Atrial Arrhythmias in Adults With Congenital Heart Disease

Judith Bouchardy, MD; Judith Therrien, MD; Louise Pilote, MD, MPH, PhD; Raluca Ionescu-Ittu, MSc; Giuseppe Martucci, MD; Natalie Bottega, MD; Ariane J. Marelli, MD

Background—Atrial arrhythmias increase disease burden in the general adult population. Adults with congenital heart lesions constitute a rapidly growing group of patients with cardiovascular disease. We hypothesized that atrial arrhythmias increase with age and impair health outcomes in this population.

Methods and Results—We conducted a population-based analysis of prevalence, lifetime risk, mortality, and morbidity associated with atrial arrhythmias in adults with congenital heart disease from 1983 to 2005. In 38,428 adults with congenital heart disease in 2005, 5812 had atrial arrhythmias. Overall, the 20-year risk of developing atrial arrhythmia was 7% in a 20-year-old subject and 38% in a 50-year-old subject. More than 50% of patients with severe congenital heart disease reaching age 18 years developed atrial arrhythmias by age 65 years. In patients with congenital heart disease, the hazard ratio of any adverse event in those with atrial arrhythmias compared with those without was 2.50 (95% confidence interval, 2.38 to 2.62; P<0.0001), with a near 50% increase in mortality (hazard ratio, 1.47; 95% confidence interval, 1.37 to 1.58; P<0.001), more than double the risk of morbidity (stroke or heart failure) (hazard ratio, 2.21; 95% confidence interval, 2.07 to 2.36; P<0.001), and 3 times the risk of cardiac interventions (hazard ratio, 3.00; 95% confidence interval, 2.81 to 3.20; P<0.001).

Conclusions—Atrial arrhythmias occurred in 15% of adults with congenital heart disease. The lifetime incidence increased steadily with age and was associated with a doubling of the risk of adverse events. An increase in resource allocation should be anticipated to deal with this increasing burden. (Circulation. 2009;120:1679-1686.)

Key Words: arrhythmia ■ epidemiology ■ heart defects, congenital ■ population

C ongenital heart disease (CHD) constitutes the most prevalent form of major birth defects and currently affects >1% of all children.1 Because of improvements in diagnosis and treatment, the population of adult patients with congenital heart disease (ACHD) is growing and aging.1 Arrhythmias play an important role in the management of ACHD patients.2-4 Previous lesion-specific studies3,5-8 have identified atrial flutter, intra-atrial reentry tachycardia, and atrial fibrillation as common late sequelae.9-16 Although atrial arrhythmias have been well studied in the general adult population,17-19 no population data have been generated in ACHD patients.

Our objectives were 3-fold: to determine the overall prevalence of atrial arrhythmias in ACHD patients in 2005, to estimate age-related lifetime risk of developing atrial arrhythmias, and to compare adverse outcomes in individuals with and without atrial arrhythmias in terms of mortality, morbidity, and need for cardiac interventions.

Data Sources
In Quebec, Canada’s second largest province, a unique healthcare number is assigned to all individuals at birth and is systematically linked to all diagnoses, hospitalizations, and health services rendered for the duration of a patient’s life. Administrative databases include the physicians’ services and drug claims database (Régie de l’Assurance Maladie du Québec), the hospital discharge summary database (Med-Echo), and the Quebec Health Insurance Board. A province-wide, population-based CHD database was created at our institution by merging the province’s 3 administration databases.1,20 During this period, diagnostic codes adhered to the International Classification of Diseases, Ninth Revision (ICD-9). Patients were identified with CHD if they had at least 1 diagnostic code for CHD and/or a CHD-specific surgical procedure. Provider codes were used to select diagnoses made by primary care physicians or cardiovascular medical specialists and procedures performed by cardiovascular surgeons. Patients were assigned 1 or 2 CHD diagnoses by primary care physicians or cardiovascular medical specialists and procedures performed by cardiovascular surgeons. Patients were assigned 1 or 2 CHD diagnoses with the use of a previously defined hierarchical algorithm.20 CHD severity was defined on the basis of anatomic diagnosis20 to include tetralogy of Fallot (TOF) and truncus arteriosus, endocardial cushion defects, transposition complex, univentricular heart, and hypoplastic left heart syndrome as “severe CHD” and the remaining diagnoses as

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“other CHD lesions” (atrial septal defect; ventricular septal defect; patent ductus arteriosus; aortic coarctation; anomalies of the pulmonary artery; congenital tricuspid, pulmonary, mitral, or aortic valve disease; anomalies of the great veins; and unspecified congenital anomalies of the heart and great vessels). All information was cross-referenced between outpatient and inpatient data sources. By law, attestation of death is sent to the Quebec Health Insurance Board, making documentation of death complete in the database, whether it occurs in or out of the hospital.

