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Thrombotic and Embolic Complications Associated With Atrial Arrhythmia After Fontan Operation

Role of Prophylactic Therapy

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ABSTRACT

BACKGROUND There are limited data about the risk of thrombotic and embolic complication (TEC) in adults with atrial arrhythmia after Fontan operation.

OBJECTIVES This study sought to determine the risk of TEC in this population and the role of anticoagulation therapy in TEC prevention.

METHODS This was a retrospective review of adults with atrial arrhythmia after Fontan operation who were evaluated at the Mayo Clinic between 1994 to 2014. TEC was classified into 2 groups: systemic TEC, defined as intracardiac thrombus, ischemic stroke, or systemic arterial embolus; and nonsystemic TEC, defined as Fontan conduit/right atrial thrombus or pulmonary embolus. Patients were divided into 3 groups: anticoagulation, antiplatelet, and no therapy cohorts.

RESULTS We followed 278 patients, mean age 31 ± 9 years, for 88 ± 14 months (1,464 patient-years). Patient groups included antiplatelet (n = 181), anticoagulation (n = 91), and no therapy (n = 6). There were 97 TEC in 81 patients (29%); 32 were systemic, yielding an event rate of 2.1 systemic TEC per 100 patient-years, and 65 were nonsystemic TEC, yielding an event rate of 4.4 nonsystemic TEC per 100 patient-years. Prevalence of TEC was 18% and 55% at 5 and 10 years, respectively. Atriopulmonary connection was a risk factor for TEC (hazard ratio: 2.31; 95% confidence interval: 1.61 to 4.64), and TEC were associated with higher risk of death and hospitalization ($p < 0.0001$). Anticoagulation was protective against TEC and resulted in a reduction of TEC risk by 2.5 TEC per 100 patient-years. Anticoagulation was also associated with lower risk of death and hospitalization ($p = 0.02$). Bleeding complications occurred in 21 (7%) patients and were similar in all groups.

CONCLUSIONS Anticoagulation was associated with lower TEC rate and lower risk of death and hospitalization, without a significant increase in bleeding risk. Perhaps anticoagulation should be the preferred preventive strategy. (J Am Coll Cardiol 2016;68:1312–9) © 2016 by the American College of Cardiology Foundation.

Atrial arrhythmias occur with a prevalence of more than 50% at 20 years after a Fontan procedure, with the highest risk occurring in the patients with atriopulmonary connection (1,2). In general, the presence of atrial arrhythmia is associated with an increased risk of thrombotic and embolic complications (TEC); this risk is heightened in the patient with history of a Fontan operation (3,4). This is related to the Fontan physiology and its associated low-flow state in the systemic and pulmonary circulation, atrial stasis, elevated central venous pressure resulting in hepatic dysfunction, coagulation

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abnormalities, ventricular dysfunction, and the common presence of right-to-left shunt (5–7).

The prevalence of TEC after a Fontan operation has ranged from 5% to 33% based on data derived from mixed cohorts of pediatric and adult patients with different rhythm status (8–14). The risk of TEC in adults with atrial arrhythmia after Fontan surgery is unknown, and there is no consensus on the most appropriate preventive strategy. This study sought to determine the risk of TEC in this population and the role of anticoagulation therapy in the prevention of TEC.

METHODS

We identified adult patients (>18 years) with a history of a Fontan operation and atrial arrhythmia (paroxysmal or persistent) followed at the Mayo Clinic from January 1, 1994 to June 30, 2014. Patients were excluded if they had a history of previous TEC or <12 months of follow-up from the time of atrial arrhythmia diagnosis.

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Atrial arrhythmia was defined as atrial flutter/intra-atrial re-entry tachycardia, atrial fibrillation, or ectopic atrial tachycardia documented on electrocardiogram, Holter monitor, event monitor, rhythm strip, and pacemaker/defibrillator intracardiac electrograms. Given the slow atrial re-entry cycle length that is commonly present in this group of patients, it was not possible to differentiate between a focal atrial tachycardia and re-entrant atrial tachycardia/atrial flutter; these diagnoses were pooled. Paroxysmal atrial arrhythmia was defined as atrial arrhythmia <7 days in duration, whereas persistent atrial arrhythmia was defined as occurring for >7 days.

TEC were classified into 2 groups: 1) systemic TEC, defined as intracardiac thrombus, ischemic stroke, or systemic arterial embolus; and 2) nonsystemic TEC, defined as Fontan conduit/right atrial thrombus or pulmonary embolus.

IMAGING. The imaging modalities used in this study were transthoracic echocardiogram (TTE), transesophageal echocardiogram, computed tomography (CT), or magnetic resonance imaging, including cardiac magnetic resonance imaging. TTE was considered the basic cardiac imaging modality, whereas other modalities were considered supplementary. The imaging reports of all patients were reviewed and the images for all patients with TEC were retrieved and viewed to confirm the diagnosis.

STUDY DESIGN. Patients were categorized based on the type of preventive medical therapy received during the study period: 1) no therapy group (did not receive any anticoagulation or antiplatelet therapy at the time of TEC or throughout the study period for patients without TEC); 2) antiplatelet therapy group (received antiplatelet therapy alone at the time of TEC or throughout the study period for patients without TEC); and 3) anticoagulation therapy group (received anticoagulation therapy with or without antiplatelet therapy at the time of TEC or throughout the study period for the patients without TEC).

For patients on warfarin therapy who experienced TEC, a subtherapeutic international normalized ratio (INR) was defined as INR below designated target range based on the last INR assay performed within 48 h of the TEC.

The primary objective was to determine the incidence and predictors of TEC in adult patients with Fontan palliation. Secondary objectives were to determine the risk of bleeding and the impact of TEC on the composite adverse event endpoint of heart failure hospitalization and all-cause mortality.

Major bleeding was defined as intracranial bleeding, pericardial or pleural hematoma requiring drainage, or any bleeding requiring transfusion of blood product. Minor bleeding was defined as cutaneous bleeding, epistaxis, gastrointestinal bleeding, or any bleeding event that did not meet the criteria for major bleeding.

STATISTICAL ANALYSIS. All statistical analyses were performed with JMP (version 10.0 software, SAS Institute Inc., Cary, North Carolina). Categorical variables were expressed as number (%) and continuous variables were expressed as mean ± SD or median (interquartile range) for skewed data. Categorical variables were compared using the chi-square test or Fisher exact test; continuous variables were compared with a 2-sided unpaired Student *t* test or Wilcoxon rank sum test, as appropriate. Cox proportional hazards models were used to identify predictors of TEC. Only the variables that achieved statistical significance on univariable analysis were used in the multivariable model. The risk associated with each variable was expressed as a hazard ratio (HR) and 95% confidence interval (CI). The TEC rates and composite adverse event rates were calculated with the Kaplan-Meier method and compared using the log-rank test. Any p value <0.05 was considered significant.

RESULTS

There were 278 patients who met the inclusion criteria; mean age was 31 ± 9 years and the mean

ABBREVIATIONS AND ACRONYMS

APC = atriopulmonary connection

CI = confidence interval

CT = computed tomography

HR = hazard ratio

INR = international normalized ratio

TEC = thrombotic and embolic complication

TTE = transthoracic echocardiogram