-101] The combination of the two surgical procedures has been associated with an approximately 85% rate of restoring sinus rhythm, a 90% rate of maintaining sinus rhythm and a significant improvement in New York Heart Association classification 8 months after combined surgery [102-103] with rates heavily dependent on the pre-operative size of the left atrium and the magnitude of the atrial fibrillatory wave[103]

Nevertheless, surgical repair of ASDs carries significant morbidity and mortality.[23,89,99,104] Percutaneous closure has recently emerged as an attractive alternative to the traditional open-chest procedures. The new modality has been associated with significant hemodynamic and electrophysiologic improvements in cardiac function. RV volumes are significantly decreased in < 24 hours after the procedure and continue to improve for up to 6 months (-not observed with surgical ASD repair due to the detrimental effects of cardioplegia.[108-110]). Improvement in RV filling pressures and function after percutaneous ASD repair have been associated (via the principle of ventricular interdependence) with an improved LV diastolic function, as suggested by normalization of the LV isovolumic relaxation time and LV end-diastolic dimension, and systolic function, as suggested by a statistically significant increase in LV ejection fraction.[84,109,111-112] Improved ventricular filling and atrial preload parameters may lead to noticeable reductions in indexed RA and LA areas (though, without complete resolution) over time in an age-dependent fashion.[96,106,113] Early percutaneous repair of ASDs has been associated with a decreased incidence of atrial tachyarrhythmias and ectopy compared to surgical closure.[105,114]

At any rate, patients who develop AF after ASD repair or PFO closure maintain the option of AF ablation irrespective of the closure (surgical or percutaneous) modality chosen. Concerns regarding gaining access to the LA via a transeptal puncture (TSP) under fluoroscopic guidance in the presence

of an intra-atrial patch closure device initially led to reasonable hesitations in percutaneously treating AF. Alterations in the septal anatomy after repair and the potential for mechanical dislodgement and damage to the closure apparatus made the complexity of the procedure, risks of complications and the fluoroscopy time prohibitive to many operators. Nevertheless, a few studies have shown that TSP under these conditions can be performed with low risk of complications. In a study of 39 pediatric patients with congenital heart disease requiring intra-atrial patch (IAP), the IAP was successfully punctured in 97.5% of the patients (38/39) with no complications; follow-up echocardiography in 79% of the patients revealed no residual shunting across the atrial septum except for two cases of atrial baffle, which were intentionally fenestrated.[115] Double TSP for AF ablation was successfully (95%) performed under the guidance of intracardiac echocardiography (ICE) in a prospective study of 20 post-ASD/PFO repair patients, age- and gender-matched with 20 control patients. Lakkireddy et al showed that surgical repairs with synthetic materials like Dacron (but not Gore-Tex) can safely be punctured to gain access to the LA, while most ASD or PFO closure devices typically occlude the anteroseptal portion of the interatrial septum, leaving a relatively wide posteroinferior area for TSP [figures 1-2]. No acute or long-term complications were noted and echocardiographic follow-up at 3 months showed residual interatrial communication in only 1 patient, which resolved in 12 months.[116]

Overall, percutaneous ASD closure is a safe and efficient procedure with only rare (less than 1%) serious complications in experienced centers. Case reports of device failure to deploy, malfunction, fracture or embolization, myocardial perforation and hemopericardium (with or without tamponade), residual shunts, thrombus formation on the device and aortic sinus-to-left atrial fistula formation have been reported.[117-122] In an effort to improve the safety and success of percutaneous (and surgical) ASD procedures, cardiac imaging such as transesophageal echocardiography (TEE) and ICE have been incorporated in all ASD closure procedures. TEE has been helpful in the selection of patients for surgical or percutaneous repair, in assessing the morphology, dimensions and relationship of ASD to the other intracardiac structures, in guiding the operator during the procedure and in early detection of any ensuing complications. Although the risks of TEE are minimal (< 0.02%), insertion of the TEE probe can potentially result in oral, esophageal or pharyngeal trauma, arrhythmias and patient discomfort. General anesthesia is usually required and additional staff (anesthesiologist, TEE operator) need to be present in the lab throughout the procedure. Experienced TEE operators are crucial for acquisition of quality images and reducing procedure and fluoroscopy times.[123-125] ICE has emerged as the preferred alternative to TEE. It provides accurate visualization of the intracardiac anatomic structures, defect(s) and closure devices or patches and

