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

Running title: Roifman et al.; Coarctation and coronary disease

Idan Roifman, MD1; Judith Therrien, MD1,2; Raluca Ionescu-Ittu, PhD1; Louise Pilote, MD, PhD, MPH3,4; Liming Guo, MSc1; Mark A. Kotowycz, MD, MBA1; Giuseppe Martucci, MD1; Ariane J. Marelli, MD, MPH1

1McGill Adult Unit for Congenital Heart Disease (MAUDE Unit); 2Jewish General Hospital, McGill University; 3Division of Internal Medicine; 4Division of Clinical Epidemiology, McGill University Health Center, Montreal, Canada

Correspondence:
Ariane J. Marelli, MD, MPH
Associate Professor of Medicine, McGill University
Director, MAUDE Unit (McGill Adult Unit for Congenital Heart Disease)
McGill University Health Center
687, Pine Ave West, Room H4-33
Montreal H3A-1A1, Canada
Tel: 514-934-1934 x43153
Fax: 514-934-4475
E-mail: ariane.marelli@mcgill.ca

Journal Subject Codes: [8] Epidemiology; [41] Pediatric and congenital heart disease, including cardiovascular surgery; [135] Risk Factors
Abstract:

**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 if 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 to those with a ventricular septal defect (VSD), who are not known to be at increased risk of CAD. Prevalence of CAD in patients with CoA vs. VSD was determined. We then employed a nested case-control design in order to determine if CoA independently predicted for the development of CAD. Of 756 patients with CoA alive in 2005, there were 37 with a history of CAD vs. 224 out of 6,481 VSD patients (4.9% vs. 3.5%, p = 0.04). Male sex (OR 2.13, 1.62-2.80), hypertension (OR 1.95, 1.44-2.64), diabetes (OR 1.68, 1.09-2.58), age (OR per 10 year increase 2.28, 2.09-2.48) and hyperlipidemia (OR 11.58, 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 CoA vs. VSD 1.44, 0.79-2.64) after adjusting for other factors.

**Conclusions** - While 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.

**Key words:** coarctation of the aorta; congenital heart disease; coronary artery disease; population
Introduction

Significant coarctation of the aorta (CoA) was first surgically repaired in the mid 1940s, while 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 paper by Presbitero et al., which showed that patients with repaired coarctations still died, on average, at a much earlier age than the general population\(^3\). Since then, researchers have been trying to examine the cause of this excess mortality. Multiple studies have shown the main cause of death in patients with corrected CoA is coronary artery disease (CAD)\(^4-8\) but none were designed to determine if 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. While 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 pro-inflammatory cytokines that persist post repair\(^9-21\).

Our own clinical observations, however, have not been consistent with the presence of a large burden of CAD in patients with CoA. To our knowledge, no studies have attempted to determine if coarctation of the aorta is a predictor of CAD independent of traditional cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia. Thus, our objectives were three fold: (1) to describe the prevalence of CAD among adults with CoA, (2) to determine if aortic coarctation independently predicts the development of CAD, and (3) to determine if aortic coarctation 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 two 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 the date of birth, date of death and sex. The province wide Quebec Congenital Heart Disease (CHD) Database was created by merging these two databases for the years 1983-2005 and developing algorithms to correctly extract CHD diagnoses\textsuperscript{22-24}. During this period, diagnoses recorded in the databases adhered to the International Classification of Diseases, Ninth Revision (ICD-9). Patients that had at least one 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 one or two CHD diagnoses via the use of a previously described hierarchical algorithm\textsuperscript{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 health care system between January 1, 1983 and December 31, 2005 inclusively\textsuperscript{22}.

Study Population

The putative CAD risk factor of interest in this study was the presence of a CoA lesion. In order 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 coronary artery disease. Patients with a final diagnosis of either CoA or VSD were selected from the Quebec Congenital Heart Disease 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 health care ethics boards.

**Study Design**

For the 1st objective, we ascertained prevalent CAD cases among the CoA/VSD cohort adult subjects alive on January 1st 2005 (Prevalence Sample, Figure 1). A patient was considered to have a history of CAD if he/she had at least one CAD diagnosis during the 1983-2005 database follow-up. Prevalence of CAD was then estimated as total number of patients with a history of CAD per 1,000 patients with an underlying diagnosis of CoA vs. VSD.

For the 2nd 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 coronary artery disease (CAD) cases were identified at the first CAD diagnosis in the database after a 5-year wash-out period, from 1983 to 1987, with no CAD diagnosis. CAD cases had to be adults (i.e. age 18 and over) 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 four non-CAD controls per each CAD case. Patients initially selected as controls could later become cases if they later acquired a diagnosis of CAD in the database.

