Congenital Heart Disease

Coarctation of the Aorta and Coronary Artery Disease
Fact or Fiction?

Idan Roifman, MD; Judith Therrien, MD; Raluca Ionescu-Ittu, PhD; Louise Pilote, MD, PhD, MPH; Liming Guo, MSc; Mark A. Kotowycz, MD, MBA; Giuseppe Martucci, MD; Ariane J. Marelli, MD, MPH

Background—Aortic coarctation (CoA) is reported to predispose to coronary artery disease (CAD). However, our clinical observations do not support this premise. Our objectives were to describe the prevalence of CAD among adults with CoA and to determine whether CoA is an independent predictor of CAD or premature CAD.

Methods and Results—The study population was derived from the Quebec Congenital Heart Disease Database. We compared patients with CoA and those with a ventricular septal defect, who are not known to be at increased risk of CAD. The prevalence of CAD in patients with CoA compared with those with ventricular septal defect was determined. We then used a nested case-control design to determine whether CoA independently predicted for the development of CAD. Of 756 patients with CoA who were alive in 2005, 37 had a history of CAD compared with 224 of 6481 patients with ventricular septal defect (4.9% versus 3.5%; P=0.04). Male sex (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.62–2.80), hypertension (OR, 1.95; 95% CI, 1.44–2.64), diabetes mellitus (OR, 1.68; 95% CI, 1.09–2.58), age (OR per 10-year increase, 2.28; 95% CI, 2.09–2.48), and hyperlipidemia (OR, 11.58; 95% CI, 5.75–23.3) all independently predicted for the development of CAD. CoA did not independently predict for the development of CAD (OR, 1.04; 95% CI, 0.68–1.57) or premature CAD (OR for CoA versus ventricular septal defect, 1.44; 95% CI, 0.79–2.64) after adjustment for other factors.

Conclusions—Although traditional cardiovascular risk factors independently predicted for the development of CAD, the diagnosis of CoA alone did not. Our findings suggest that cardiovascular outcomes of these patients may be improved with tight risk factor control. (Circulation. 2012;126:16-21.)

Key Words: aortic coarctation ■ coronary artery disease ■ heart diseases ■ population groups

S
ignificant coarctation of the aorta (CoA) was first surgically repaired in the mid-1940s, whereas percutaneous repair has been developed over the last 30 years.1 Initially, there was great hope of a potential cure if the lesion was repaired properly.2 Much of that enthusiasm waned with the publication of a descriptive article by Presbitero et al3 showing that patients with repaired coarctations still died, on average, at a much earlier age than the general population. Since then, researchers have been trying to examine the cause of this excess mortality. Multiple studies have shown that the main cause of death in patients with corrected CoA is coronary artery disease (CAD).4–8 but no studies were designed to determine whether CoA is an independent risk factor for CAD. Based largely on these studies, prevailing conventional wisdom states that CoA is associated with accelerated or premature CAD despite repair. Although a portion of the attributed risk of CAD is thought to be related to residual hypertension, findings of intrinsic vascular reactivity abnormalities specific to CoA patients are also thought to partially account for the risk of CAD. Some studies in CoA patients have shown evidence of endothelial dysfunction and increased proinflammatory cytokines that persist after repair.9–21

Editorial see p 5
Clinical Perspective on p 21

Our own clinical observations, however, have not been consistent with the presence of a large burden of CAD in patients with CoA. To the best of our knowledge, no studies have attempted to determine whether CoA is a predictor of CAD independently of traditional cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia. Thus, our objectives were 3-fold: to describe the prevalence of CAD among adults with CoA, to determine whether CoA independently predicts the development of CAD, and to determine whether CoA independently predicts the development of premature CAD.
Methods

