Short and Intermediate-Term Effects of Transcatheter Closure of Secundum Atrial Septal Defect on Cardiac Remodeling In Children and Adults

Thesis

Submitted for partial fulfillment of Master degree

in **Cardiology**

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2012

Introduction

Atrial septal defects (ASDs) are the second most common congenital lesion in adults (behind bicuspid aortic valves). They represent approximately 7% of all cardiac anomalies ***(Rigatelli et al., 2005).*** These defects are often undetected until adulthood due to the lack of prominent clinical symptoms initially. If untreated, an ASD can eventually result in right ventricular (RV) heart failure, pulmonary hypertension, atrial arrhythmias, or paradoxical embolization and ischemic cerebral events.

Often, atrial tachyarrhythmias may coexist or precede symptoms. Study has shown that the incidence of arrhythmias increase with age as well as an increase in pulmonary pressures ***(Berger et al., 1999).*** However, it is still unclear whether atrial arrhythmias improve with the closure of the defect, although some trials have shown that atrial flutter may improve with atrial septal defect (ASD) closure as opposed to atrial fibrillation, which usually remains unchanged following closure ***(Berger et al., 1999).*** As a result, the development of an atrial tachyarrhythmia alone does not constitute an immediate need for ASD closure.

Traditionally, as shown in the pediatric literature, patients with a significant pulmonary to systemic blood flow (Qp/Qs) ratio $\geq$ 1.5 have demonstrated the most benefit after ASD closure. One study in adults has shown that asymptomatic and

mildly symptomatic patients with a Qp/Qs as low as 1.2 may also benefit from ASD closure ***(Brochu et al., 2002).***

Historically, ASDs have been closed surgically. More recently, these Procedures have been accomplished with minimally invasive surgical Techniques as well as a percutaneous transcatheter technique. The latter Technique has been increasing in popularity due to the avoidance of cardiac surgery and the associated risks.

ASD repair with the transcatheter technique has been shown to have a high closure rate ***(Wilson et al., 2008).*** Unfortunately, anatomy of the defect often limits their use. Currently, transcatheter closure is limited to secundum-type defects which are less than 36 mm in size.

Patients with severe fixed pulmonary hypertension may actually do worsen with ASD closure due to the need for partial right-to-left shunting of blood to decrease right-sided pressures ***(Steele et al., 1987).*** Early diagnosis and follow-up of ASDs offers the best opportunity to avoid late complications from pulmonary hypertension, heart failure, arrhythmia, and stroke.

Aim of the work

This study aims to investigate the short and intermediate-term effects of transcatheter secundum atrial septal defect (ASD) closure on cardiac remodeling in children and adults.

Chapter (1)

Embryology and anatomy

Embryology:

Throughout cardiac embryogenesis an avenue for inter atrial blood flow is maintained, despite the development of two separate septal structures ***(Allen et al., 2008).***

The septum primum, which is the first septum to develop, is an incomplete thin walled partition in which the anteroinferior free edge is above the atrioventricular canal and becomes lined by tissue derived from the superior and inferior endocardial cushions. Before the resultant inter atrial opening (ostuim pirmum) becomes sealed by endocardial cushion tissue, new fenestrations form along the anterosuperior aspect of the septum primum. These fenestrations coalesce to form a large second interatrial communication (ostuim secundum) maintaining inter atrial blood flow.

At this time, to the right of the first septum, an anterosuperior infolding of the atrial roof occurs and forms a second septal structure (septum secundum) which expands posteroinferiorly as a thick-walled muscular ridge to form an incomplete partition that overlies the ostium secundum. The channel for inter atrial blood flow through the ostium secundum is known as the foramen ovale ***(Van Mierop, 1976).***

Concurrently with atrial septation, the left horn of the sinous venosus forms the coronary sinus, and the right sinus horn becomes a part of the right atrium. Infolding at the sinoatrial junction forms the right and left venous valves, whereas the right venous valve is maintained and forms the rudimentary valves of the inferior vena cava and the coronary sinus, the left venous valve becomes fused to the superior, posterior, and the inferior margins of the fossa ovalis ***(Porter et al., 2000).***

Genetic base:

Atrial septal dysmorphogenesis, evident as increased frequency of patent foramen ovale (PFO) and atrial septal aneurysm (ASA) has recently been correlated with heterozygous mutations of the cardiac homeodomain transcription factor NKX2-5 ***(Schott, 1998)***. This observation provides evidence for the first time that the incidence of PFO may be related to genetic factors, and that the PFO represents an index of septal dysmorphogenesis encompassing other defects as ASA and ASD ***(Windeker et al., 2002)***.

Li et al. (1997) eported that Holt and Oram syndrome is caused by mutations in TBX5, a member of the Brachyury (T) gene family.