**Figure 3:** Closure of an atrial septal defect (ASD) under ICE guidance. (A) Colour Doppler demonstrating an ASD located in the inferior part of the atrial septum. (B) Relation of the ASD (arrow) to intracardiac structures. (C) Positioning of the Amplatzer closure device. (D) After several minutes, flattening of the closure device occurs. The device is positioned stable in between the right and left atria. Ao, aorta; LA, left atrium; RA, right atrium; RV, right ventricle
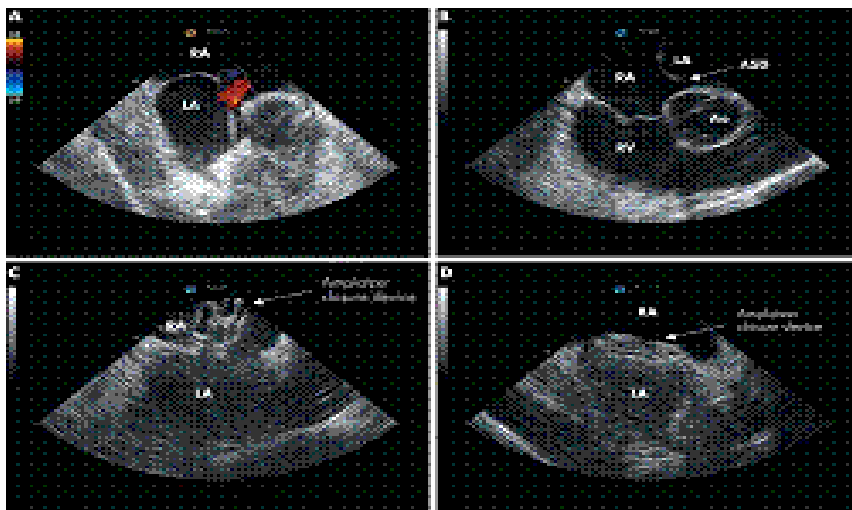
guides the operator in interventions, such as TSPs and placement of closure devices, thus preventing complications associated with the procedure [figure 3]. It also helps in microbubble monitoring for power adjustment during radiofrequency ablation and in visualization of thrombus formation on catheters and sheaths.[126-132] In contrast to TEE though, it avoids esophageal probe insertion (and its associated risks), patient discomfort and general anesthesia.

### Medical Management of AF in ASD Patients

### Atrial Extrasystoles:

Since AF is so common in the group of ASD (and especially, the unrepaired or adult-repaired ASD) patients, medical management remains essential. Pharmacologic agents to convert AF and prevent relapses have traditionally included antiarrhythmic drugs of the Vaughan-Williams class I and III. However, these agents are notorious for their proarrhythmic effects and poor tolerability. Latest breakthroughs in the understanding of the pathophysiologic mechanisms behind the initiation and

maintenance of AF (and other atrial tachyarrhythmias) have inspired rigorous interest in the pharmacologic targeting of the various steps. The concept of electrical remodeling in AF has led research efforts towards "atrial-selective" drugs, that is, modulators targeting ion-specific-channels [figure 4] (most notably Ikur[133] and IkAch,[134]), stretch-activated nonselective cation channels (SACs)[135] and atrial structures (such as atrially expressed connexins[136]), to affect atrial electrophysiologic activity.

Most of the currently investigated modulators though are not in strict terms "specific", but rather one or two orders of magnitude more selective in inhibiting the target(s) of interest compared to other potential targets.[137] Structural remodeling due to interstitial fibrosing is another potential target of pharmacotherapy and important feature of AF substrate. Several profibrotic factors have been discovered, most notably, AngII, TGF-b1, PDGF and connective tissue growth factor, and the renin – angiotensin – aldosterone pathway has extensively been implicated in the process.[73] Recent therapeutic agents such as ACE inhibitors, angiotensin II type 1 receptor blockers and anti-

**Figure 4:** Regional Difference in Ionic Current Contribution to APs. Differences in key ion currents between atrial (blue) and ventricular (red) action potentials (APs). Atrial APs have smaller AP amplitude and less negative resting membrane potential. Currents (green) identified above the line illustrating the APs are present in both regions; atrially expressed ionic currents are illustrated below the AP schematic (blue). IKACh _ acetylcholine-regulated potassium current; IKur _ ultrarapid delayed-rectifier potassium current; INa _sodium current (courtesy of Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll Cardiol. 2008 Feb 26;51(8):787-92)
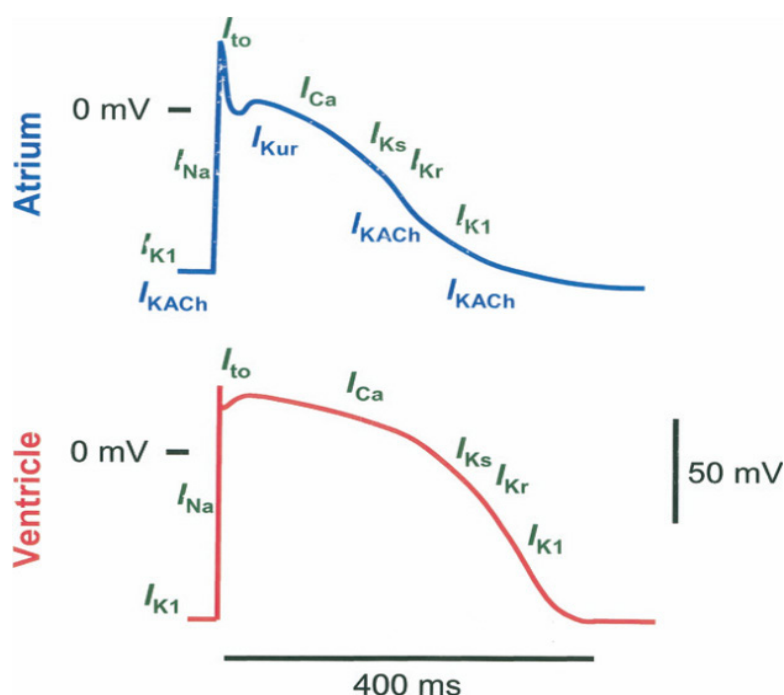
aldosterone therapies specifically target the latter and have been shown in multiple studies to substantially reduce fibroting changes and AF.[140-141] Similarly, 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors[142-143] and omega-3 polyunsaturated fatty acids were found to delay tissue fibrosis and thus prevent AF.[144] Gene therapy remains the last frontier in AF therapy with the most promise for atrial selectivity but is still lacking clinical applications.