Data Sources
In Quebec, a unique healthcare number is assigned to every individual at birth. This number is then used to record all diagnoses, hospitalizations, and health services given to that individual throughout his or her lifetime. This information is recorded into 2 databases: the medical claims database of the provincial authority, the Regie de l’assurance Maladie du Quebec (RAMQ), and the hospital discharge summary database (Med-Echo). The RAMQ database also includes patient demographic information, including date of birth, date of death, and sex. The province-wide Quebec Congenital Heart Disease Database was created by merging these 2 databases for the years 1983 to 2005 and developing algorithms to correctly extract congenital heart disease (CHD) diagnoses.22–24 During this period, diagnoses recorded in the databases adhered to the International Classification of Diseases, ninth revision (ICD-9). Patients who had at least 1 diagnostic code for CHD and/or a CHD-specific surgical procedure were identified. Provider codes were used to select those CHD billings made by cardiovascular disease specialists, ultrasonographers, and primary care physicians. Patients were assigned 1 or 2 CHD diagnoses with the use of a previously described hierarchical algorithm.23 All information was cross-referenced between outpatient and inpatient data sources. Our CHD database therefore contained comprehensive longitudinal, demographic, diagnostic, and therapeutic records of all patient encounters with the provincial healthcare system from January 1, 1983, through December 31, 2005.22

Study Population
The putative CAD risk factor of interest in this study was the presence of a CoA lesion. To investigate the impact of CoA on CAD, we used the ventricular septal defect (VSD) population in the CHD database as a negative “control” group because there is no known association between VSD and accelerated CAD. Patients with a final diagnosis of either CoA or VSD were selected from the Quebec CHD database to form a retrospective longitudinal cohort of CoA and VSD patients hereafter referred to as the CoA/VSD cohort. This study was approved by the provincial and McGill University healthcare ethics boards.

Study Design
For the first objective, we ascertained prevalent CAD cases among the CoA/VSD cohort adult subjects alive on January 1, 2005 (prevalence sample, Figure 1). A patient was considered to have a history of CAD if he or she had at least 1 CAD diagnosis during the 1983 to 2005 database follow-up. Prevalence of CAD was then estimated as total number of patients with a history of CAD per 1000 patients with an underlying diagnosis of CoA versus VSD.

For the second objective, we performed a nested case-control study within the CoA/VSD cohort. The selection of CAD cases and non-CAD controls is described in Figure 1 (nested case-control sample). Specifically, incident CAD cases were identified at the first CAD diagnosis in the database after a 5-year washout period, from 1983 to 1987, with no CAD diagnosis. CAD cases had to be adults (ie, ≥18 year of age) at the time of the first CAD diagnosis. For each case, we constructed a risk set including all adult subjects free of CAD at the time when the CAD case was diagnosed. Finally, we randomly selected from each risk set 4 non-CAD controls per each CAD case. Patients initially selected as controls could later become cases if they acquired a diagnosis of CAD in the database.

For the third objective, we used the same study design as for the second objective, but we restricted the cases to premature CAD (first diagnosis at 18–55 years of age, inclusive). Given the importance of age in the development of premature CAD, for this analysis, we matched the premature CAD cases to non-CAD controls on both exact age and calendar time. However, because the number of eligible non-CAD controls of exact age was relatively small, we used 2:1 matching instead of 4:1.

Measurements
We defined the CAD outcome on the basis of the presence of at least 1 diagnostic/procedural code for acute myocardial infarction (ICD-9 codes 410.0–414.9), coronary artery bypass grafting, and/or percutaneous coronary intervention billed by one of the following
specialists: cardiologists, cardiothoracic surgeons, internists, and emergency physicians.

Potential confounders were selected a priori as factors known to be related to the development of CAD and likely to be differently distributed among CoA versus VSD patients. These included dyslipidemia, diabetes mellitus, hypertension, older age, and male sex. For each matched case-control pair, the covariates related to the comorbid history of the patient were measured in the 5 years before the day of the first CAD diagnosis of the case (the pair’s index date) with the use of corresponding ICD-9 diagnostic codes. Age was measured at the index date for each case-control pair.

