UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de médecine

Service de cardiologie

Arythmies supraventriculaires chez les patients adultes porteurs d'une cardiopathie congénitale

THESE

préparée sous la direction du Docteur Nicole Sekarski

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Judith BOUCHARDY CLÉMENT

Médecin diplômé de la Confédération Suisse
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Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

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Rapport de synthèse

Mon projet de recherche s'est articulé autour des arythmies supraventriculaires chez les patients adultes porteurs d'une cardiopathie congénitale (Adults with Congenital Heart Disease ou ACHD). Grâce aux progrès de la chirurgie cardiaque et de la cardiologie, la survie à l'âge adulte des enfants nés avec une malformation cardiaque est excellente et la population des ACHD ne cesse de croitre, tout en vieillissant. Les arythmies cardiaques sont une complication à long terme bien connue chez ces patients et une des principales causes de mortalité et de morbidité.

Mon travail de recherche comporte une perspective épidémiologique avec une étude de population et une perspective anatomique, avec une étude d'imagerie cardiaque par échographie.

1.Étude épidémiologique : Arythmies auriculaires (AA) chez les patients porteurs d'une cardiopathie congénitale.

Sous le titre anglais *Atrial Arrhythmias in Adults with Congenital Heart Disease,* cette étude a été publiée dans le journal américain *Circulation*. A travers les résultats de cette étude, j'ai démontré, pour la première fois dans une aussi grande population, que les AA étaient fréquentes chez les patients ACHD, que le risque à long-terme pour ces patients de développer des AA était élevé, et que le développement d'AA avait un impact négatif en termes de mortalité, de morbidité et d'intervention.

2. Étude anatomique : Les paramètres échographiques associés à la fibrillation auriculaire (FA) chez les patients adultes porteurs d'une cardiopathie congénitale.

Sous le titre anglais *Mirror image atrial dilatation in Adult Patients with Atrial Fibrillation and Congenital Heart Disease*, cette étude a été publiée dans le journal américain *International Journal of Cardiology*. J'ai démontré dans cette étude que les patients ACHD avec une pathologie isolée du cœur gauche présentaient une dilatation progressive de l'oreillette gauche (OG) lorsqu'ils développaient de la FA. Chez les patients avec une pathologie isolée du cœur droit, j'ai décrit une image « *miroir* » : l'oreillette droite (OD) était toujours plus grande que l'OG et présentait une dilatation progressive lors de FA. Ces résultats soutiennent l'hypothèse que la FA pourrait provenir de l'OD dilatée chez les patients ACHD avec une pathologie du cœur droit et ouvrent de nouvelles perspectives diagnostiques et thérapeutiques chez ces patients.

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Atrial Arrhythmias in Adults With Congenital Heart Disease

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Atrial Arrhythmias in Adults With Congenital Heart Disease

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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

Congenital 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 studies[3,5–8] 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.

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Clinical Perspective on p 1686

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.

Methods

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 with the use of a previously defined hierarchical algorithm.[20] CHD severity was defined on the basis of anatomic diagnosis[20] 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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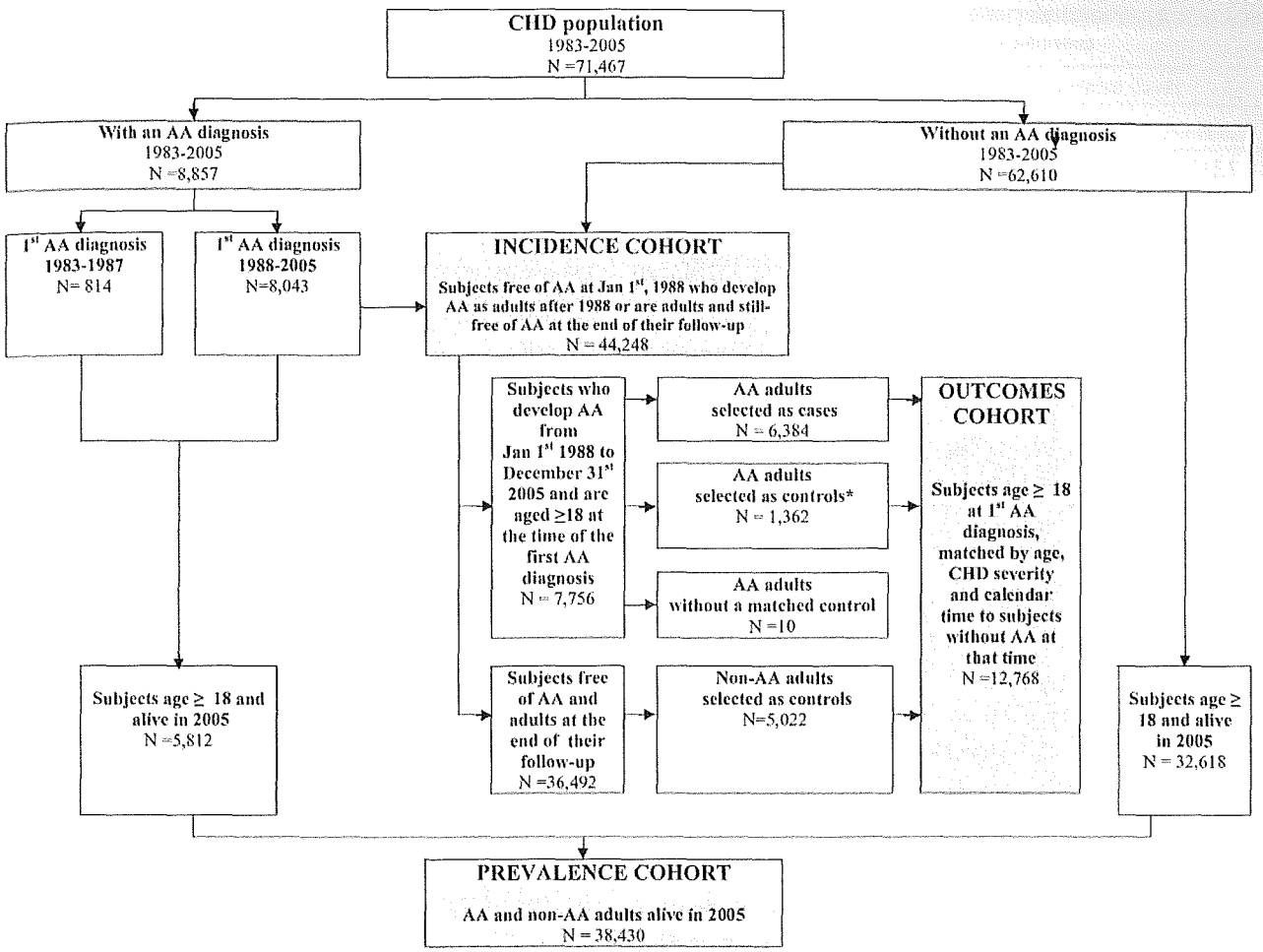

* In the main analysis, those patients were followed as control until they developed the event or until the end of the study, regardless whether they developed AA during the follow-up. In sensitivity analysis, these patients were censored at the time during follow-up when they developed AA (see Methods: study population and statistical section).