Anatomy of the Interatrial Septum:

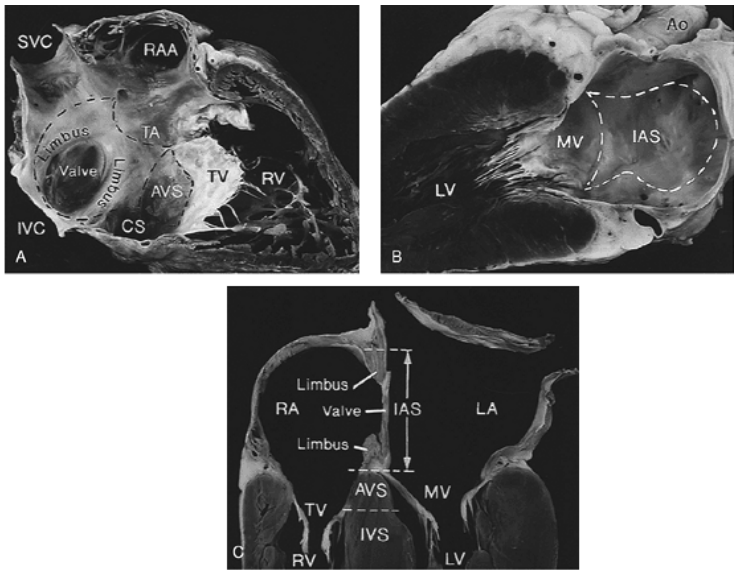

Figure (1): Atrial septal anatomy. A: Two-chamber view, right-sided. B: Two-chamber view, left-sided. The interatrial septum (IAS, outlined by dotted lines) is relatively small and is associated primarily with the limbus and valve of the fossa ovalis. Anterosuperiorly, the aortic root indents the right atrial free wall as the torus aorticus (TA). C: Four-chamber view. The IAS lies between the right and left atria (RA, LA), whereas the atrioventricular septum (AVS) lies between the RA and left ventricle (LV) ***(Allen et al., 2008).***

The inter atrial septum occupies an area on the right atrial medial wall, in its center lies the fossa ovalis bordered by a curved ridge of atrial myocardium called the limbus. The prominence and circumferential extent of the limbus varies in shape it may be circular, oval, or shaped like the letter C or an inverted U. The average area of the atrial septum was 8.9 cm^2 and that of the fossa ovalis 2.4 cm^2 as measured in adult autopsies by Sweeney and rosenquist ***(Sweeney et al., 1979).***

Schwinger et al. (1990) used transesophageal echocardiography (TEE) to study the thickness of the atrial septum. They

found that the latter was thickest peripherally (i.e. near its attachment to the atrial free wall) and was most thin at the fossa ovalis. In 82% of their 119 patients, the atrial septum on either side of the fossa ovalis was of approximately uniform thickness which varied enormously, from 2 to 20 mm. Atrial septal thickness at the fossa ovalis was only 1.8 ± 0.7 mm (mean).

The septum has quite different characteristics on its right and left sides. ***Anderson et al. (1987)*** described the anatomy of the interior of the right atrium, when the right atrium is opened through a wide incision, a large expanse of the atrial "septum" is seen between the orifices of the superior and inferior caval veins and the attachment of the septal leaflet of the tricuspid valve. Only a small part of this area separates the cavities of the two atrial chambers, namely the floor of the fossa ovalis and its muscular margins (the limbus fossae ovalis).

The superior limbus, often called the septum secundum is made up in its larger part of an infolding of atrial wall between the base of the superior vena caval vien and the insertion of the right pulmonary viens to the left atruim. This is the area known to the surgeons as waterston's groove; a substantial cleavage plane extends down to the margin of the fossa which can be opened by external dissection. The internal aspect of this groove is the prominent muscle band which separates the fossa from the orifice of the superior caval vien. The part of the limbus immediately adjacent to the fossa is a true septal structure ***(Beerman et al., 1979).***

More anteriorly the margin of the limbus continues as a septal structure, but its larger part is the anterior atrial wall overlying the aortic root. Postero-inferiorly the fossa ovalis becomes directly continuous with the wall of the inferior caval vien. Antero-inferiorly the morphology becomes more complicated, since the fossa separated from the orifice of the coronary sinus by the sinus septum. Through the sinus septum runs the tendon of todaro, which is the continuation of the commissure of the Eustachian and Thebesian valves.

The muscular structure between the mouths of the inferior caval vien and the coronary sinus is not septal, but is rather the free wall of the right atruim. The part of the atrial wall between the tendon of todaro and the septal leaflet of the tricuspid valve is an atrioventricular rather than inter atrial septal structure. This is because the tricuspid valve is attached to the septum more apically than the mitral valve, so the septum between them separates the right atruim from the left ventricle. Thus, only the thin translucent floor of the fossa ovalis (septum primum) together with the margins of the limbus immediately adjacent to the fossa is a true inter atrial septal structure.