Statistical Analysis

Descriptive statistics include proportions, medians, and interquartile ranges. Medians and proportions were compared by Wilcoxon rank-sum and χ² tests, respectively. Prevalence of CAD was estimated in the CoA versus VSD population alive in 2005 (the last year of our database) as the number of CAD patients per 1000 population and compared by χ² tests.

A conditional multivariable logistic regression model adjusted for age, sex, history of hypertension, history of diabetes mellitus, and history of hyperlipidemia was performed in the nested-case-control studies to estimate the impact of CoA versus VSD on the risk of CAD and premature CAD. All covariates adjusted for in the analysis were selected a priori and kept in the model regardless of their statistical significance. Adjustment for age was not necessary in the multivariable regression model for premature CAD (third objective) because the cases and controls were matched for age in this subset of the cohort. We report odds ratios (ORs) and 95% confidence intervals (CIs) from the multivariable conditional logistic models performed for adult CAD and premature adult CAD. Analyses were performed with SAS statistical software (version 9.2).

Results

Prevalence of CAD

The prevalence of CAD in 2005 was slightly higher in the CoA group compared with the VSD group (4.9% versus 3.5%; P=0.04; the Table). Compared with VSD, patients in the CoA group who were alive in 2005 had higher rates of hypertension (44.8% versus 16.2%; P<0.0001), hyperlipidemia (4.0% versus 2.4%; P=0.01), congestive heart failure (14.8% versus 7.4%; P<0.0001), stroke (5.6% versus 2.6%; P<0.0001), and peripheral vascular disease (13.1% versus 2.7%; P=0.0001).

Characteristics of CoA Patients Who Were CAD Cases and Non-CAD Controls in the Nested Case-Control Sample

In the nested-case-control sample, there were 481 CAD cases and 1924 matched controls. Of the 481 cases, 48 had CoA and 433 had VSD. Of the 1924 controls, 234 had CoA and 1690 had VSD. Patients with CoA and CAD were significantly older (median, 55.4 versus 32.6 years; P<0.0001) and had significantly higher rates of cardiovascular risk factors, including hypertension (56.3% versus 25.2%; P<0.0001) and hyperlipidemia (10.4% versus 0.4%; P<0.0001), than patients with CoA who did not have CAD.

The Effect of CoA on CAD

The logistic regression analysis was performed in the nested case-control sample of 481 adult CAD cases and 1924 risk-set–matched adult non-CAD controls (Figure 1). After adjustment for age, sex, hypertension, diabetes mellitus, and hyperlipidemia, CoA did not predict for the presence of CAD (OR, 1.04; 95% CI, 0.68–1.57). On the other hand, age (OR, 2.28; 95% CI, 2.09–2.48), male sex (OR, 2.13; 95% CI, 1.62–2.80), hypertension (OR, 1.95; 95% CI, 1.44–2.64), hyperlipidemia (OR, 11.58; 95% CI, 5.75–23.31), and diabetes mellitus (OR, 1.68; 95% CI, 1.09–2.58) were all independent predictors of CAD (Figure 2).

The Effect of CoA on Premature CAD

The premature CAD analysis was performed in the nested case-control sample of 124 premature CAD cases and risk-set age-matched 248 non-CAD controls (Figure 1). Similar to our primary analysis results, we found that in the young patient cohort (age, 18–55 years), CoA was not an independent predictor of CAD (OR, 1.44; 95% CI, 0.79–2.64). However, male sex (OR, 1.62; 95% CI, 1.03–2.54), hypertension (OR, 2.41; 95% CI, 1.40–4.15), and diabetes mellitus (OR, 2.75; 95% CI, 1.12–6.79) were all found to be independent predictors of premature CAD (Figure 3).