Figure 1. Study population and design, illustrating the derivation of the study population and cohorts. AA indicates atrial arrhythmia.

"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 atrial arrhythmia during the follow-up. In sensitivity analysis, these pa-

tients 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.[21] 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).

Table 1. Baseline and Clinical Characteristics in 2005 in ACHD Patients With and Without Atrial Arrhythmias

	2005 Prevalence Cohort		
	AA Adults	Non-AA Adults	Prevalence, %
Overall	5812	32 618	15.1
Sociodemographic characteristics			
Median age in 2005, y (IQR)	70 (56–79)	38 (26–56)	NA
Severe CHD, n (IQR)	41 (31–56)	28 (23–39)	NA
Male, n (%)	2801 (48)	14 015 (43)	16.6
Selected underlying CHD diagnoses			
Atrioventricular canal defect	98	1186	7.6
TOF/truncus arteriosus	205	1114	15.5
Transposition of the great arteries	120	308	28.0
Univentricular hearts	77	241	24.2
Ebstein's malformation of tricuspid valve	37	75	33.0
Atrial septal defect	1362	5835	18.9
Ventricular septal defect	322	6248	4.9
Coarctation of the aorta	58	694	7.6
Patent ductus arteriosus	30	596	4.8
Clinical characteristics			
CHD surgery history, n (%)	3062 (53)	4624 (14)	NA
Hypertension diagnosis, n (%)	4038 (69)	9597 (29)	NA
Acute myocardial infarction during a hospitalization, n (%)	681 (12)	841 (3)	NA
Diabetes mellitus, n (%)	1577 (27)	3360 (10)	NA

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.

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 2. Cumulative Risk of Atrial Arrhythmias in Percentages at Different Ages in Patients With Severe and Other CHD

	Period Risk in 5-Year Intervals, %										
Age, y	5	10	15	20	25	30	35	40	45	50	Lifetime Risk* (95% CI)
Severe CHD											
20	3.7	8.4	12.8	18.0	22.7	30.5	37.0	43.3	50.4	57.1	63.0 (58.8–67.2)
25	4.9	9.5	15.1	20.1	28.3	35.1	41.8	49.2	56.3		62.6 (58.1–67.0)
30	5.0	10.9	16.3	25.1	32.3	39.5	47.5	55.1			61.8 (57.1–66.5)
35	6.3	12.0	21.3	29.1	36.7	45.2	53.2				60.3 (55.3–65.2)
40	6.2	16.4	24.9	33.2	42.5	51.3					59.0 (53.8–64.3)
45	11.1	20.3	29.4	39.5	49.1						57.5 (51.8–63.3)
50	11.0	21.8	33.8	45.2							55.2 (48.6–61.9)
55	12.5	26.5	39.7								51.3 (44.3–58.5)
60	16.6	32.4									46.3 (38.3–54.3)
65	19.6										36.9 (28.3–45.5)
70											22.7 (14.2–31.2)
Other CHD											
20	1.0	2.0	3.4	5.4	8.6	12.9	17.8	23.9	31.0	38.8	46.7 (45.8–67.6)
25	1.0	2.5	4.5	7.8	12.2	17.1	23.4	30.5	38.4		46.5 (45.6–47.4)
30	1.5	3.6	6.9	11.4	16.4	22.7	30.0	38.1			46.2 (45.3–47.2)
35	2.1	5.5	10.1	15.2	21.7	29.1	37.4				45.7 (44.8–46.6)
40	3.5	8.2	13.4	20.1	27.8	36.2					44.8 (43.9–45.8)
45	4.9	10.4	17.4	25.5	34.3						43.3 (42.4–44.3)
50	5.9	13.4	21.9	31.4							41.0 (40.1–42.0)
55	8.1	17.4	27.7								38.2 (27.2–39.2)
60	10.4	21.9									33.6 (32.6–34.6)
65	13.4										26.9 (26.0–27.9)
70											16.2 (15.7–17.5)

Lifetime risks for atrial fibrillation in severe and other CHD at selected index ages are shown.
*To age 75 years.

151/1000. 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 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; $P<0.0001$), 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