When viewed from the left atrial aspect, the morphology is far less complex. The floor of the fossa is smooth but in its anterosuperior margin it is roughened and wrinkled. Only a small part of this anterior region is septum, the rest being the area where the septum primum is fused with the anterior atrial wall ***(Beerman et al., 1979).***

Patent foramen ovale:

In the fetus, the interatrial septum consists mainly of the septum secundum, which is a non-mobile, flat structure deficient in its center. Immediately to the left of this is the septum primum, a mobile flap that allows blood to flow from right to left. All through intrauterine life blood flows through this valve–like foramen ovale from right to the left atrium, but at birth the left atrial preasure rises above of the right atrium, and the flap like septum primum closes the foramen ovale and forms the floor of the fossa ovalis.

Fusion of the septum primum with septum secundum occurs at a variable time after birth in the majority of individuals, thus sealing off the two atria from each other permanently. In a minority of otherwise normal persons, such fusion does not occur, though the foramen ovale remains functionally closed. In other words, an oblique, slit-like potential communication persists between the right and the left atrium. In a series of 965 autopsies from the Mayo clinic ***(Hegan et al., 1984)***, 27% had a valve–patent foramen ovale, the prevalence being higher (34%) in children and young adults than in elderly (20%).

Right to left blood flow through a patent foramen ovale may be demonstrable on color flow Doppler, usually best seen in the four chamber subcostal view on routine 2-Dimensional (2D) echocardiography or in a two-chamber atrial view transecting the foramen ovale region on TEE. ***Mosvowtiz et al. (1992)*** and ***Chenzbraun et al. (1993)*** found the best TEE plane

for this purpose to be a vertical plane passing through the fossa ovalis as well as both venae cavae. Ten milliliters of agitated saline solution is injected into an arm vien, resulting in dense right atrial opacification by micro bubbles. A right-to-left shunt is judged to be present if micro bubbles are found in the left atruim within three cardiac cycles after complete right atrial opacification ***(Siostrzonk et al., 1991)***. Five or more micro bubbles must be visualized ***(Lynch et al., 1984)*** others say more than 3 micro bubbles ***(Mas et al., 2002)***.

Right –to-left shunting through a patent foramen ovale can be enhanced or provoked by the Valsalva maneuver or coughing, both of which cause abrupt transient elevation of right –sided heart pressure. Between 10% and 18% of apparently healthy normal persons have a patent foramen ovale by contrast TEE ***(Lynch et al., 1984)***.

Aneurysm of the atrial septum:

Since the floor of the fossa ovalis is developed from the septum primum of the embryo, aneurysms of this region are sometimes referred to as septum primum aneurysms. The floor of the fossa ovalis is commonly taut and flush with the limbos of the fossa and adjacent atrial septum or the floor of the fossa maybe mildly depressed with the limbus a conspicuous ridge or shoulder. In yet other cases, the thin fossa floor is somewhat lax or floppy on pressure but cannot be pushed far into either atrium; such mild redundancy is considered within the range of normal variance and should not be called an IAS aneurysm. The latter term should be reserved for cases with severe redundancy

such that the aneurysmal bulge protrudes far into the atrial cavity ***(Hanely et al., 1985).***

Quantitative measurements of IAS aneurysms were reported by ***Silver et al. (1978)*** in their 16 autopsy cases. The diameter of the base of the aneurysm varied from 1.5 to 2.5 cm, and the aneurysm projected 1.1 to 2.4 cm into the atrium (usually the right). The Mayo Clinic's echocardiographic criteria for diagnosis of IAS aneurysm ***(Hanely et al., 1985)*** were 1.5-cm protrusion beyond the plane of the atrial septum and a base diameter of at least 1.5 cm. Recently ***Mas et al. (2002)*** suggested reduction of measurement to 1.1 cm. In some patients, such aneurysmal bulges are "fixed "`in others, the aneurysm is mobile and moves rapidly to and fro between the two atria with every cardiac cycle, presumably reflecting transient phasic pressure differences between the two chambers. In certain situations, including tamponade, phasic motion of the IAS aneurysm into the left atrium may be respiratory (during inspiration).