## Conclusions:

In conclusion, AF in ASD patients is mainly the byproduct of RA and LA dilation. Changes in atrial refractoriness, ionic currents and atrial conduction properties (electrical remodeling), along with tissue remodeling due to atrial fibrosis (structural remodeling) generate a favorable substrate for the initiation and domestication of AF (and other atrial tachyarrhythmias). Surgical repair of ASD remains the standard therapeutic modality except for a selective population of patients, for which a percutaneous approach is preferred. Adult repair is associated with similar rates of AF in comparison to unrepaired ASD, partly due to residual RA dilation with fibrotic changes. Current AF treatment in ASD patients includes the modified Cox-Maze procedure (usually concomitantly with the ASD repair), percutaneous AF ablation via TSP and pharmacologic modalities, currently focusing on atrially expressed targets and pathophysiologic steps in atrial remodeling. Genetic manipulation is a promising research field in AF.

## References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer ED. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001 May 9;285(18):2370-5CrossRef PubMed

2. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995 Aug 15;92(4):835-41.

3.Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol. 1994 Aug 1;74(3):236-41.CrossRef PubMed

4. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG.Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications.Arch Intern Med. 1995 Mar 13;155(5):469-73.CrossRef PubMed

5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987 Sep;147(9):1561-4.CrossRef PubMed

6. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology. 2003 Nov;14(6):666-72.CrossRef PubMed

7. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart. 2001 Nov;86(5):516-21.CrossRef PubMed

8. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982 Apr 29;306(17):1018-22.

9. Petersen P, Godtfredsen J.Atrial fibrillation-a review of course and prognosis.Acta Med Scand.1984;216(1):5-9. 10. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Annu Rev Med. 1988;39:41-52.CrossRef PubMed

11. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA. 1985 Dec 27;254(24):3449-53.CrossRef PubMed

12. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup DM, Frye RL. The natural history of lone atrial fibrillation. A population-based study over three decades. N Engl J Med. 1987 Sep 10;317(11):669-74.

13. Davidson E, Rotenberg Z, Weinberger I, Fuchs J, Agmon J. Diagnosis and characteristics of lone atrial fibrillation. Chest. 1989 May;95(5):1048-50.CrossRef PubMed

14. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation. 2003 Aug 12;108(6):711-6. Epub 2003 Jul 28.CrossRef PubMed

15. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart. 2004 Mar;90(3):286-92.CrossRef PubMed

16. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, Guize L. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J. 2004 Jan;147(1):121-6.CrossRef PubMed

17. Campbell M, Neill C, Suzman S. The prognosis of atrial septal defect. Br Med J. 1957 Jun 15;1(5032):1375-83.

18. Campbell M. Natural history of atrial septal defect. Br Heart J. 1970 Nov;32(6):820-6.PubMed

19. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. Circulation. 2006 Oct 10;114(15):1645-53. CrossRef PubMed

20. Ward C. Secundum atrial septal defect: routine surgical treatment is not of proven benefit. Br Heart J. 1994 Mar;71(3):219-23. PubMed

21. McNamara DG, Latson LA.Long-term follow-up of patients with malformations for which definitive surgical repair has been available for 25 years or more. Am J Cardiol. 1982 Sep;50(3):560-8. CrossRef PubMed

22. Rostad H, Sørland SJ. Atrial septal defects of secundum type in

patients less than 40 years of age. A follow-up study. Acta Med Scand Suppl. 1981;645:29-35.

23. Bink-Boelkens MT, Velvis H, van der Heide JJ, Eygelaar A, Hardjowijono RA. Dysrhythmias after atrial surgery in children. Am Heart J. 1983 Jul;106(1 Pt 1):125-30.CrossRef PubMed

24. Meyer RA, Korfhagen JC, Covitz W, Kaplan S. Long-term follow-up study after closure of secundum atrial septal defect in children: an echocardiographic study. Am J Cardiol. 1982 Jul;50(1):143-8.CrossRef PubMed

25. Konstantinides S, Geibel A, Olschewski M, Görnandt L, Roskamm H, Spillner G, Just H, Kasper W. A comparison of surgical and medical therapy for atrial septal defect in adults. N Engl J Med. 1995 Aug 24;333(8):469-73.CrossRef PubMed

26. Roesler, H. Interatrial Septal Defect. Arch Int Med 1934;54:339-80.

27. Sideris DA, Toumanidis ST, Thodorakis M, Kostopoulos K, Tselepatiotis E, Langoura C, Stringli T, Moulopoulos SD. Some observations on the mechanism of pressure related atrial fibrillation. Eur Heart J. 1994 Nov;15(11):1585-9.