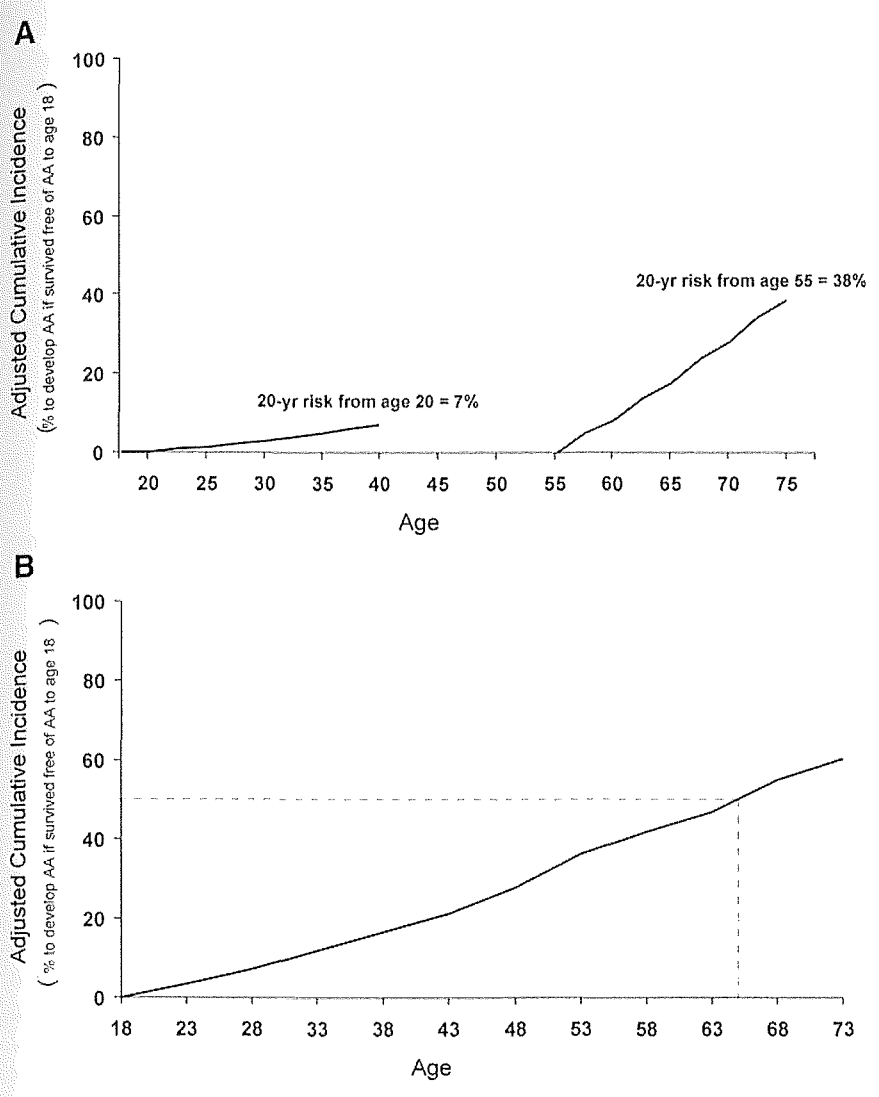

Figure 2. Lifetime cumulative incidence of atrial arrhythmias in ACHD. A, Overall 20-year risk of 7% of developing atrial arrhythmia (AA) from the age of 20 years and 38% from the age of 55 years. B, Lifetime risk of developing atrial arrhythmia in patients with severe CHD. The cumulative incidence is 50% by age 65 years.

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[30] to >30% in a Dutch patient population.[10] A Canadian retrospective study from the Toronto Congenital Cardiac Centre looking at the prevalence of atrial arrhythmia in TOF reported a prevalence of 12%,[9] 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.[11,13,15,31–33]

In the growing population of adults with CHD,[1] 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.[17,19] In the Framingham Heart Study,[19] 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,[17] 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.[34]

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.[18,26,35,36] 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,[4,37] as well as for

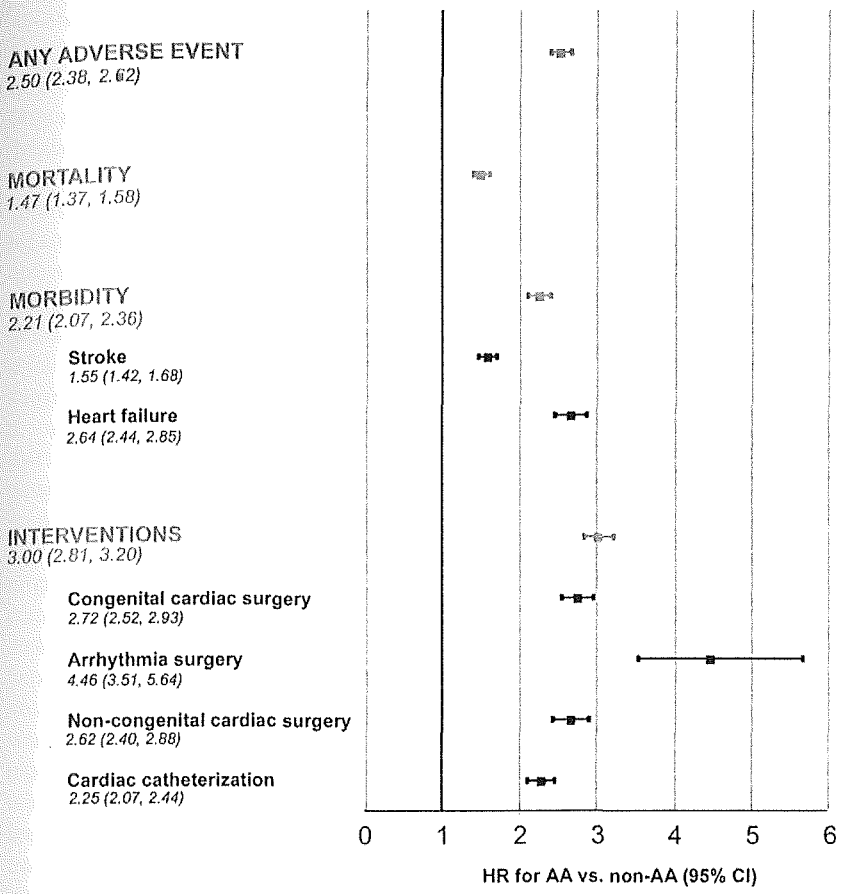

Figure 3. HR for outcomes in ACHD with and without atrial arrhythmias (AA). The HR for all outcomes in patients with atrial arrhythmia compared with patients without is shown. Atrial arrhythmia confers an increased risk in all adverse events, represented by a HR >1.

specific lesions such as TOF[38] or the Fontan procedure.[39] Studies examining the impact of atrial fibrillation or flutter on mortality have also shown an increase in mortality, particularly in patients with TOF[9,10] or the Fontan procedure, in whom it has been linked to thromboembolic death.[39]

In the general population, atrial fibrillation can be risk stratified to predict stroke rates.[35,36,40] 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[41] and Eisenmenger complex.[42] 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.[43,44] In patients with TOF, atrial arrhythmias have been linked to significant pulmonary regurgitation,[9] reflecting the need for timely intervention to protect right ventricular function.[45]

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.[1] 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.[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, but 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.[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

1. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–172.
2. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation*. 2007;115:534–545.
3. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart*. 2002;87:383–389.
4. Walsh EP. Arrhythmias in patients with congenital heart disease. *Card Electrophysiol Rev*. 2002;6:422–430.
5. Harris L, Gow RM, Kirsh JA, Klein GJ, Siu SC. Atrial arrhythmias and special circumstances. *Can J Cardiol*. 2005;21(suppl B):51B–60B.
6. Li W, Somerville J. Atrial flutter in grown-up congenital heart (GUCH) patients: clinical characteristics of affected population. *Int J Cardiol*. 2000;75:129–137; discussion 138–139.
7. Akar JG, Kok LC, Haines DE, DiMarco JP, Mounsey JP. Coexistence of type I atrial flutter and intra-atrial re-entrant tachycardia in patients with surgically corrected congenital heart disease. *J Am Coll Cardiol*. 2001; 38:377–384.
8. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. *Am J Cardiol*. 2002;90:338–340.
9. Harrison DA, Siu SC, Hussain F, MacLoghlin CJ, Webb GD, Harris L. Sustained atrial arrhythmias in adults late after repair of tetralogy of Fallot. *Am J Cardiol*. 2001;87:584–588.
10. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot: correlations with clinical, exercise, and echocardiographic findings. *Circulation*. 1995;91: 2214–2219.
11. Ghai A, Harris L, Harrison DA, Webb GD, Siu SC. Outcomes of late atrial tachyarrhythmias in adults after the Fontan operation. *J Am Coll Cardiol*. 2001;37:585–592.
12. Weipert J, Noebauer C, Schreiber C, Kostolny M, Zrenner B, Wacker A, Hess J, Lange R. Occurrence and management of atrial arrhythmia after long-term Fontan circulation. *J Thorac Cardiovasc Surg*. 2004;127: 457–464.
13. 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;340:839–846.
14. 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;24:190–197.
15. Khairy P, Landzberg MJ, Lambert J, O'Donnell CP. Long-term outcomes after the atrial switch for surgical correction of transposition: a meta-analysis comparing the Mustard and Senning procedures. *Cardiol Young*. 2004;14:284–292.
16. Gelatt M, Hamilton RM, McCrindle BW, Connelly M, Davis A, Harris L, Gow RM, Williams WG, Trusler GA, Freedom RM. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. *J Am Coll Cardiol*. 1997;29:194–201.
17. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam Study. *Eur Heart J*. 2006;27:949–953.
18. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
19. Lloyd-Jones DM, Wang TJ, Leip EP, Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
20. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. *Am J Cardiol*. 2007;99:839–843.
21. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008;51:793–801.
22. Beiser A, D'Agostino RB Sr, Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence, including lifetime risk: Alzheimer's disease