Discussion

Our results indicate that patients with CoA in our population had a slightly higher prevalence of CAD compared with the VSD population but that CoA in itself was not an independent predictor of CAD. Our 4.9% prevalence of CAD in the COA population is consistent with prevalence estimates from previous studies. Verheugt et al. 25 conducted a systematic review looking at mortality and morbidity in a population of adults with CHD. They found a 5.1% prevalence of CAD as defined by the presence of myocardial infarction or revascularization. Other research has found a similar prevalence of

| Table. Baseline Characteristics of Patients With Aortic Coarctation and Ventricular Septal Defect From the Quebec Congenital Heart Disease Database in 2005 (Prevalence Sample)* |
|----------------------------------|----------------|----------------|----------|
|                                | CoA (n=756) | VSD (n=6481) | P        |
| Age, median (IQR), y            | 31.1 (24.1–43.4) | 30.0 (22.9–40.4) | 0.10    |
| Male, n (%)                     | 397 (52.5) | 2,854 (44) | <0.0001 |
| Prevalence of CAD, n (%)        | 37 (4.9) | 224 (3.5) | 0.04    |
| AMI                             | 23 (3) | 181 (2.8) | 0.69    |
| CABG                            | 12 (1.6) | 83 (1.3) | 0.48    |
| PCI/PTCA                        | 12 (1.6) | 51 (0.8) | 0.03    |
| Cardiovascular risk factors, n (%) |        |            |         |
| Hypertension                    | 339 (44.8) | 1052 (16.2) | <0.0001 |
| Diabetes mellitus               | 44 (5.8) | 380 (5.9) | 0.96    |
| Hyperlipidemia                  | 30 (4.0) | 157 (2.4) | 0.01    |
| Congestive heart failure        | 112 (14.8) | 482 (7.4) | <0.0001 |
| Stroke                          | 42 (5.6) | 171 (2.6) | <0.0001 |
| Chronic renal failure           | 6 (0.8) | 55 (0.9) | 0.88    |
| Peripheral vascular disease     | 99 (13.1) | 176 (2.7) | <0.0001 |

*The distribution of covariates in CoA versus VSD patients in the CoA-VSD cohort was compared by the Wilcoxon rank-sum and χ² tests.

CoA indicates aortic coarctation; VSD, ventricular septal defect; IQR, interquartile range; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous coronary intervention/percutaneous transluminal coronary angioplasty.
CAD,6,26 and these results concur with our contemporary findings. Furthermore, peripheral vascular disease and stroke both occurred with a significantly higher prevalence in CoA compared with VSD patients. A possible explanation for this finding stems from the known association between hypertension and both stroke and peripheral vascular disease.27–29 The phenomenon of a higher prevalence of hypertension in CoA patients is also well described.4,18 This finding was replicated in our study. It is therefore not surprising that our CoA patients were also found to have higher rates of both stroke and peripheral vascular disease.

To the best of our knowledge, we are the first group to attempt to determine whether CoA is an independent risk factor for the development of CAD. This question is important because of the postulated vascular reactivity abnormalities in CoA. Several studies have shown that patients with CoA may have higher rates of endothelial dysfunction, circulating levels of proinflammatory cytokines, and vascular stiffness, and some of these studies have shown that these abnormalities may persist even after repair, suggesting the possibility of an inherent defect in vascular reactivity.9,10,13,17 If these patients have innate vascular reactivity defects, they can potentially predispose to the development of CAD regardless of repair. Although some of these studies looked at potential novel mechanisms of disease, many of them enrolled only a small number of patients; thus, the potential for drawing clinical conclusions from them is limited.

Our results indicate that CoA does not predict the development of CAD after adjustment for other risk factors. In fact, we found that CAD in this population is caused mainly by the same major cardiac risk factors that predispose the general population to this disease. CAD risk factors that we assessed are well described in the literature and have been validated in several large population-based studies.30–34 These results are important because they argue against an inherent and untreatable vascular reactivity defect in these patients and suggest that by carefully and methodically targeting traditional cardiovascular risk factors, we may be able to enhance the clinical outcome of these patients significantly.