For the 3rd objective we used the same study design as for the 2nd objective, but we restricted the cases to premature CAD (first diagnosis at age 18-55, 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 based on the presence of at least one diagnostic/ procedural code for acute myocardial infarction (AMI) (ICD-9 codes 410.0-414.9), coronary artery bypass grafting (CABG) and/or percutaneous coronary intervention (PTCA/PCI) billed by one of the following specialists: cardiologists, cardiothoracic surgeons, internists and emergency physicians.

Potential confounders were selected a priori as factors that are known to be related to the development of CAD and are likely to be differently distributed among CoA vs. 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) using corresponding ICD-9 diagnostic codes. Age was measured at the index day 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 $\chi^2$ tests, respectively. Prevalence of CAD was estimated in the CoA vs. VSD population alive in the year 2005 (the last year of our database) as the number of CAD patients / 1,000 population and compared by $\chi^2$ tests.

A conditional multivariable logistic regression model adjusted for age, sex, history of
hypertension, history of diabetes 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 (3rd 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 coronary artery disease (Table 1)
The prevalence of CAD in 2005 was slightly higher in the CoA group vs. the VSD group (4.9 vs. 3.5%, p=0.04). When compared to VSD, patients in the CoA group alive in the year 2005 had higher rates of hypertension (44.8 vs. 16.2%, p<0.0001), hyperlipidemia (4.0 vs. 2.4%, p=0.01), congestive heart failure (CHF) (14.8 vs. 7.4%, p <0.0001), stroke (5.6 vs. 2.6%, p <0.0001) and peripheral vascular disease (PVD) (13.1 vs. 2.7%, p=0.0001).

Characteristics of CoA patients who are 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 vs. 32.6, p <0.0001), and had significantly higher rates of cardiovascular risk factors including hypertension (56.3 vs.
25.2%, p<0.0001) and hyperlipidemia (10.4 vs. 0.4%, p <0.0001) than patients with CoA who
did not have CAD.

**The effect of coarctation of aorta on coronary artery disease (Figure 2)**

The logistic regression analysis was performed in the nested case-control sample of 481 adult
CAD cases and risk-set matched 1,924 adult non-CAD controls (**Figure 1**). After adjusting for
age, sex, hypertension, diabetes mellitus and hyperlipidemia, aortic coarctation did not predict
for the presence of coronary artery disease (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 1.0-2.58) were all independent predictors of CAD.

**The effect of coarctation of aorta on premature coronary artery disease (Figure 3)**

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 between 18-55), coarctation of
the aorta 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.

**Discussion**

Our results indicate that patients with coarctation of the aorta in our population did have a
slightly higher prevalence of CAD when compared to 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. conducted a systematic review looking at mortality and morbidity in a population of adults with congenital heart disease. 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 CAD and these results concur with our contemporary findings. Furthermore, peripheral vascular disease and stroke both occurred with a significantly higher prevalence in CoA vs. VSD patients. We feel that a possible explanation for this stems from the known association between hypertension and both stroke and peripheral vascular disease. Multiple studies have shown that hypertension is a risk factor for the development of both stroke and peripheral vascular disease. The phenomenon of a higher prevalence of hypertension in CoA patients is also well described. 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 our knowledge, we are the first group to attempt to determine if coarctation of the aorta is an independent risk factor for the development of CAD. This question is important due to postulated vascular reactivity abnormalities in CoA. Several studies have shown that patients with coarctation of the aorta may have higher rates of endothelial dysfunction, circulating levels of pro-inflammatory 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. If there are innate vascular reactivity defects in these patients, they can potentially predispose to the development of CAD regardless of repair. While some of these studies looked at potential novel mechanisms of disease, many of them enrolled only a small number of patients, and as such, the potential for drawing clinical conclusions from them is limited.
Our results indicate that coarctation of the aorta does not predict the development of coronary artery disease after adjusting for other risk factors. In fact, we found that coronary artery disease in this population is mainly caused 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.\textsuperscript{30-34} We feel that 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 significantly enhance the clinical outcome of these patients.

Limitations

Limitations of our study should be noted. First, this is a retrospective study using an administrative database, and, as such, 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 validated\textsuperscript{22,23} as well as cross referencing data amongst the three provincial databases. With respect to CAD, we minimized the potential bias by using hard cardiovascular endpoints in our definition (i.e. PTCA/PCI, CABG and/or acute MI). Importantly, several studies have validated the specificity of disease definitions based on medical services claims.\textsuperscript{35,36} In addition, we have published several studies using the Quebec CHD database validating disease-specific codes for each study\textsuperscript{22,37,38}. Not withstanding this limitation, we believe that the strength of administrative data for our study question is in 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 to those with VSD drawn from the same population and matched for age, so absence of smoking is not likely to bias our estimates for CoA vs. VSD. Moreover, although we could not measure whether or not 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 coarctation of the aorta on CAD then it would have been important to determine if the observation was driven by patients with coarctation of the aorta who are un-operated or 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 aortic coarctation patients outside our observation period between 1983-2005. Finally, we had a relatively small number of CAD events in CoA patients. However, the total number of events that were used in our multivariate analysis were sufficient to allow us to simultaneously control for potential confounders which were identified a-priori and measured in our database.39

Conclusions

Our results indicate that patients with coarctation of the aorta do have a higher prevalence of CAD when compared to the VSD population. However, our novel finding is that aortic coarctation does not predict for the development of CAD after adjusting for other risk factors. Rather, aging, associated hypertension, hypercholesterolemia and diabetes predispose to CAD in this patient population. Results of our study would suggest that by carefully targeting conventional risk factors, we could possibly decrease the morbidity and mortality of these patients.
Funding Sources: 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 Fond de la Recherche en Sante du Quebec and holds a James McGill Chair at McGill University.