in the Framingham Study: the Practical Incidence Estimators (PIE) macro. *Stat Med.* 2000;19:1495–1522.
23. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA.* 2002;287:1003–1010.
24. Rothman K. *Modern Epidemiology.* 1st ed. Boston, Mass: Little, Brown & Co; 1986:236–279.
25. Cummings P, McKnight B, Greenland S. Matched cohort methods for injury research. *Epidemiol Rev.* 2003;25:43–50.
26. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am.* 2008;92:17–40.
27. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart.* 2001;86:516–521.
28. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. 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;285:2370–2375.
29. 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;74:236–241.
30. Nakazawa M, Shinohara T, Sasaki A, Echigo S, Kado H, Niwa K, Oyama K, Yokota M, Iwamoto M, Fukushima N, Nagashima M, Nakamura Y. Arrhythmias late after repair of tetralogy of Fallot: a Japanese Multicenter Study. *Circ J.* 2004;68:126–130.
31. Puley G, Siu S, Connelly M, Harrison D, Webb G, Williams WG, Harris L. Arrhythmia and survival in patients >18 years of age after the mustard procedure for complete transposition of the great arteries. *Am J Cardiol.* 1999;83:1080–1084.
32. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart.* 2004;90:307–313.
33. Brown ML, Dearani JA, Danielson GK, Cetta F, Connolly HM, Warnes CA, Li Z, Hodge DO, Driscoll DJ. Functional status after operation for Ebstein anomaly: the Mayo Clinic experience. *J Am Coll Cardiol.* 2008; 52:460–466.
34. Garson A Jr, Bink-Boelkens M, Hesslein PS, Hordof AJ, Keane JF, Neches WH, Porter CJ. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol.* 1985;6:871–878.
35. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med.* 1998;158:229–234.
36. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359–364.
37. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation.* 2008;118:e714–e833.
38. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet.* 2000;356:975–981.
39. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation.* 2008;117:85–92.
40. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001; 285:2864–2870.
41. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Cote JM, Lavoie JP, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. *Circulation.* 2006; 113:2391–2397.
42. Perloff JK, Marelli AJ, Miner PD. Risk of stroke in adults with cyanotic congenital heart disease. *Circulation.* 1993;87:1954–1959.
43. Dearani JA, Danielson GK, Puga FJ, Schaff HV, Warnes CW, Driscoll DJ, Schleck CD, Ilstrup DM. Late follow-up of 1095 patients undergoing operation for complex congenital heart disease utilizing pulmonary ventricle to pulmonary artery conduits. *Ann Thorac Surg.* 2003;75:399–410; discussion 411.
44. Graham TP Jr, Bernard YD, Mellen BG, Celermajer D, Baumgartner H, Cetta F, Connolly HM, Davidson WR, Dellborg M, Foster E, Gersony WM, Gessner IH, Hurwitz RA, Kaemmerer H, Kugler JD, Murphy DJ, Noonan JA, Morris C, Perloff JK, Sanders SP, Sutherland JL. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. *J Am Coll Cardiol.* 2000;36:255–261.
45. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? *J Am Coll Cardiol.* 2000;36: 1670–1675.
46. Therrien J, Dore A, Gersony W, Iserin L, Liberthson R, Meijboom F, Colman JM, Oechslin E, Taylor D, Perloff J, Somerville J, Webb GD. CCS Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease, part I. *Can J Cardiol.* 2001;17:940–959.
47. Tchervenkov CI, Roy N. Congenital Heart Surgery Nomenclature and Database Project: pulmonary atresia–ventricular septal defect. *Ann Thorac Surg.* 2000;69:S97–S105.

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 >38 000 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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Mirror image atrial dilatation in adult patients with atrial fibrillation and congenital heart disease ☆

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ABSTRACT

Background: Atrial fibrillation (AF) is largely regarded to be initiated from left atrial (LA) dilatation, with subsequent dilatation of the right atrium (RA) in those who progress to chronic AF. We hypothesized that in adult patients with right-sided congenital heart disease (CHD) and AF, RA dilatation will predominate with subsequent dilatation of the left atrium, as a mirror image.

Methods: Adult patients with diagnosis of right-sided, ASD or left-sided CHD who had undergone an echocardiographic study and electrocardiographic recording in 2007 were included. RA and LA area were measured from the apical view. AF was diagnosed from a 12-lead electrocardiogram or Holter recording. A multivariate logistic regression model was used to identify predictors of AF and linear regression models were performed to measure relationship between RA and LA area and AF.

Results: A total of 291 patients were included in the study. Multivariate analysis showed that age ($p=0.0001$), RA ($p=0.025$) and LA area ($p=0.0016$) were significantly related to AF. In patients with pure left-sided pathologies, there was progressive and predominant LA dilatation that paralleled the development of AF from none to paroxysmal to chronic AF. In patients with pure right-sided pathologies, there was a mirror image of progressive and predominant RA dilatation with the development of AF.

Conclusion: We observed a mirror image atrial dilatation in patients with right sided disease and AF. This may provide novel mechanistic insight as to the origin of AF in these patients and deserves further studying in the form of targeted electrophysiological studies.

Mechanisms underlying development and maintenance of paroxysmal, persistent and permanent atrial fibrillation are complex, still incompletely understood and need further research [1] but an increase in left atrial (LA) size caused by pressure and/or volume overload of the (LA) is a well established echocardiographic predictor for developing atrial fibrillation (AF) [2–4]. Atrial dilatation results in atrial remodeling [5], with damaged muscle bundles connections [6], local conduction heterogeneities, focal spread of activation [7] and increased stretch at the junction of the pulmonary veins and LA myocardial tissue [8]. This acts as triggers and substrate for onset and maintenance of AF [5]. Once AF goes from paroxysmal to chronic, right atrium (RA) also undergoes progressive dilatation [9].