The CHD database in the province of Quebec therefore contained comprehensive longitudinal, demographic, diagnostic, and therapeutic records of all patient-linked encounters with the healthcare system from January 1, 1983, to December 31, 2005 (inclusive) for all Quebec residents identified with CHD. The study was approved by the McGill University Health Centre ethics board and the Quebec government agency responsible for privacy of access to information.

Study Population
The study’s population cohorts were derived from Quebec’s CHD database (Figure 1). All patients were either adults or had turned 18 years of age during the study period. Patients were included as having atrial arrhythmia if a diagnosis of atrial fibrillation or intra-atrial reentry tachycardia (ICD-9 code 4273) was made by selected specialists (anesthetists, cardiologists, cardiothoracic surgeons, emergency doctors, general practitioners, internists, neurologists, and pediatricians) over the 18-year study period.

The prevalence of atrial arrhythmias in 2005 was estimated with the use of a cohort of CHD patients aged >18 years and alive on January 1 of that year. For estimation of age-related lifetime risk, we defined an incidence cohort that included subjects free of atrial arrhythmia in January 1, 1988, who were or became adults between 1988 and 2005. The incidence cohort started in 1988 (ie, 5 years after the start of the database) to allow the identification and exclusion of prevalent atrial arrhythmia cases from the incidence cohort. Subjects in the incidence cohort who developed atrial arrhythmia were considered incident atrial arrhythmia cases and were used in the calculation of the age-specific lifetime atrial arrhythmia risk.

For comparison of outcomes in those with and without atrial arrhythmias, we created a matched outcome cohort in which atrial arrhythmia cases identified in the incidence cohort were matched to non–atrial arrhythmia controls by age, sex, severity of CHD, and time of the first atrial arrhythmia diagnosis of the case. In the main analysis, controls who developed atrial arrhythmia during the follow-up were followed as control until they developed the event or until the end of the study, regardless of whether they developed AA during the follow-up. In sensitivity analysis, these patients were censored at the time during follow-up when they developed AA (see Methods; study population and statistical section).

Figure 1. Study population and design, illustrating the derivation of the study population and cohorts. AA indicates atrial arrhythmia.
patients were censored at the time during follow-up when they developed atrial arrhythmia. We excluded from the cohort 11 atrial arrhythmia cases for which a control could not be found.

Study Design
The retrospective cohorts were open and followed for a maximum of 18 years. For the matched-cohort analysis, time zero for each case-control pair in this matched cohort design was the time of the first atrial arrhythmia diagnosis for the case. Once selected as a control, a subject was kept in all analyses as a control, regardless of whether he or she subsequently developed atrial arrhythmia (n=1372) or not. Once patients received an atrial arrhythmia diagnosis, they were considered “cases” even if the arrhythmia was paroxysmal and not chronic.

Outcomes were defined as mortality, morbidity, interventions, and the combination of the 3 (any adverse event). Mortality was defined as death during follow-up in the matched outcomes cohort. Morbidity was defined as an episode of congestive heart failure and/or stroke during the follow-up in the matched outcomes cohort and was measured with the use of ICD-9 diagnostic codes in the 2 administrative databases. Interventions were separated into surgery and percutaneous interventions and were identified by procedural billing codes in the medical claims database. Surgery was further divided into cardiac congenital surgery, cardiac noncongenital surgery (coronary artery bypass grafting), and arrhythmia surgery (ablation procedures and device implantation). Adverse event is defined as the first occurrence of any of the aforementioned 3 clinical outcomes during the follow-up.

Confounders were defined as clinical diagnoses known to be risk factors for atrial arrhythmia and each of the 3 outcomes. These included a history of hypertension, coronary artery disease, diabetes mellitus, stroke, heart failure, and recent cardiac surgery. The medical confounders were measured in the 5 years before the time zero in the matched outcomes cohort with the use of ICD-9 codes in the 2 administrative databases, and recent cardiac surgery was measured in the 30 days before time zero with the use of procedure claim codes.

Statistical Analysis
Descriptive statistics include medians, interquartile ranges, and proportions. Prevalence of atrial arrhythmia in the year 2005 (Figure 1) was measured in the prevalence cohort as the ratio between the number of ACHD patients alive in 2005 who had an atrial arrhythmia diagnosis from 1983 to 2005 and the total ACHD population alive in 2005.