Conflict of Interest Disclosures: None

References:


### Table 1. Baseline characteristics of patients with CoA and VSD from the Quebec CHD database in the year 2005 (prevalence sample) *

<table>
<thead>
<tr>
<th></th>
<th>CoA</th>
<th>VSD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median (IQR))</td>
<td>31.1 (24.1-43.4)</td>
<td>30.0 (22.9-40.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>397 (52.5)</td>
<td>2,854 (44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prevalence of CAD (%)</td>
<td>37 (4.9)</td>
<td>224 (3.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>AMI (%)</td>
<td>23 (3)</td>
<td>181 (2.8)</td>
<td>0.69</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>12 (1.6)</td>
<td>83 (1.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>PCI/PTCA (%)</td>
<td>12 (1.6)</td>
<td>51 (0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>339 (44.8)</td>
<td>1,052 (16.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>44 (5.8)</td>
<td>380 (5.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>30 (4.0)</td>
<td>157 (2.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Congestive Heart Failure (%)</td>
<td>112 (14.8)</td>
<td>482 (7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>42 (5.6)</td>
<td>171 (2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic Renal Failure (%)</td>
<td>6 (0.8)</td>
<td>55 (0.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>99 (13.1)</td>
<td>176 (2.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The distribution of covariates in CoA vs. VSD patients in the CoA-VSD cohort was compared by Wilcoxon rank sum and chi-square tests. IQR, inter-quartile range; COA, aortic coarctation; VSD, ventricular septal defect; AMI, Acute Myocardial Infarction; CAGB, Coronary Artery Bypass Grafting; PTCA, Percutaneous Coronary Intervention/Percutaneous Transluminal Coronary Angioplasty*
Figure Legends:

Figure 1. Derivation of the study samples

Figure 2. Multivariable analysis of the effect of CoA vs. VSD on CAD (nested case-control sample)

Figure 3. Multivariable analysis of the effect of CoA vs. VSD on premature CAD (nested case-control sample – premature CAD)
Quebec CHD Database
1983 – 2005
N=71,467

Coarctation
1983 – 2005
N=1,359

Age ≥ 18
1988 – 2005
N=798

Alive in 2005
N=756

PREVALENCE SAMPLE
Subjects age ≥ 18
and alive in 2005
N=7,237

VSD
1983 – 2005
N=14,333

Alive in 2005
N=6,481

Age ≥ 18
1988 – 2005
N=7,003

Without CAD
N=745

With CAD
N=53

1st CAD Diagnosis in 1988 – 2005
N=49

1st CAD Diagnosis made at age ≥ 18
N=48

With CAD
N=487

1st CAD Diagnosis in 1988 – 2005
N=437

1st CAD Diagnosis made at age ≥ 18
N=433

Without CAD
N=6,516

NESTED CASE-CONTROL SAMPLE
CAD CASES
N=481(n=124 premature CAD)

NESTED CASE-CONTROL SAMPLE
MATCHED NON-CAD CONTROLS*
N=1,924(n=248 controls for premature CAD)

* For 481 cases(age18+), we matched 4:1 within calendar time riskset
The n=124 premature CAD were matched separately 2:1 by exact age within calendar time riskset
Lower Risk for CAD

CoA vs. VSD
OR: 1.04 (0.68, 1.57)

Males vs. Females
OR: 2.13 (1.62, 2.80)

Hypertension
OR: 1.95 (1.44, 2.64)

Diabetes
OR: 1.68 (1.09, 2.58)

Hyperlipidemia
OR: 11.58 (5.75, 23.31)

Age (per 10 years increase)
OR: 2.28 (2.09, 2.48)

Higher Risk for CAD

Log Odds Ratio* (95% Confidence Interval)
Lower Risk for CAD

CoA vs. VSD
OR: 1.44 (0.79, 2.64)

Males vs. Females
OR: 1.62 (1.03, 2.54)

Hypertension
OR: 2.41 (1.40, 4.15)

Diabetes
OR: 2.75 (1.12, 6.79)

Higher Risk for CAD

Log Odds Ratio (95% Confidence Interval)
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. published online June 6, 2012;
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/early/2012/06/04/CIRCULATIONAHA.111.088294

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/