The adult congenital heart disease (ACHD) population is growing and getting older [10]. Arrhythmias play an important role in the management and outcomes of these patients [11–14]. Various studies [12,15–18] have identified atrial flutter, intra-atrial reentry tachycardia and AF as being common late sequelae seen in as many as 30% of ACHD patients. Interestingly, predominant right-sided pathologies are observed in at least one third of these patients [10].

Experimental animal studies have demonstrated that isolated RA stretch and dilatation can, on their own, lead to development of atrial fibrillation [19–22]. The relationship of isolated RA dilatation and the propensity to develop AF has never been studied in humans.

We hypothesized that in ACHD with isolated right-sided cardiac pathology, RA dilatation would 1) be the predominant lesion, 2) be related to the development and the chronicity of AF and 3) be associated, in CAF, with LA enlargement, developed as a consequence of atrial fibrillation.

1. Methods

1.1. Study population

The MAUDE Unit database was searched between April 1st, 2007 and March 31st, 2008 for all adult patients with repaired or unrepaired pure left or right-sided congenital heart disease (CHD) who had undergone a cardiac ultrasound and an electrocardiographic recording within the same 12 months. Pure left or right-sided lesions were defined anatomically as lesions originating in the left or right heart without contralateral sequelae. Left-sided CHD lesions included mitral valve anomalies (mitral valve prolapse (MVP), mitral stenosis or insufficiency), aortic valve anomalies (bicuspid

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aortic valve (BAV) with stenosis or insufficiency) and coarctation of the aorta. Right-sided CHD lesions included tricuspid valve anomalies (Ebstein's malformation, stenosis and insufficiency), pulmonary valve anomalies (stenosis, insufficiency, and atresia), tetralogy of Fallot (ToF), Eisenmenger, tricuspid atresia with the Fontan procedure, and double chambered right ventricle (DCR). Biatrial disease included patients with atrial septal defect (ASD). Patients with a previous atrial switch procedure (Mustard and Senning) were excluded due to surgical scarring in the atria which can act as a trigger for AF [23] independent of atrial dilatation. The study protocol was approved by Research Ethics Board of McGill University Health Centre.

1.2. Baseline data source

Baseline data were obtained from the patients' files at the most recent clinical visit that correlated to the transthoracic echocardiogram and included sex, age, type of CHD, prior cardiac intervention (surgical and catheter-based), risk factors for coronary artery disease (diabetes, hypertension), prior MI, prior stroke, symptoms of heart failure assessed by NYHA class, thyroid disease and medication use.

1.3. Diagnosis of atrial fibrillation

Patients were separated into three rhythm categories upon chart review. Patients were classified as sinus rhythm (SR), paroxysmal atrial fibrillation (PAF) and chronic atrial fibrillation (CAF). The diagnosis of atrial fibrillation at any time during follow-up was made from an electrocardiogram (ECG) or a Holter-recording upon chart review. PAF was defined as an episode of AF documented in the chart with subsequent demonstration of reversion to sinus rhythm. CAF was defined as AF documented on ≥2 ECGs with the patient being in AF at the time of last clinical visit. Persistent AF with drugs or direct current cardioversion to sinus rhythm was considered as PAF for the purpose of the study. Long-lasting AF and permanent AF were grouped as chronic AF. Patients with atrial flutter were classified as "sinus rhythm" if they had no demonstrated episode of atrial fibrillation.

1.4. Echocardiographic data

Data for all echocardiographic studies were collected retrospectively off-line. Echocardiographic studies were done using Vivid 7 dimension 06 echocardiograms and were interpreted on EchoPAC reading station (GE Healthcare). Echographic measurements were performed by two skilled investigators (DC and JB) who were blinded to the patient's diagnosis. LA and RA measurements adhered to recently published recommendations [4,24–27]. LA and RA size measurements were performed from an apical 4-chamber view at the end of ventricular systole to obtain maximal atrial diameters and areas, within 12 months of Holter monitor or 12-lead electrocardiogram recording.

1.5. Statistical analysis

Data analysis was performed using Microsoft Office Excel for Windows, version 2003 and SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Descriptive data for continuous variable are expressed as means +/− standard deviations (SD) or median with interquartile range (IQR). Values in different groups were compared using unpaired Student t-tests, Fisher's exact tests, Wilcoxon and X^2, whenever appropriate. A p-value<0.05 was considered statistically significant.

A multivariate logistic regression model with AF as dependent variable was used to identify the predictors of AF. Results were reported using odds ratios (ORs) and 95% CIs.

Linear regression analysis were performed in the 3 groups (isolated right-sided CHD, ASD, and isolated left-sided CHD), to measure the relationship between RA and LA area and AF. Parameter estimate of regression coefficients with 95% CIs were reported.

Interobserver differences in atrial area were expressed as the mean +/−SD. Pearson correlation coefficient was calculated. Interobserver variability was expressed as the ratio of the SD of the difference and the mean of the two measurements. Interobserver variability was expressed in percentage.

2. Results

2.1. Baseline characteristics

Over the 12-month study period, 314 ACHD patients were identified. Twenty three (7%) of them were excluded due to inadequate echocardiogram quality. Of the 291 remaining patients, 117 had right-sided CHD, 68 had ASD and 106 had left-sided CHD. Baseline patient characteristics, cardiac diagnosis, rhythmic status, comorbidities and medications are depicted in Table 1.

In patients with ASD, 51 patients (75%) were in sinus rhythm, 11 (16%) had PAF and 6 (9%) were in CAF. In patients with right-sided CHD, 107 patients (91%) were in SR, 8 (7%) had PAF and 2 patients (2%) were in CAF. In patients with left-sided CHD, 98 patients (92%) were in SR, 4 patients (4%) presented PAF and 4 patients (4%) were in CAF.

There was a female predominance in ASD (62%) and in right-sided CHD (55%), but a male predominance in left-sided CHD (59%).

NYHA class was available in 84% of the patients. Most patients were in NYHA class 1 and no patient was in NYHA class 4. For patients in sinus rhythm, 203 patients (86%) were in NYHA class 1, 29 (12%) in NYHA class 2 and 5 (2%) in NYHA class 3. For patients in PAF, 17 (74%) were in NYHA class 1, 2 (9%) in NYHA class 2 and 4 (17%) in NYHA class 3.

Table 1
Baseline and clinical characteristics in ACHD patients with ASD, isolated right-sided CHD and isolated left-sided CHD. The table depicts the baseline and clinical characteristics of patients with ASD, right-sided and left-sided CHD. ASD = atrial septal defect; CHD = congenital heart disease; AF = atrial fibrillation; BP = blood pressure; SD = standard deviation; PS = pulmonary stenosis; DCRV = double-chambered right ventricle; BAV = bicuspid aortic valve; PAF = paroxysmal atrial fibrillation; CAF = chronic atrial fibrillation; NYHA = New-York Heart Association; MI = myocardial infarction; ARB = angiotensin receptors blockers; RA = right atrium; LA = left atrium.