28. Tse HF, Pelosi F, Oral H, Knight BP, Strickberger SA, Morady F. Effects of simultaneous atrioventricular pacing on atrial refractoriness and atrial fibrillation inducibility: role of atrial mechanoelectrical feedback. J Cardiovasc Electrophysiol. 2001 Jan;12(1):43-50.CrossRef PubMed

29. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation. 1997 Sep 2;96(5):1686-95.

30. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995 Mar 1;91(5):1588-95.

31. Morton JB, Sanders P, Vohra JK, Sparks PB, Morgan JG, Spence SJ, Grigg LE, Kalman JM. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. Circulation. 2003 Apr 8;107(13):1775-82. Epub 2003 Mar 10.CrossRef PubMed

32. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol. 1996 Sep;7(9):833-42.CrossRef PubMed

33. Chen YJ, Chen SA, Tai CT, Yu WC, Feng AN, Ding YA, Chang MS. Electrophysiologic characteristics of a dilated atrium in patients with paroxysmal atrial fibrillation and atrial flutter. J Interv Card Electrophysiol. 1998 Jun;2(2):181-6.CrossRef PubMed

34. Power JM, Beacom GA, Alferness CA, Raman J, Wijffels M, Farish SJ, Burrell LM, Tonkin AM. Susceptibility to atrial fibrillation: a study in an ovine model of pacing-induced early heart failure. J Cardiovasc Electrophysiol. 1998 Apr;9(4):423-35.CrossRef PubMed

35. Oliver JM, Gallego P, González A, Benito F, Mesa JM, Sobrino JA. Predisposing conditions for atrial fibrillation in atrial septal defect with and without operative closure. Am J Cardiol. 2002 Jan 1;89(1):39-43.CrossRef PubMed

36. Sparks PB, Mond HG, Vohra JK, Jayaprakash S, Kalman JM. Electrical remodeling of the atria following loss of atrioventric-ular synchrony: a long-term study in humans. Circulation. 1999 Nov 2;100(18):1894-900.

37. Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM. Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. Circulation. 1999 Oct 19;100(16):1714-21.

38. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995 Oct 1;92(7):1954-68.

39. Suttorp MJ, Kingma JH, Jessurun ER, Lie-A-Huen L, van Hemel NM, Lie KI. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. J Am Coll Cardiol. 1990 Dec;16(7):1722-7.

40. Gold RL, Haffajee CI, Charos G, Sloan K, Baker S, Alpert JS. Amiodarone for refractory atrial fibrillation. Am J Cardiol. 1986 Jan 1;57(1):124-7.CrossRef PubMed

41. Waris E, Kreus KE, Salokannel J. Factors influencing persistence of sinus rhythm after DC shock treatment of atrial fibrillation. Acta Med Scand. 1971 Mar;189(3):161-6.

42. Bjerkelund C, Orning OM. An evaluation of DC shock treatment of atrial arrhythmias. Acta Med Scand. 1968 Dec;184(6):481-91.

43. Crijns HJ, van Wijk LM, van Gilst WH, Kingma JH, van Gelder IC, Lie KI. Acute conversion of atrial fibrillation to sinus rhythm: clinical efficacy of flecainide acetate. Comparison of two regimens. Eur Heart J. 1988 Jun;9(6):634-8.

44. Suttorp MJ, Kingma JH, Lie-A-Huen L, Mast EG. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. Am J Cardiol. 1989 Mar 15;63(11):693-6.CrossRef PubMed

45. Crozier IG, Ikram H, Kenealy M, Levy L. Flecainide acetate for conversion of acute supraventricular tachycardia to sinus rhythm. Am J Cardiol. 1987 Mar 1;59(6):607-9.CrossRef PubMed

46. Allessie M, Ausma J, Schotten U.Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002 May;54(2):230-46.CrossRef PubMed

47. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. Circulation. 1996 Dec 1;94(11):2953-60.

48. Bolens M, Friedli B. Sinus node function and conduction system before and after surgery for secundum atrial septal defect: an electrophysiologic study. Am J Cardiol. 1984 May 15;53(10):1415-20.CrossRef PubMed

49. Gaspo R, Bosch RF, Talajic M, Nattel S. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation. 1997 Dec 2;96(11):4027-35.

50. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. Circulation. 1998 Nov 17;98(20):2202-9.

51. Sparks PB, Jayaprakash S, Vohra JK, Kalman JM. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. Circulation. 2000 Oct 10;102(15):1807-13.

52. Shinagawa K, Li D, Leung TK, Nattel S. Consequences of atrial tachycardia-induced remodeling depend on the preexisting atrial substrate. Circulation. 2002 Jan 15;105(2):251-7.CrossRef PubMed

53. Li D, Melnyk P, Feng J, Wang Z, Petrecca K, Shrier A, Nattel S. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. Circulation. 2000 Jun 6;101(22):2631-8.

54. Nattel S, Li D. Ionic remodeling in the heart: pathophysiological significance and new therapeutic opportunities for atrial fibrillation. Circ Res. 2000 Sep 15;87(6):440-7.

55. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res. 1997 Oct;81(4):512-25.

56. Yu WC, Lee SH, Tai CT, Tsai CF, Hsieh MH, Chen CC, Ding YA, Chang MS, Chen SA. Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res. 1999 May;42(2):470-6.CrossRef PubMed

57. Roberts-Thomson KC, Stevenson IH, Kistler PM, Haqqani HM, Goldblatt JC, Sanders P, Kalman JM. Anatomically determined functional conduction delay in the posterior left atrium relationship to structural heart disease. J Am Coll Cardiol. 2008 Feb 26;51(8):856-62.CrossRef PubMed

58. Saffitz JE, Kanter HL, Green KG, Tolley TK, Beyer EC. Tissue-specific determinants of anisotropic conduction velocity in canine atrial and ventricular myocardium. Circ Res. 1994 Jun;74(6):1065-70.

59. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J Am Coll Cardiol. 2008 Feb 26;51(8):779-86.CrossRef PubMed

60. Ortiz J, Niwano S, Abe H, Rudy Y, Johnson NJ, Waldo AL. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. Circ Res. 1994 May;74(5):882-94.

61. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg. 1991 Mar;101(3):406-26.

62. Markides V, Schilling RJ, Ho SY, Chow AW, Davies DW, Peters NS. Characterization of left atrial activation in the intact human heart. Circulation. 2003 Feb 11;107(5):733-9.CrossRef PubMed

63. Gerstenfeld EP.Functional block in the posterior left atrium another piece in the puzzle of atrial fibrillation initiation. J Am Coll Cardiol. 2008 Feb 26;51(8):863-4.CrossRef PubMed

64. Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, Munson JT, Douglas PS. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol. 1994 Jun;23(7):1535-40.

65. Sun H, Gaspo R, Leblanc N, Nattel S. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia. Circulation. 1998 Aug 18;98(7):719-27.

66. Daoud EG, Marcovitz P, Knight BP, Goyal R, Man KC, Strickberger SA, Armstrong WF, Morady F. Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation. 1999 Jun 15;99(23):3024-7.

67. Boyden PA, Tilley LP, Pham TD, Liu SK, Fenoglic JJ Jr, Wit AL. Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. Am J

Cardiol. 1982 Jun;49(8):1896-908.CrossRef PubMed

68. Boyden PA, Tilley LP, Albala A, Liu SK, Fenoglio JJ Jr, Wit AL. Mechanisms for atrial arrhythmias associated with cardiomyopathy: a study of feline hearts with primary myocardial disease. Circulation. 1984 May;69(5):1036-47.

69. Carver W, Nagpal ML, Nachtigal M, Borg TK, Terracio L. Collagen expression in mechanically stimulated cardiac fibroblasts. Circ Res. 1991 Jul;69(1):116-22.

70. Riser BL, Cortes P, Heilig C, Grondin J, Ladson-Wofford S, Patterson D, Narins RG. Cyclic stretching force selectively upregulates transforming growth factor-beta isoforms in cultured rat mesangial cells. Am J Pathol. 1996 Jun;148(6):1915-23.

71. Zou Y, Akazawa H, Qin Y, Sano M, Takano H, Minamino T, Makita N, Iwanaga K, Zhu W, Kudoh S, Toko H, Tamura K, Kihara M, Nagai T, Fukamizu A, Umemura S, Iiri T, Fujita T, Komuro I. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat Cell Biol. 2004 Jun;6(6):499-506. Epub 2004 May 16.CrossRef PubMed

72. Malhotra R, Sadoshima J, Brosius FC 3rd, Izumo S. Mechanical stretch and angiotensin II differentially upregulate the renin-angiotensin system in cardiac myocytes In vitro. Circ Res. 1999 Jul 23;85(2):137-46.

73. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008 Feb 26;51(8):802-9.CrossRef PubMed

74. Hinescu ME, Gherghiceanu M, Mandache E, Ciontea SM, Popescu LM. Interstitial Cajal-like cells (ICLC) in atrial myocardium: ultrastructural and immunohistochemical characterization. J Cell Mol Med. 2006 Jan-Mar;10(1):243-57.CrossRef PubMed

75. Popescu LM, Gherghiceanu M, Hinescu ME, Cretoiu D, Ceafalan L, Regalia T, Popescu AC, Ardeleanu C, Mandache E. Insights into the interstitium of ventricular myocardium: interstitial Cajal-like cells (ICLC). J Cell Mol Med. 2006 Apr-Jun;10(2):429-58.CrossRef PubMed

76. Boyden PA, Hoffman BF. The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. Circ Res. 1981 Dec;49(6):1319-31.

77. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999 Jul 6;100(1):87-95.

78. Kalman JM, Sparks PB. Electrical remodeling of the atria as a consequence of atrial stretch. J Cardiovasc Electrophysiol. 2001 Jan;12(1):51-5.CrossRef PubMed

79. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res. 1986 Mar;58(3):356-71.

