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ORIGINAL ARTICLE

Atrial flutter/fibrillation in patients receiving transcatheter closure of atrial septal defect

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Background/purpose: Atrial flutter/fibrillation (AFL/Af) is a common late complication in atrial septal defect (ASD) patients even after occluder implantation. We try to delineate the risk factors of persistent AFL/Af.
Methods: From 1998 to 2010, all patients older than 18 years of age who received ASD occluder implantation in our hospital were enrolled, and their records were retrospectively reviewed. In addition, renin–angiotensin system gene polymorphisms including angiotensinogen gene, A1166C polymorphism on the angiotensin II type I receptor gene, and insertion/deletion (I/D) patterns on the angiotensin-converting enzyme gene were checked using direct sequencing.
Results: A total of 517 patients (male/female 127/390) were enrolled. The mean age of patients receiving occluder deployment was 41.5 ± 14.5 years. Prior to occluder deployment, 3.9% of patients had persistent Af, 3.1% of patients had paroxysmal Af, and 0.8% had AFL. After a follow-up of 1894 patient-years, 3.5% had persistent Af and 1.9% of patients had paroxysmal Af. The greatest risk factors of AFL/Af genesis included age, occluder size, presence of multiple ASDs, and underlying thyroid or mitral valve disorder ($p < 0.001$, $p < 0.001$, $p = 0.033$, $p = 0.016$, and $p = 0.012$, respectively). Preoperative AFL/Af status is the most important factor in determining AFL/Af resolution and progression after an intervention. The renin–angiotensin system gene polymorphisms had no association with AFL/Af genesis, and progression or resolution after intervention.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: AFL/Af is common after ASD occluder implantation, and predisposed by older age, larger and multiple ASDs, and underlying disorders. Preoperative atrial arrhythmia status is the most important predictor of AFL/Af progression or resolution. Renin–angiotensin system gene polymorphisms had no association with AFL/Af.

Introduction

Atrial septal defect (ASD) is one of the most common congenital heart diseases in the adult population.[1] Prevalence was as high as 3.2/1000 live births in our previous population-based study.[2] Without treatment, the mortality and morbidity rate of hemodynamically significant ASD increases significantly after 25 years of age.[3] ASD occluder implantation is now the mainstay of treatment for hemodynamically significant ASD patients.[4] We reported no procedure mortality and low morbidity in the ASD patients undergoing ASD occluder implantation in 2008.[5] One of the most common late complications of ASD is atrial flutter/fibrillation (AFL/Af), which may be related to atrial dilatation after a long-term left to right shunt at the atrial level.[6] Without intervention, the prevalence of atrial arrhythmia increases significantly with age, with reported prevalence up to 13% after the age of 40 years, which is significantly higher than that in general population.[7] Although several reports have shown improvement of AFL/Af after ASD repair, either through surgical repair or after ASD occluder implantation, AFL/Af still complicates certain patients with an incidence of 10–25% at the short-term follow-up.[8,9]

AFL/Af is a common arrhythmia in elderly people. Several recent studies have shown a genetic predisposition, especially in the renin–angiotensin system (RAS) gene in Af patients.[10,11] Angiotensin II activation can trigger the proliferation of fibroblasts and cause myocardial fibrosis.[11,12] Moreover, RAS gene haplotypes have a strong association with Af.[10] Whether this association exists in these ASD patients remains unknown. Using a large ASD cohort, we attempted to define Af incidence and risk factors in ASD patients receiving occluder deployment. We also tried to identify the role of RAS gene polymorphisms in AFL/Af genesis.

Materials and methods

From 1998 to 2010, all adult patients (>18 years of age) who received ASD occluder implantation in National Taiwan University Hospital were retrospectively included in our study. The occluders we used were Amplatzer septal occluders (AGA Medical Corporation, Plymouth, MN, USA). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in an *a priori* approval by the Human Research Committee in National Taiwan University Hospital. The basic clinical characteristics, hemodynamic and cardiac catheterization reports, and follow-up data were collected through a chart review. We evaluated the pre- and postoperative clinical symptoms, electrocardiography (EKG) data, and 24-hour Holter study results. Persistent Af is defined as Af that persists for longer than 7 days (at all available EKG and Holter reports). Paroxysmal Af is defined as self-terminating Af if it ceased spontaneously during the 24-hour Holter examination, or if it did not persist in the whole surface EKG. The cardiac catheterization data, including pulmonary blood flow/systemic blood flow (Qp/Qs), pulmonary artery pressure, and occluder size, were also recorded. For patients with multiple ASDs, either multiple occluders were implanted or one occluder was deployed for the larger hole. For patients with significant pulmonary hypertension, fenestrated occluders were deployed for safety. We considered postoperative AFL/Af positive when the AFL/Af occurred after discharge. The arrhythmias developing during or immediately after the procedure, but self-terminating thereafter were regarded as negative, as these might relate to the procedure only. Mitral valve disease in our study is defined as more than moderate degree mitral regurgitation or mitral stenosis during echocardiography examination, no matter what the etiology is.

The RAS gene polymorphisms were analyzed after receiving informed consent. Five milliliters of fresh blood were withdrawn and stored in an EDTA tube. Genomic DNA was then extracted. Previously identified I/D polymorphisms on the angiotensin-converting enzyme (ACE) gene; T174M, M235T, G-6A, A-20C, G-152A, and G-217A polymorphisms on the angiotensinogen gene; and A1166C polymorphism on the angiotensin II type I receptor gene were checked using direct sequencing. Previously used primer pairs were used to amplify these exons.[10] A polymerase chain reaction was conducted using 50 ng template DNA, 2.5 pmol primers, 1 μL Mg^{2+} (25mM), and 1 μL Master Mix containing deoxyribonucleotide triphosphate (dNTP) and Taq polymerase. Dye terminator sequencing using an ABI 3730 automatic sequencer (Applied Biosystems, Foster City, CA, USA) was then performed. The results were analyzed using the Genotyper program (Life Technologies, San Francisco, CA, USA). The results of the RAS gene haplotypes were compared between those with and without AFL/Af.

Statistical analysis

The data were presented as mean (±standard deviation). Student *t* test was used for a numerical data comparison. The chi-square test and Fisher's exact test were used for a categorical data comparison. Logistic regression was used for multivariate risk factor analysis. Statistical significance was defined as $p < 0.05$.

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