	Right-Sided (n = 117)	ASD (n = 68)	Left-Sided (n = 106)
Socio-Demographic Characteristics			
Males (%)	53 (45)	26 (38)	62 (59)
Median age (range)	31 (18–68)	42 (18–82)	32 (18–82)
Sinus rhythm	30 (18–68)	37 (18–59)	30 (74–18)
Paroxysmal AF	44 (24–65)	52 (20–82)	65 (86–43)
Chronic AF	59 (50–67)	66 (42–80)	54 (31–68)
Mean BP (SD)	129/69 (12/11)	120/71 (13/9)	125/72 (14/9)
Cardiac Diagnosis (%)			
ASD		68(100)	
Tetralogy of Fallot/ Truncus arteriosus	50 (43)		
PS	33 (28)		
DCRV	11 (9)		
Tricuspid valve anomalies	9 (8)		
Others	14 (12)		
BAV			53 (50)
Mitral valve anomalies			27 (26)
Coarctation of the aorta			15 (14)
Subaortic stenosis/Shone syndrome			11(10)
Percutaneous or Surgical Repair (%)	91 (78%)	56 (82)	53 (50)
Cardiac Rhythm Status			
Non AF (%	107 (91)	51 (75)	98 (92)
PAF (%)	8 (7)	11 (16)	4 (4)
CAF (%)	2 (2)	6 (9)	4 (4)
Comorbidities			
NYHA class I–II (%)	104 (95)	61 (94%)	92 (94)
NYHA class III–IV (%)	5 (5)	4 (6%)	6 (6)
MI	1 (1)	1 (1)	0 (0)
Stroke	1 (1)	1 (1)	2 (2)
Diabetes	0 (0)	2 (2)	2 (2)
Hypothyroidism	9 (8)	4 (6)	2 (2)
Medication (%)			
Antiplatelet agent	26 (22)	27 (40)	14 (13)
Coumadin	18 (15)	13 (19)	18 (17)
ACE inhibitor, ARB	5 (4)	4 (6)	25 (24)
B-blockers	31 (27)	15 (22)	29 (27)
Diuretic	9 8)	4 (6)	5 (5)
Antiarrhythmic drugs	7 (6)	9 (13)	12 (11)
Lipid lowering agents	8 (7)	7 (10)	8 (8)
Calcium channel blockers	1 (1)	0 (0)	6 (6)
Echocardiographic parameters			
RA area (mean cm^2)			
No AF	17	16	14
AF	26	23	20
LA area (mean cm^2)			
No AF	13	15	15
AF	17	23	27

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Table 2
Univariate and multivariate analysis. The table depicts the parameters associated with atrial fibrillation by univariate and multivariate analysis. ASD = atrial septal defect; CHD = congenital heart disease; AF = atrial fibrillation; SR = sinus rhythm; IQR = inter-quartile range; NYHA = New-York Heart Association; LA = left atrium; RA = right atrium; LVEF = left ventricle ejection fraction; RV MPI = right ventricle myocardial performance index; OR = odd ratio; CI = confidence interval.

Univariate analysis				
N = 291	AF N = 35		SR N = 255	p-value
Male (%)	19 (54%)		123 (48%)	0.5019
Age (Median (IQR))	56 (42, 66)		26 (20,41)	<0.0001
NYHA (Median (IQR))	1 (1,3)		1 (1,1)	0.0002
LA area (Median (IQR))	18 (15,27)		14 (12,17)	<0.0001
RA area (Median (IQR))	21 (17,31)		14 (12,18)	<0.0001
LVEF_% (Median (IQR))	60 (60, 60)		60 (60, 60)	0.1232
RV MPI (Median (IQR))	0.21 (0.12, 0.31)		0.15 (0.06, 0.26)	0.1777
Multivariate analysis				
N = 291	AF N = 35	SR N = 255	Multivariate OR 95% C.I.	p-value
Age (Median (IQR))	56 (42, 66)	26 (20,41)	1.073 (1.039, 1.108)	<0.0001
NYHA (Median (IQR))	1 (1,3)	1 (1,1)	0.910 (0.418, 1.979)	0.8118
LA area (Median (IQR))	18 (15,27)	14 (12,17)	1.153 (1.056, 1.259)	0.0016
RA area (Median (IQR))	21 (17,31)	14 (12,18)	1.081 (1.010, 1.156)	0.0250

For patients in CAF, 4 patients (33%) were in NYHA class 1, 2 (17%) patients were in NYHA class 2 and 6 patients (50%) were in NYHA class 3.

RA and LA area were within the norms (<20 cm2) when in sinus rhythm in the 3 groups of CHD. In AF patients, we observed a predominant RA dilatation in right-sided CHD, a biatrial dilatation in ASD, and a predominant LA dilatation in left-sided.

2.2. Logistic regression analysis (Table 2)

On univariate analysis, NYHA ($p = 0.0002$), age ($p < 0.0001$), RA ($p < 0.0001$) and LA area ($p < 0.0001$), were significantly associated with AF.

On multivariate analysis however, only age ($p = 0.0001$), RA ($p = 0.025$) and LA area ($p = 0.0016$) significantly predicted AF (see Table 2).

2.3. Linear regression analysis

On linear regression analysis, depicted in Fig. 1, RA area had the strongest association with CAF in right sided pathology, compared to ASD and left sided disease. A similar pattern was observed for PAF albeit with wider CI. In contrast, LA area had the strongest association with CAF in left sided heart disease compare to ASD and became non significant in right sided heart disease.

2.4. RA/LA ratio

With the progression of AF, the observed RA/LA ratio pattern in patients with right sided disease was inversed to that observed in the left sided disease group (see Fig. 2). Patients with ASDs maintained a ratio close to 1 throughout the disease process.