Lifetime cumulative incidence of atrial arrhythmia in ACHD patients was calculated in the incidence cohort with the use of the Practical Incidence Estimators methodology.22,23 The Practical Incidence Estimators methodology estimates the lifetime cumulative incidence of atrial arrhythmia (ie, cumulative risk of developing atrial arrhythmia from a baseline age to age 75 years in patients free of atrial arrhythmia at the baseline age) adjusted for competing risk of death. We estimated the lifetime cumulative incidence in ACHD patients with severe and other lesions from different baseline ages (18, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, and 70 years). From these analyses, we report the lifetime risks of developing atrial arrhythmia and the corresponding 95% confidence intervals (CIs).

Cox multiple regression analysis was performed with adjustment for hypertension, diabetes mellitus, ischemic heart diseases, stroke, and heart failure, with 1 model for each adverse outcome. Adjustment was not necessary for age, sex, and severity of CHD because cases and controls were matched for these variables at the design stage.

The multiple Cox regression analysis was not stratified on the matched pair because with administrative databases, no imbalance was expected to arise between the exposed and unexposed study subjects with respect to loss of follow-up and/or missing data.24,25 All confounders adjusted for through modeling were defined a priori and kept in the model regardless of their statistical significance. The proportionality of hazards assumption was tested with the use of the −log [log(S(T))] plot, and no violation was detected. From this analysis, we report hazard ratios (HRs) for atrial arrhythmia versus non–atrial arrhythmia and 95% CIs. A sensitivity analysis was performed in which case-control pairs were censored at the time when the control developed an atrial arrhythmia. All statistical analyses were performed with the use of SAS statistical software (version 9.1).

Results
Baseline Characteristics and Prevalence of Atrial Arrhythmia
The patient’s baseline characteristics and prevalence of atrial arrhythmia in different subgroups are presented in Table 1. In 2005, 38 430 CHD patients were alive, of whom 5812 had atrial arrhythmia, corresponding to an overall prevalence of

<table>
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<th>Table 1. Baseline and Clinical Characteristics in 2005 in ACHD Patients With and Without Atrial Arrhythmias</th>
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<td>2005 Prevalence Cohort</td>
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<td>Hypertension diagnosis, n (%)</td>
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<td>Acute myocardial infarction during a hospitalization, n (%)</td>
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Baseline and clinical characteristics of the patients in the prevalence cohort for the year 2005 and overall prevalence (as percentage) in the prevalence cohort as well as prevalence in different cardiac congenital lesions are shown. AA indicates atrial arrhythmia; IQR, interquartile range; and NA, not applicable.
Patients in the atrial arrhythmia population were older (median age 70 years old versus 38 in the non–atrial arrhythmia population), they had undergone more CHD surgeries (53% versus 14%), and they had more cardiovascular risk factors. Patients with severe CHD in the prevalence cohort were younger, with a median age of 30 years, and they represented 9% of the overall population as well as 9% of the atrial arrhythmia population, with a prevalence of 144/1000. Prevalence varied according to lesions, from 48/1000 in patent ductus arteriosus to 330/1000 in Ebstein anomaly.

**Age-Related Lifetime Risk**

Lifetime risks up to age 75 years for atrial arrhythmia in severe and other CHD at selected index ages are shown in Table 2. Overall, the 20-year risk of developing atrial arrhythmia was 7% in a 20-year-old patient and increased to 38% in a 55-year-old patient, as shown in Figure 2A. More than 50% of patients with severe CHD reaching 18 years of age developed atrial arrhythmia by age 65 years (Figure 2B). For other CHD patients, the lifetime risk to age 70 was 47%, such that nearly 1 in 2 patients with ACHD aged 20 years developed atrial arrhythmia by age 70 years (Table 2).

**Outcomes**

ACHD patients with atrial arrhythmia present a significant increased risk in all outcomes compared with ACHD patients without atrial arrhythmia (Figure 3). The hazard ratio (HR) of any adverse event in those with atrial arrhythmia compared with those without was 2.50 (95% CI, 2.38 to 2.62; \( P < 0.001 \)), with a near 50% increase in mortality, corresponding to a HR of 1.47 (95% CI, 1.37 to 1.58; \( P < 0.001 \)). There was more than double the risk of stroke and heart failure with a HR of 2.21 (95% CI, 2.07 to 2.36; \( P < 0.001 \)) and 3 times the risk of cardiac interventions with a HR of 3.00 (95% CI, 2.81 to 3.20; \( P < 0.001 \)).