80. Lammers WJ, Schalij MJ, Kirchhof CJ, Allessie MA. Quantification of spatial inhomogeneity in conduction and initiation of reentrant atrial arrhythmias. Am J Physiol. 1990 Oct;259(4 Pt 2):H1254-63.

81. Everett TH 4th, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, Haines DE. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation. 2000 Sep 19;102(12):1454-

60.

82. Saxena A, Divekar A, Soni NR. Natural history of secundum atrial septal defect revisited in the era of transcatheter closure. Indian Heart J. 2005 Jan-Feb;57(1):35-8.

83. John Sutton MG, Tajik AJ, McGoon DC. Atrial septal defect in patients ages 60 years or older: operative results and long-term postoperative follow-up. Circulation. 1981 Aug;64(2):402-9.

84. Satoh A, Katayama K, Hiro T, Yano M, Miura T, Kohno M, Fujii T, Matsuzaki M. Effect of right ventricular volume overload on left ventricular diastolic function in patients with atrial septal defect. Jpn Circ J. 1996 Oct;60(10):758-66.CrossRef PubMed

85. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM, McGoon DC, Puga FJ, Kirklin JW, Danielson GK. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med. 1990 Dec 13;323(24):1645-50.

86. 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 Mar 18;340(11):839-46.CrossRef PubMed

87. Medeiros A, Iturralde P, Márquez M, Ramírez S, de Micheli A, Guevara M, Buendía A. Permanent rhythm and conduction disorders in patients surgically treated for atrial septal defect. Arch Inst Cardiol Mex. 2000 Jan-Feb;70(1):46-54.

88. Shah D, Azhar M, Oakley CM, Cleland JG, Nihoyannopoulos P. Natural history of secundum atrial septal defect in adults after medical or surgical treatment: a historical prospective study. Br Heart J. 1994 Mar;71(3):224-7; discussion 228.PubMed

89. Favilli S, Zuppiroli A, Mori F, Santoro G, Manetti A, Dolara A. Should the patient with an interatrial defect recognized in adulthood always be operated on? G Ital Cardiol. 1999 Nov;29(11):1302-7.

90. Thilén U, Berlind S, Varnauskas E. Atrial septal defect in adults. Thirty-eight-year follow-up of a surgically and a conservatively managed group. Scand Cardiovasc J. 2000;34(1):79-83.CrossRef PubMed

91. Meijboom F, Hess J, Szatmari A, Utens EM, McGhie J, Deckers JW, Roelandt JR, Bos E. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. Am J Cardiol. 1993 Dec 15;72(18):1431-4.CrossRef PubMed

92. Perloff JK. Surgical closure of atrial septal defect in adults. N Engl J Med. 1995 Aug 24;333(8):513-4.CrossRef PubMed

93. Ghosh S, Chatterjee S, Black E, Firmin RK. Surgical closure of atrial septal defects in adults: effect of age at operation on outcome. Heart. 2002 Nov;88(5):485-7.CrossRef PubMed

94. Horvath KA, Burke RP, Collins JJ Jr, Cohn LH. Surgical treatment of adult atrial septal defect: early and long-term results. J Am Coll Cardiol. 1992 Nov 1;20(5):1156-9.

95. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. Eur Heart J. 2003 Jan;24(2):190-7. CrossRef PubMed

96. Kort HW, Balzer DT, Johnson MC. Resolution of right heart enlargement after closure of secundum atrial septal defect with transcatheter technique. J Am Coll Cardiol. 2001 Nov 1;38(5):1528-32.CrossRef PubMed

97. Waldo AL. Pathogenesis of atrial flutter. J Cardiovasc Electrophysiol. 1998 Aug;9(8 Suppl):S18-25.

98. Feld GK, Shahandeh-Rad F. Mechanism of double potentials recorded during sustained atrial flutter in the canine right atrial crush-injury model. Circulation. 1992 Aug;86(2):628-41.

99. Tomita Y, Matsuo K, Sahadevan J, Khrestian CM, Waldo AL. Role of functional block extension in lesion-related atrial flutter. Circulation. 2001 Feb 20;103(7):1025-30.

100. Cox JL, Jaquiss RD, Schuessler RB, Boineau JP. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. J Thorac Cardiovasc Surg. 1995 Aug;110(2):485-95.CrossRef PubMed

101. Bonchek LI, Burlingame MW, Worley SJ, Vazales BE, Lundy EF. Cox/maze procedure for atrial septal defect with atrial fibrillation: management strategies. Ann Thorac Surg. 1993 Mar;55(3):607-10.

102. Sandoval N, Velasco VM, Orjuela H, Caicedo V, Santos H, Rosas F, Carrea JR, Melgarejo I, Morillo CA. Concomitant mitral valve or atrial septal defect surgery and the modified Cox-maze procedure. Am J Cardiol. 1996 Mar 15;77(8):591-6.CrossRef PubMed

103. Kamata J, Kawazoe K, Izumoto H, Kitahara H, Shiina Y, Sato Y, Nakai K, Ohkubo T, Tsuji I, Hiramori K. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operations. Ann Thorac Surg. 1997 Aug;(2):394-8. CrossRef PubMed

104. Galal MO, Wobst A, Halees Z, Hatle L, Schmaltz AA, Khougeer F, De Vol E, Fawzy ME, Abbag F, Fadley F, et al. Peri-operative complications following surgical closure of atrial septal defect type II in 232 patients--a baseline study. Eur Heart J. 1994 Oct;15(10):1381-4.