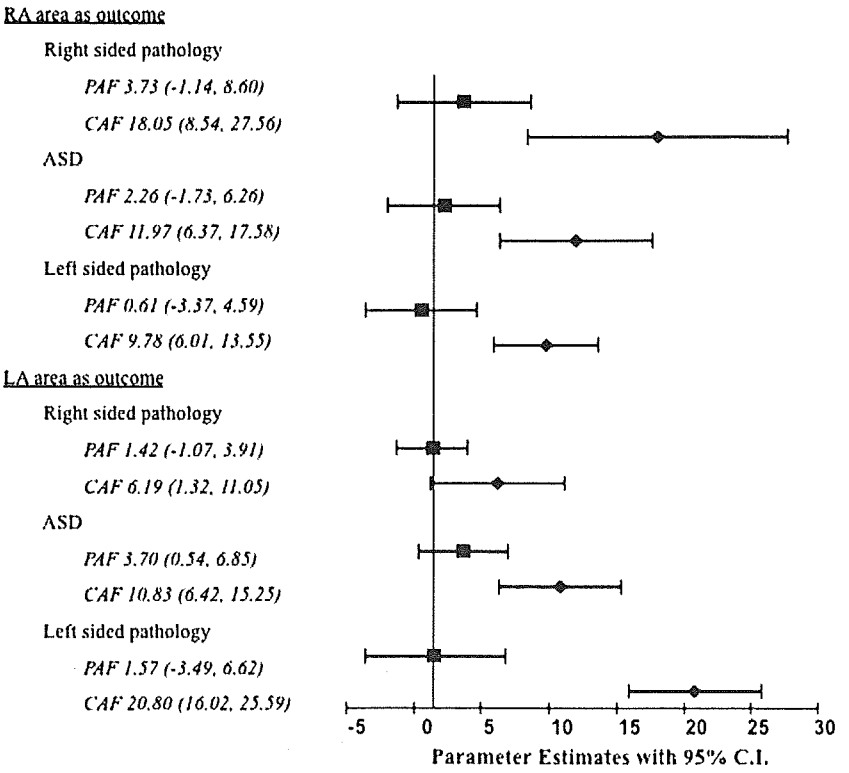

Fig. 1. Linear regression analysis. The bar-graph demonstrates the correlation between left and right atrium area and atrial fibrillation in different subgroups. RA = right atrium; PAF = paroxysmal atrial fibrillation; CAF: chronic atrial fibrillation; ASD = atrial septal defect.

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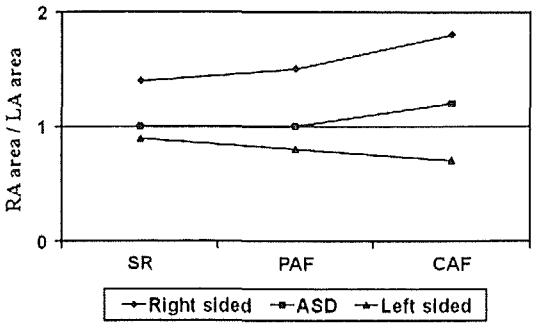

Fig. 2. Mirror image atrial dilatation. Fig. 2 depicts the "Mirror image atrial dilatation" as expressed by RA/LA area ratio in function of different rhythmic status in right-sided CHD, ASD and left-sided CHD. RA = right atrium; LA = left atrium; SR = sinus rhythm; PAF = paroxysmal atrial fibrillation; CAF = chronic atrial fibrillation; ASD = atrial septal defect.

Mean interobserver difference for atrial area measurements was 1 mm^2 +/− 1 mm^2 with an interobserver variability was 7%. Interobserver correlation was good, with a correlation coefficient of 0.95 for area ($p<0.001$).

3. Discussion

We have demonstrated that in patients with isolated right-sided cardiac pathology and CAF, right atrial dilatation has the greatest influence in the development of AF and predominates over left atrial dilatation throughout the disease process. In contrast and not surprisingly, LA area has the greatest influence in the development of CAF in patients with left sided pathology and predominated over RA dilatation throughout the disease process. Interestingly, patients with ASD behave like biatrial disease with equal contribution of RA vs. LA dilatation.

AF is very prevalent in the aging CHD patient population [14] occurring with a prevalence of up to 30% in certain subgroups [28,29]. Our group has recently shown that its mere presence more than doubles these patients' morbidity and increases their mortality by 50% [14].

Correlations between AF and LA size have been well-described in the non-congenital cardiac population [4,30]. Increased LA volume has been identified as a risk factor for the development of AF [2], the recurrence of AF after catheter ablation [31] or cardioversion [30] and as a risk factor in the progression of PAF to CAF [30,32]. Progressive RA dilatation has also been observed in patients with PAF and acquired left-heart disease [33] and has been ascribed to a passive "resulting effect" of AF [34,35] of the contralateral atrium. In this study, we were able to show in our CHD population with isolated left-sided cardiac disease that LA dilatation had the greatest influence on CAF development and that LA dilatation predominated over RA dilatation throughout the establishment of AF. A similar trend was also seen for PAF but not significant due to the low event rate and the wide CI.

By contrast, in our CHD patients with isolated right-sided pathologies, RA dilatation had the greatest influence on the development of CAF with RA dilatation predominating over LA dilatation throughout the disease process. Again, a similar trend was seen for PAF but was not significant due to the low event rate.

Our findings are concordant with observations made in a rabbit model of atrial stretch by Ravelli and colleagues [20]. In this animal study, the interatrial septum was perforated, and after occlusion of the caval and pulmonary veins, biatrial pressures were increased simultaneously by raising the level of an outflow cannula in the pulmonary artery. For a similar rise in atrial pressure, the right atrial effective refractory periods were considerably shorter than on the left. The monophasic action potentials significantly decreased and the inducibility of atrial fibrillation was more pronounced in the RA. In other words, the RA was not only able to initiate AF but did so at a much lower threshold of pressure rise than the LA. Similarly, studies done on dogs revealed that saline infusion facilitated the induction of AF by stretching the RA [19] and that the higher the RA pressure, the higher the probability of inducing AF [36].

We have also recently published a population-based study showing that patients with right sided CHD not only had a greater life incidence risk of developing AF [37] but did so at a younger age [38], in keeping with the theory that the RA is more prone to initiate AF for a similar pressure rise or degree of dilatation.

Interestingly, recent histological studies on human hearts have shown similar histologies at the junctions between the RA myocardium and the inferior and superior vena cavae to that of the junction between the LA myocardium and the pulmonary veins [39].

Furthermore, isolated cases of PAF originating from the superior vena cava and RA junction have been reported and have responded successfully to radiofrequency catheter ablation of the junction [40]. Similarly, case reports of successful treatment of paroxysmal atrial fibrillation originating from the inferior vena cava and right atrial junction have recently emerged [41].

Based on this present study and the aforementioned basic, population studies and case reports, one could invoke a mechanistic role of the RA in the initiation of AF in our ACHD patients with isolated right-sided cardiac pathology and predominant RA dilatation. Electrophysiological studies aimed at targeting potential initiating sites of AF in ACHD patients with isolated right-sided disease and RA dilatation would be the next logical step.

Contrary to previous reports [42–44] our study would suggest that ASDs behave more like a biatrial disease with equal dilatation of both the right and left atrium concomitant with the establishment of AF. Patients in our ASD group were slightly older than in the right or left lesion group. Contribution of concomitant hypertension or left ventricular dysfunction perhaps might have played a role in the LA dilatation.