In a sensitivity analysis performed to determine the impact of censoring cases and controls when they developed atrial arrhythmia, the impact of atrial arrhythmia on outcomes was even stronger, with a HR of 2.91 (95% CI, 2.76 to 3.07; \( P < 0.001 \)) for any adverse event, 1.88 (95% CI, 1.73 to 2.04; \( P < 0.001 \)) for mortality, 2.62 (95% CI, 2.44 to 2.82; \( P < 0.001 \)) for morbidity, and 3.85 (95% CI, 3.58 to 4.14; \( P < 0.001 \)) for interventions.

**Discussion**

This population-based study documents the prevalence and lifetime risk of atrial arrhythmia in adults with CHD and quantifies their impact on adverse events. In this cohort of 38 430 adults with CHD, atrial arrhythmias were common, with a prevalence of 15.1%. The prevalence of atrial fibrillation in the general population has been measured to be between 0.4% and 5.5%,\(^{17,26–29}\) depending on age. In our
relatively young population, with a median age of 42 years in 2005, the prevalence of atrial arrhythmia was 15.1%, which is nearly 3 times higher than in the general population.

The prevalence of atrial arrhythmia was measured in subgroups of ACHD patients in our population-based CHD database and is in agreement with published data from lesion-specific clinical studies. In TOF, the reported prevalence varied from 2.5% in a Japanese patient population to >30% in a Dutch patient population. A Canadian retrospective study from the Toronto Congenital Cardiac Centre looking at the prevalence of atrial arrhythmia in TOF reported a prevalence of 12%, which is comparable to our finding of a 15.5% prevalence in patients with TOF. The prevalence of atrial arrhythmia in our study was even higher in Ebstein anomaly (33.0%), transposition complex (28.0%), univentricular heart (24.2%), and atrial septal defect (18.9%), consistent with reports in the literature.

In the growing population of adults with CHD, we present new knowledge on the lifetime incidence of atrial arrhythmia. The risk of atrial fibrillation in the general population has been well described in men and women aged >40 years. In the Framingham Heart Study, the lifetime risk of atrial fibrillation was 26% for 40-year-old men and 23% for 40-year-old women. In our study, lifetime risk was calculated up to age 75 years and was 63% in 20-year-old patients with severe CHD and 47% in 20-year-old patients with other forms of CHD. In the Rotterdam study, the 20-year risk of developing atrial fibrillation was 7% for 55-year-old women and 10% for 55-year-old men. In our study, overall, the 20-year risk of developing atrial arrhythmia was 7% in a 20-year-old patient and increased to 38% in a 50-year-old patient. Strikingly, our findings suggest that 20-year-old patients with CHD have a 20-year risk of developing atrial arrhythmia equivalent to that of 55-year-old women in the general population. These findings support the observation that patients with CHD are young patients with aged hearts.

We present information quantifying the impact of atrial arrhythmia on mortality in ACHD. In the general population, atrial fibrillation has been associated with reduced survival, most notably in patients with cardiac comorbidities. In our study, mortality increased within the first year after the first diagnosis of atrial arrhythmia, persisting in long-term follow-up in all patient subgroups and in all age categories, increasing the risk of death by nearly 50%. Mortality related to sudden death and ventricular arrhythmias has been reported in the general ACHD population, as well as for...
specific lesions such as TOF or the Fontan procedure. Studies examining the impact of atrial fibrillation or flutter on mortality have also shown an increase in mortality, particularly in patients with TOF or the Fontan procedure, in whom it has been linked to thromboembolic death.

In the general population, atrial fibrillation can be risk stratified to predict stroke rates. No such data exist in the CHD population. The risk of stroke in ACHD patients has been described in relation to persistence of shunts and paradoxical emboli and Eisenmenger complex. In this study, we demonstrate a 50% increase in the risk of stroke in patients with ACHD and atrial arrhythmia compared with those with CHD and no atrial arrhythmia. Further studies are needed to construct a risk score to refine our understanding of the interaction between atrial arrhythmia and CHD-specific comorbidities to determine possible benefits of anticoagulation therapy.

Not surprisingly, the presence of atrial arrhythmia conferred a 2- to 3-fold increased risk of congestive heart failure and the occurrence of cardiac intervention in ACHD. These data underscore the need to look for hemodynamically reversible causes of arrhythmia to maximize precarious ventricular function in patients with systemic right ventricles and univentricular hearts. In patients with TOF, atrial arrhythmias have been linked to significant pulmonary regurgitation, reflecting the need for timely intervention to protect right ventricular function.