105. Santoro G, Pascotto M, Sarubbi B, Cappelli Bigazzi M, Calvanese R, Iacono C, Pisacane C, Palladino MT, Pacileo G, Russo MG, Calabrò R. Early electrical and geometric changes after percutaneous closure of large atrial septal defect. Am J Cardiol. 2004 Apr 1;93(7):876-80.CrossRef PubMed

106. Salehian O, Horlick E, Schwerzmann M, Haberer K, McLaughlin P, Siu SC, Webb G, Therrien J. Improvements in cardiac form and function after transcatheter closure of secundum atrial septal defects. J Am Coll Cardiol. 2005 Feb 15;45(4):499-504. CrossRef PubMed

107. Du ZD, Cao QL, Koenig P, Heitschmidt M, Hijazi ZM. Speed of normalization of right ventricular volume overload after transcatheter closure of atrial septal defect in children and adults. Am J Cardiol. 2001 Dec 15;88(12):1450-3, A9.

108. Eidem BW, O'Leary PW, Tei C, Seward JB. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. Am J Cardiol. 2000 Sep 15;86(6):654-8.CrossRef PubMed

109. Dhillon R, Josen M, Henein M, Redington A. Transcatheter closure of atrial septal defect preserves right ventricular function. Heart. 2002 May;87(5):461-5.CrossRef PubMed

110. Shaheen J, Alper L, Rosenmann D, Klutstein MW, Falkowsky G, Bitran D, Tzivoni D. Effect of surgical repair of secundum-type atrial septal defect on right atrial, right ventricular, and left ventricular volumes in adults. Am J Cardiol. 2000 Dec 15;86(12):1395-7, A6.

111. Walker RE, Moran AM, Gauvreau K, Colan SD. Evidence of adverse ventricular interdependence in patients with atrial septal defects. Am J Cardiol. 2004 Jun 1;93(11):1374-7, A6.

112. Giardini A, Donti A, Formigari R, Specchia S, Prandstraller D, Bronzetti G, Bonvicini M, Picchio FM. Determinants of cardiopulmonary functional improvement after transcatheter atrial septal defect closure in asymptomatic adults. J Am Coll Cardiol. 2004 May 19;43(10):1886-91.CrossRef PubMed

113. Schussler JM, Anwar A, Phillips SD, Roberts BJ, Vallabhan RC, Grayburn PA. Effect on right ventricular volume of percutaneous Amplatzer closure of atrial septal defect in adults. Am J Cardiol. 2005 Apr 15;95(8):993-5.CrossRef PubMed

114. Schenck MH, Sterba R, Foreman CK, Latson LA. Improvement in noninvasive electrophysiologic findings in children after transcatheter atrial septal defect closure. Am J Cardiol. 1995 Oct 1;76(10):695-8.CrossRef PubMed

115. El-Said HG, Ing FF, Grifka RG, Nihill MR, Morris C, Getty-Houswright D, Mullins CE. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. Catheter Cardiovasc Interv. 2000 Aug;50(4):434-9; discussion 440.CrossRef PubMed

116. Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract].PubMed

117. Rickers C, Hamm C, Stern H, Hofmann T, Franzen O, Schräder R, Sievert H, Schranz D, Michel-Behnke I, Vogt J, Kececioglu D, Sebening W, Eicken A, Meyer H, Matthies W, Kleber F, Hug J, Weil J. Percutaneous closure of secundum atrial septal defect with a new self centering device ("angel wings"). Heart. 1998 Nov;80(5):517-21.

118. Mashman WE, King SB, Jacobs WC, Ballard WL. Two cases of late embolization of Amplatzer septal occluder devices to the pulmonary artery following closure of secundum atrial septal defects. Catheter Cardiovasc Interv. 2005 Aug;65(4):588-92.CrossRef PubMed

119. Ruge H, Wildhirt SM, Libera P, Vogt M, Holper K, Lange R. Images in cardiovascular medicine. Left atrial thrombus on atrial septal defect closure device as a source of cerebral emboli 3 years after implantation. Circulation. 2005 Sep 6;112(10):e130-1.CrossRef PubMed

120. Knirsch W, Dodge-Khatami A, Balmer C, Peuster M, Kadner A, Weiss M, Prêtre R, Berger F. Aortic sinus-left atrial fistula after interventional closure of atrial septal defect. Catheter Cardiovasc Interv. 2005 Sep;66(1):10-3.CrossRef PubMed

121. Costache V, Chavanon O, Thony F, Blin D. Aortic arch embolization of an Amplatzer occluder after an atrial septal defect closure: hybrid operative approach without circulatory arrest. Eur J Cardiothorac Surg. 2005 Aug;28(2):340-2.CrossRef PubMed

122. Sievert H, Babic UU, Ensslen R, Merle H, Osypka P, Rubel C, Scherer D, Spies H, Wiederspahn T, Zeplin HE. Occlusion of atrial septal defect with a new occlusive device. Z Kardiol. 1996 Feb;85(2):97-103.