In our study, NYHA class tends to be correlated to AF, as one would expect. However, the correlation failed to reach significance by multivariate analysis, probably due to the small number of patients in NYHA class > 1.

3.1. Limitations

The design of this study was cross sectional so that a "cause and effect" relationship between the atrium size and AF could not be established. Only a careful longitudinal study with precise recording of atrial size and timing of AF initiation would be able to answer this question in a definitive manner.

Holter monitoring was not done routinely on all of our patients. It was only performed when clinically indicated. Asymptomatic PAF may have been under-diagnosed.

4. Conclusions

The observed predominance of RA dilatation and the mirror image pattern of atrial dilatation in patient with right sided heart CHD disease and AF may provide novel mechanistic insight as to the origin of AF in these patients. Basic electrophysiological studies are now needed to lend support to our echocardiographic-driven hypothesis of RA dilatation acting as the trigger for AF initiation.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [45].

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References

[1] Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: Executive summary of the proceedings from the 2nd afnet-ehra consensus conference 'research perspectives in af'. Eur Heart J 2009;30:2969–2977c.

[2] Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The framingham heart study. Circulation 1994;89: 724–30.

[3] Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: Is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018–23.

[4] Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: Physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357–63.

[5] Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the european society of cardiology (esc). Eur Heart J 2010;31:2369–429.

[6] Allessie MA, de Groot NM, Houben RP, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: Longitudinal dissociation. Circ Arrhythm Electrophysiol 2010;3:606–15.

[7] de Groot NM, Houben RP, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: Epicardial breakthrough. Circulation 2010;122:1674–82.

[8] Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415:219–26.

[9] Sanfilippo AJ, Abascal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990;82: 792–7.

[10] Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: Changing prevalence and age distribution. Circulation 2007;115:163–72.

[11] Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation 2007;115:534–45.

[12] Triedman JK. Arrhythmias in adults with congenital heart disease. Heart 2002;87: 383–9.

[13] Walsh EP. Arrhythmias in patients with congenital heart disease. Card Electrophysiol Rev 2002;6:422–30.

[14] Bouchardy J, Therrien J, Pilote L, et al. Atrial arrhythmias in adults with congenital heart disease. Circulation 2009;120:1679–86.

[15] Harris L, Gow RM, Kirsh JA, Klein GJ, Siu SC. Atrial arrhythmias and special circumstances. Can J Cardiol 2005;21(Suppl. B):51B–60B.

[16] Li W, Somerville J. Atrial flutter in grown-up congenital heart (guch) patients. Clinical characteristics of affected population. Int J Cardiol 2000;75:129–37 discussion 138–129.

[17] Akar JG, Kok LC, Haines DE, DiMarco JP, Mounsey JP. Coexistence of type i atrial flutter and intra-atrial re-entrant tachycardia in patients with surgically corrected congenital heart disease. J Am Coll Cardiol 2001;38:377–84.

[18] Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. Am J Cardiol 2002;90:338–40.

[19] Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996;7:833–42.

[20] 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;96:1686–95.

[21] Zarse M, Deharo JC, Mast F, Allessie MA. Importance of right and left atrial dilation and linear ablation for perpetuation of sustained atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:164–71.

[22] Boyden PA, Hoffman BF. The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. Circ Res 1981;49:1319–31.

[23] Love BA, Mehta D, Fuster VF. Evaluation and management of the adult patient with transposition of the great arteries following atrial-level (senning or mustard) repair. Nat Clin Pract Cardiovasc Med 2008;5:454–67.

[24] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: A report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

[25] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108.

[26] Muller H, Burri H, Lerch R. Evaluation of right atrial size in patients with atrial arrhythmias: Comparison of 2d versus real time 3d echocardiography. Echocardiography 2008;25:617–23.

[27] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the american society of echocardiography endorsed by the european association of echocardiography, a registered branch of the european society of cardiology, and the canadian society of echocardiography. J Am Soc Echocardiogr 2010;23:685–713 quiz 786–688.

[28] Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214–9.

[29] Brown ML, Dearani JA, Danielson GK, et al. Functional status after operation for ebstein anomaly: The mayo clinic experience. J Am Coll Cardiol 2008;52: 460–6.

[30] Henry WL, Morganroth J, Pearlman AS, et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976;53:273–9.

[31] Shin SH, Park MY, Oh WJ, et al. Left atrial volume is a predictor of atrial fibrillation recurrence after catheter ablation. J Am Soc Echocardiogr 2008;21:697–702.

[32] Kerr CR, Humphries KH, Talajic M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: Results from the canadian registry of atrial fibrillation. Am Heart J 2005;149:489–96.

[33] Tanabe T, Deguchi Y, Handa S, Takahashi A, Fukushi H. Longer longitudinal atrial dimension in patients with idiopathic paroxysmal atrial fibrillation: A possible cause of atrial fibrillation. Am Heart J 2001;142:669–78.

[34] Keren G, Etzion T, Sherez J, et al. Atrial fibrillation and atrial enlargement in patients with mitral stenosis. Am Heart J 1987;114:1146–55.

[35] John B, Stiles MK, Kuklik P, et al. Electrical remodelling of the left and right atria due to rheumatic mitral stenosis. Eur Heart J 2008;29:2234–43.

[36] Sideris DA, Toumanidis ST, Tselepatiotis E, et al. Atrial pressure and experimental atrial fibrillation. Pacing Clin Electrophysiol 1995;18:1679–85.

[37] Bernier M, Marelli AJ, Pilote L, et al. Atrial arrhythmias in adult patients with right- versus left-sided congenital heart disease anomalies. Am J Cardiol 2010;106:547–51.

[38] Bernier M, Marelli AJ, Pilote L, et al. Atrial arrhythmias in adult patients with right- versus left-sided congenital heart disease anomalies. Am J Cardiol 2010;106:547–51.

[39] Kholova I, Kautzner J. Morphology of atrial myocardial extensions into human caval veins: A postmortem study in patients with and without atrial fibrillation. Circulation 2004;110:483–8.

[40] Tsai CF, Tai CT, Hsieh MH, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: Electrophysiological characteristics and results of radiofrequency ablation. Circulation 2000;102:67–74.

[41] Mansour M, Ruskin J, Keane D. Initiation of atrial fibrillation by ectopic beats originating from the ostium of the inferior vena cava. J Cardiovasc Electrophysiol 2002;13:1292–5.

[42] Wagdi P. Incidence and predictors of atrial fibrillation following transcatheter closure of interatrial septal communications using contemporary devices. Clin Res Cardiol 2010;99:507–10.

[43] Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. 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;24:190–7.

[44] Sakakibara M, Kobayashi S, Imai H, Watanabe S, Masuda Y, Inagaki Y. diagnosis of atrial septal defect using magnetic resonance imaging. J Cardiol 1987;17:817–29.

[45] Shewan LG, Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010;144:1–2.

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