The limitations of our study should be noted. This study is retrospective and uses administrative databases in which diagnoses can be misclassified because of coding errors for CHD diagnoses and atrial arrhythmia. Because 4-digit ICD-9 codes were used, we were not able to distinguish between certain subtypes of CHD (eg, complete transposition of great arteries and congenitally corrected transposition of the great arteries) that have the same 4-digit number (7451). We minimized misclassification by using all available data for a given subject aged >18 years, including inpatient, outpatient, procedural, and provider information. This was done by cross-referencing our data sources among the 3 available province-wide administrative databases. Manual audits of 28% of the raw data were performed to detect and adjust for discrepancies between data sources. We were limited by billing codes for the diagnosis of atrial arrhythmia because there is a single 4-digit ICD-9 code for atrial arrhythmia. Thus, we were not able to distinguish between atrial fibrillation, atrial flutter, and intra-atrial reentrant tachycardia. For the same reasons, we could not verify the specificity of the atrial arrhythmia diagnosis by ECG. To minimize false-positive results, we preselected specialists from whom we accepted the diagnosis of atrial arrhythmia. Even though we may have missed the diagnosis of atrial arrhythmia, this would bias our results toward the null hypothesis, strengthening our conclusions. Although our target population was the CHD population of the entire province of Quebec, we may have excluded subjects who failed to come into contact with the healthcare system during the 18 years of follow-up or those who may have migrated out of the province. However, utilization of health services in Quebec was 80% for the
population at large from 1998 to 2004, and we have previously shown that 87% of adults with CHD used specialist services and 51% were hospitalized from 1996 to 2000.\textsuperscript{20} Migration rates in Quebec suggest that we may have overestimated the size of the CHD population by only 0.05%. For the matched cohort analysis of outcomes, once selected as a control, a subject was kept in all analyses as a control, regardless of whether he or she subsequently developed atrial arrhythmia. However, the sensitivity analysis performed censoring the case-control pairs at the time when the control developed atrial arrhythmia demonstrated that the impact of atrial arrhythmia on outcomes was even stronger. This suggests that any bias from our study may have been toward the null hypothesis. A limitation of our outcomes analysis is that subjects who developed atrial arrhythmia later in the database were less likely to be treated as cases. However, the random selection of the controls within each risk set ensures that the depletion of cases is independent of all factors that might affect the onset of atrial arrhythmia and/or the outcomes and thus has minimal impact on the study generalizability. It must be emphasized that we reported an association between atrial arrhythmia and outcomes, and our study was not designed to demonstrate that maintaining those patients in sinus rhythm would lead to fewer adverse outcomes. We reported all-cause mortality rather than cardiovascular mortality. Because atrial arrhythmia is expected to have a higher impact on cardiovascular mortality than on other-causes mortality, the impact of atrial arrhythmia on cardiovascular mortality may be higher than the one we estimated for all-cause mortality. The province of Quebec accounts for 25% of Canada’s adults, making our results generalizable to the rest of Canada. Although this is not a US-based population study, standards of care for CHD patients have largely followed North American trends and guidelines, with data from this country’s largest centers yielding surgical outcomes comparable to those of US CHD surgical centers.\textsuperscript{46,47}

**Conclusions**

Heart lesions constitute the most common group of congenital malformations. As this population ages and increases in size, acquired cardiovascular risk factors will compound the risks associated with atrial arrhythmias. We have provided new information, the results of which will inform future clinical trials aimed at reducing the morbidity and mortality associated with atrial arrhythmias in ACHD. Although evidence-based therapy is well established for the treatment of atrial fibrillation in the general adult population, data from small centers and lesion-specific studies have been insufficient to provide a basis for risk stratification aimed at producing comparable data in patients with CHD. Our study will provide a departure point for the generation of such data.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

This is the first population study to analyze lifetime risk of developing atrial arrhythmia in adults with congenital heart disease. The population of adults with congenital heart disease is growing and aging, and arrhythmias play a major role in the long-term follow-up. In a population of >36 000 adults with congenital heart disease, the overall prevalence of atrial arrhythmias is 15%, and the lifetime risk of developing atrial arrhythmia ranges between 48% and 63%, depending on the severity of the congenital heart disease. This implies that young adults have nearly 1 chance in 2 of developing atrial arrhythmia if they reach 75 years of age. This study compares outcomes in those with and without atrial arrhythmia and reveals significantly increased adverse outcomes associated with atrial arrhythmia, with a near 50% increase in mortality and double the risk of morbidity (stroke or heart failure). In conclusion, this study provides new, comprehensive data on atrial arrhythmias in adults with congenital heart disease, showing that atrial arrhythmias are frequent in this population and significantly alter outcomes. From a clinical point of view, these findings underscore the need for close follow-up of these patients with special attention to their rhythmic status.
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