123. Peterson GE, Brickner ME, Reimold SC. Transesophageal echocardiography: clinical indications and applications. Circulation. 2003 May 20;107(19):2398-402.CrossRef PubMed

124. Brochu MC, Baril JF, Dore A, Juneau M, De Guise P, Mercier LA. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. Circulation. 2002 Oct 1;106(14):1821-6.CrossRef PubMed

125. Figueroa MI, Balaguru D, McClure C, Kline CH, Radtke WA, Shirali GS. Experience with use of multiplane transesophageal echocardiography to guide closure of atrial septal defects using the amplatzer device. Pediatr Cardiol. 2002 Jul-Aug;23(4):430-6. CrossRef PubMed

126. Jongbloed MR, Schalij MJ, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Bax JJ. Clinical applications of intracardiac echocardiography in interventional procedures. Heart. 2005 Jul;91(7):981-90.CrossRef PubMed

127. Bartel T, Konorza T, Arjumand J, Ebradlidze T, Eggebrecht H, Caspari G, Neudorf U, Erbel R. Intracardiac echocardiography is superior to conventional monitoring for guiding device closure of interatrial communications. Circulation. 2003 Feb 18;107(6):795-7.CrossRef PubMed

128. Earing MG, Cabalka AK, Seward JB, Bruce CJ, Reeder GS, Hagler DJ. Intracardiac echocardiographic guidance during transcatheter device closure of atrial septal defect and patent foramen ovale. Mayo Clin Proc. 2004 Jan;79(1):24-34.

129. Miyamoto N, Kyo S, Motoyama T, Hung JS, Suzuki S, Aihara S, Matsumura M, Omoto R, Dohi Y, Matsuo H. Usefulness of intracardiac echocardiography for guidance of transseptal puncture procedure. J Cardiol. 1995 Jan;25(1):29-35.

130. Epstein LM, Smith T, TenHoff H. Nonfluoroscopic transseptal catheterization: safety and efficacy of intracardiac echocardiographic guidance. J Cardiovasc Electrophysiol. 1998 Jun;9(6):625-30.CrossRef PubMed

131. Szili-Torok T, Kimman G, Theuns D, Res J, Roelandt JR, Jordaens LJ. Transseptal left heart catheterisation guided by intracardiac echocardiography. Heart. 2001 Nov;86(5):E11.PubMed

132. Citro R, Ducceschi V, Salustri A, Santoro M, Salierno M, Gregorio G. Intracardiac echocardiography to guide transseptal catheterization for radiofrequency catheter ablation of left-sided accessory pathways: two case reports. Cardiovasc Ultrasound. 2004 Oct 8;2:20.CrossRef PubMed

133. Wettwer E, Hála O, Christ T, Heubach JF, Dobrev D, Knaut M, Varró A, Ravens U. Role of IKur in controlling action potential shape and contractility in the human atrium: influence of chronic atrial fibrillation. Circulation. 2004 Oct 19;110(16):2299-306. Epub 2004 Oct 11.CrossRef PubMed

134. Cha TJ, Ehrlich JR, Chartier D, Qi XY, Xiao L, Nattel S. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. Circulation. 2006 Apr 11;113(14):1730-7. Epub 2006 Apr 3.CrossRef PubMed

135. Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation.Nature. 2001 Jan 4;409(6816):35-6.CrossRef PubMed

136. Hagendorff A, Schumacher B, Kirchhoff S, Lüderitz B, Willecke K. Conduction disturbances and increased atrial vulnerability in Connexin40-deficient mice analyzed by transesophageal stimulation. Circulation.1999 Mar 23;99(11):1508-15.

137. Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll

Cardiol. 2008 Feb 26;51(8):787-92.CrossRef PubMed

138. Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. Cardiovasc Res. 2003 Nov 1;60(2):315-25. CrossRef PubMed

139. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation. 2001 Nov 20;104(21):2608-14.CrossRef PubMed

<p class="Manuscript-Body"/>140. Sakabe M, Fujiki A, Nishida K, Sugao M, Nagasawa H, Tsuneda T, Mizumaki K, Inoue H. Enalapril prevents perpetuation of atrial fibrillation by suppressing atrial fibrosis and over-expression of connexin43 in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Pharmacol. 2004 Jun;43(6):851-9.CrossRef PubMed

141. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc Res. 2002 May;54(2):456-61.CrossRef PubMed

142. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2008 Feb 26;51(8):828-35.CrossRef PubMed

143. Shiroshita-Takeshita A, Brundel BJ, Burstein B, Leung TK, Mitamura H, Ogawa S, Nattel S. Effects of simvastatin on the development of the atrial fibrillation substrate in dogs with congestive heart failure. Cardiovasc Res. 2007 Apr 1;74(1):75-84. Epub 2007 Jan 11.CrossRef PubMed

144. Sakabe M, Shiroshita-Takeshita A, Maguy A, Dumesnil C, Nigam A, Leung TK, Nattel S. Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. Circulation. 2007 Nov 6;116(19):2101-9. Epub 2007 Oct