Limitations

Limitations of our study should be noted. First, this is a retrospective study using an administrative database; thus, it is prone to the potential of misclassification bias. Diagnoses can be misclassified because of coding errors for CHD diagnoses and CAD. With respect to CHD diagnoses, we minimized the potential for this bias by using well-defined search algorithms that were previously validated22,23 and cross-referencing data among the 3 provincial databases. With respect to CAD, we minimized the potential bias by using hard cardiovascular end points in our definition (ie, percutaneous coronary intervention, coronary artery bypass grafting, and/or acute myocardial infarction). Importantly, several studies have validated the specificity of disease definitions based on medical services claims.35,36 In addition, we have published several studies using the Quebec CHD database, validating disease-specific codes for each study.22,37,38 This limitation notwithstanding, we believe that the strength of the administrative data for our study question is the large population-based sample size. Second, our database does not allow us to ascertain smoking as a potential confounder. However, there is no reason to believe that the prevalence of smoking is different in patients with CoA compared with those with VSD drawn from the same population and matched for age, so the absence of smoking is not likely to bias our estimates for CoA versus VSD. Moreover, although
we could not measure whether all subjects in our study population underwent a coarctation repair at some point in their lifetime, we know that our population is composed of a mixture of repaired/unrepaired patients. We have found no impact of CoA despite having a certain proportion of the population unrepaired. Had we found a significant effect of CoA on CAD, then it would have been important to determine whether the observation was driven by patients with CoA who are not operated on or are operated later on in life. By comparing all CoA patients in the Quebec population with all VSD patients, we designed a study that avoids limitations related to incomplete surgical information in CoA patients outside our observation period between 1983 to 2005. Finally, we had a relatively small number of CAD events in CoA patients. However, the total number of events used in our multivariate analysis was sufficient to allow us to simultaneously control for potential confounders that were identified a priori and measured in our database.69

Conclusions
Our results indicate that patients with CoA have a higher prevalence of CAD compared with the VSD population. However, our novel finding is that CoA does not predict for CAD following operation for coarctation of the aorta at all. Rather, aging, associated hypertension, hypercholesterolemia, and diabetes mellitus predispose to CAD in this patient population. Results of our study suggest that by carefully targeting conventional risk factors, we could possibly decrease the morbidity and mortality of these patients.

Sources of Funding
Dr Marelli is funded by the Canadian Institute of Health Research, the Heart and Stroke Foundation of Canada, and the Fond de la Recherche en Sante du Quebec. Dr Pilote is funded by the Fondation James McGill Chair at Fond de la Recherche en Sante du Quebec and holds a James McGill Chair at Fondation James McGill. Dr Pilote is funded by the Heart and Stroke Foundation of Canada, and the Fondation James McGill Chair at Fondation James McGill. Dr Pilote is funded by the Fondation James McGill Chair at Fondation James McGill.

Disclosures
None.

References
Aortic coarctation is reported to predispose to the development of coronary artery disease (CAD). Despite recent advances in surgical and percutaneous management of these patients, recent data indicate that patients with aortic coarctation still die at a much earlier age than the general population. The number 1 cause of death in this population is thought to be CAD. These data raise the question of whether coarctation of the aorta is an independent risk factor for the development of CAD. Our main objectives were to describe the prevalence of CAD among adults with aortic coarctation and to determine whether aortic coarctation is an independent predictor of CAD. Using a population-based congenital heart disease database with longitudinal follow-up of >20 years, we found, not surprisingly, that traditional cardiovascular risk factors independently predicted for the development of CAD in our cohort. However, the presence of aortic coarctation did not independently predict for the development of CAD. To the best of our knowledge, this is the first study to attempt to examine whether coarctation of the aorta is an independent risk factor for the development of CAD. Our results are significant because they are actionable. Our findings suggest that cardiovascular outcomes of patients with coarctation of the aorta may be improved with tighter risk factor control.
Coarctation of the Aorta and Coronary Artery Disease: Fact or Fiction?
Idan Roifman, Judith Therrien, Raluca Ionescu-Ittu, Louise Pilote, Liming Guo, Mark A. Kotowycz, Giuseppe Martucci and Ariane J. Marelli

Circulation. 2012;126:16-21; originally published online June 6, 2012;
doi: 10.1161/CIRCULATIONAHA.111.088294
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/1/16

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/