Certain aspects of the pathology of IAS aneurysm may have clinical implications: (1) fine fibrin-like tags have been noted on the aneurysm's convexity,causing a rough or ragged appearance of the latter, (2) rarely, small annular thrombi have been seen in the groove formed between the aneurysm and the limbic ridge, (3) multiple small perforations on the order of 1 or 2mm often occur at the apex of the IAS aneurysm, presumably the result of progressive thinning and eventual fenestrations (such tiny holes are not recognizable by conventional echocardiography but have been detected by TEE), and

(4) valve-patent patent foramen ovale and (5) mitral valve prolapse are more common in patients with IAS aneurysms than in the general population ***(Burston et al., 1990).***

Association with strokes:

There has been a surge of interest in the potential role of IAS aneurysms in the causation of cerebrovascular or other systemic embolism. The issue has been assessed using either conventional 2D echocardiography or TEE ***(Shenoy et al., 1987 ; Pearson et al., 1991).*** These studies have yielded the following findings: (1) TEE is more sensitive than transthoracic 2D echocardiography in detecting IAS aneurysms; (2) these aneurysms are more prevalent in patients with strokes than in those without strokes, and (3) a surprisingly high proportion of IAS aneurysms (about three-quarters) show right to left shunting on contrast echocardiography.

How do IAS aneurysms cause strokes? One theory is that small thrombi form in the aneurysm or the groove at the base of the aneurysm and are then swept into the left atrium to embolize. The other theory postulates that; venous thrombi pass through the inferior vena cava (IVC) and then through the fenestrations of the IAS aneurysm into the left side of the heart. Although micro bubbles from saline contrast injections into an arm vein are seen to pass into the left atrium in many or most of such patients, fenestrations that permit such small right-to-left shunts are probably too tiny to allow any but the smallest thrombi through ***(Windeker et al., 2002).***

Pathologic anatomy of atrial septal defects:

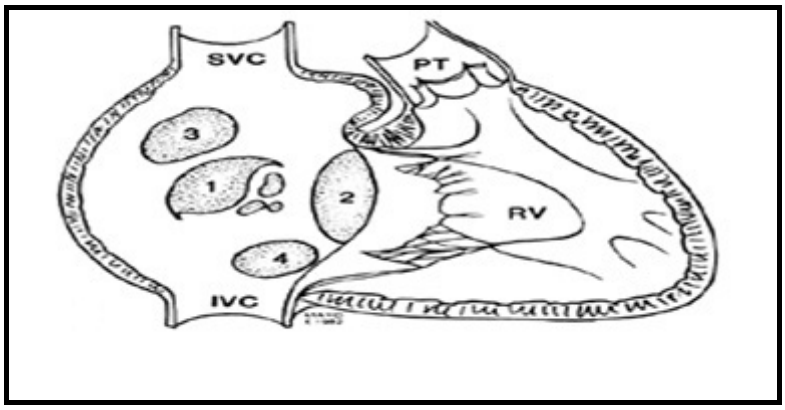

Figure (2): Schematic diagram showing the location of atrial septal defects, numbered in decreasing order of frequency: 1, secundum; 2, primum; 3, sinus venosus; 4, coronary sinus (CS) type. (IVC), inferior vena cava; (IVS), interventricular septum; (MV), mitral valve; (PT), pulmonary trunk; (RAA), right atrial appendage; (RV), right ventricle; (SVC), superior vena cava; (TV), tricuspid valve ***(Allen et al., 2008).***

Abnormal communications between the two atria constitute the most common major congenital heart defect encountered in the adult population ***(Latson, 2002)***.

The accurate classification of atrial septal defects is important, not because the location of the defect alters heamodynamics, but rather because of differences in the incidence of associated anomalies and differences in techniques of surgical repair. It's obviously important for the surgeon in planning repair to be aware of the anomalously connecting the pulmonary viens which accompany a sinus venosus defect or of the atrioventricular valve abnormalities which go with an ostuim primum defect (atrioventricular septal defect) ***(Beerman et al., 1987)***.

Ostium secundum ASD:

This is by far the most common variety, accounting for about two-thirds of all ASDs. They are restricted to the fossa ovalis region, though variable in size within the area enclosed by the ridge or the limbus of the fossa ovalis. An ASD can permit flow from the left to the right atruim or in a reversed direction and is a different heamodynamic situation from a valve-patent foramen ovale, which allows only right to left shunting if right atrial pressure exceeds left atrial pressure***.(Anderson et al., 2010).***

A secundum ASD can result either from excessive resorption of the septum primum or from deficient growth of the septum secundum. Some believe that gross right atrial dilatation, due to right –sided heart failure in a patient with patent foramen ovale, can stretch the latter so as to convert it into a true ASD in the sense that a hiatus is formed in part of the fossa ovalis floor.

A physiologically common atrium should not be confused with an anatomically common atrium characterized by total or almost complete absence of the atrial septum, an anomaly seldom seen in adults but often noted in infants and young children with endocardial cushion defects and or visceral heterotaxis ***(Anderson et al., 2010).***

The fossa ovalis is not always in an identical position within the atrial septum and in anatomic relation to various right atrial structures. In a study of 100 cases with ASD located