Circulation

ORIGINAL RESEARCH ARTICLE

Sex-Related Differences in Patients Undergoing Thoracic Aortic Surgery

Evidence From the Canadian Thoracic Aortic Collaborative

BACKGROUND: Contemporary outcomes after surgical management of thoracic aortic disease have improved; however, the impact of sex-related differences is poorly understood.

METHODS: A total of 1653 patients (498 [30.1%] female) underwent thoracic aortic surgery with hypothermic circulatory arrest between 2002 and 2017 in 10 institutions of the Canadian Thoracic Aortic Collaborative. Outcomes of interest were in-hospital death, stroke, and a modified Society of Thoracic Surgeons–defined composite for mortality or major morbidity (stroke, renal failure, deep sternal wound infection, reoperation, prolonged ventilation). Multivariable logistic regression was used to determine independent predictors of these outcomes.

RESULTS: Women were older (mean±SD, 66±13 years versus 61±13 years; *P*<0.001), with more hypertension and renal failure, but had less coronary disease, less previous cardiac surgery, and higher ejection fraction than men. Rates of aortic dissection were similar between women and men. Rates of hemiarch, and total arch repair were similar between the sexes; however, women underwent less aortic root reconstruction including aortic root replacement, Ross, or valve-sparing root operations (29% versus 45%; *P*<0.001). Men experienced longer cross-clamp and cardiopulmonary bypass times, but similar durations of circulatory arrest, methods of cerebral perfusion, and nadir temperatures. Women experienced a higher rate of mortality (11% versus 7.4%; *P*=0.02), stroke (8.8% versus 5.5%; *P*=0.01), and Society of Thoracic Surgeons–defined composite end point for mortality or major morbidity (31% versus 27%; *P*=0.04). On multivariable analyses, female sex was an independent predictor of mortality (odds ratio, 1.81; *P*<0.001), stroke (odds ratio, 1.90; *P*<0.001), and Society of Thoracic Surgeons–defined composite end point for mortality or major morbidity (odds ratio, 1.40; *P*<0.001).

CONCLUSIONS: Women experience worse outcomes after thoracic aortic surgery with hypothermic circulatory arrest. Further investigation is required to better delineate which measures may reduce sex-related outcome differences after complex aortic surgery.

Jennifer Chung, MD, MSc
Louis-Mathieu Stevens, MD, PhD
Maral Ouzounian, MD, PhD
Ismail El-Hamamsy, MD, PhD
Ismail Bouhout, MD
Francois Dagenais, MD
Andreanne Cartier, MD
Mark D. Peterson, MD, PhD
Munir Boodhwani, MD, MMSc
Ming Guo, MD
John Bozinovski, MD, MSc
Michael H. Yamashita, MDCM, MPH
Carly Lodewyks, MD
Rony Atoui, MD
Bindu Bittira, MD
Darrin Payne, MD
Christopher Tarola, MD
Michael W. A. Chu, MD, MEd
On behalf of the Canadian Thoracic Aortic Collaborative*

*A list of all members of the Canadian Thoracic Aortic Collaborative is given in the Appendix.

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Clinical Perspective

What Is New?

- This study addresses the knowledge gap of the impact of sex on thoracic aortic surgery outcomes using a contemporary, multicenter, retrospective database.
- Women undergo thoracic aortic surgery at an older age and with larger indexed aortic aneurysm size than men.
- Intraoperatively, women undergo fewer concomitant procedures such as aortic root repairs and have shorter cardiopulmonary bypass times, and they experience similar rates of contemporary brain protective strategies.
- Nevertheless, women experience significantly worse outcomes with female sex identified as an independent predictor of mortality, stroke, and a composite end point for mortality and morbidity, after multivariable analysis.

What Are the Clinical Implications?

- Sex-specific considerations are important when considering thoracic aortic surgery.
- Future research should focus on the development of a personalized approach to thoracic aortic surgery with respect to sex; for example, use of a lower size threshold for women may be considered to allow for earlier intervention and improved outcomes.

Well-recognized differences between women and men in the pathophysiology, treatment, and outcomes in cardiovascular disease have prompted calls for a sex-specific approach to research and clinical care.[1] In recent years, sex-related differences have been identified across the spectrum of valve surgery, coronary surgery, and mechanical circulatory support.[2–6] In abdominal aortic aneurysm disease, multiple large studies have found women to be less likely to undergo surgery, as well as survive to discharge after both open and endovascular repair.[7–9] Similar studies in patients with thoracic aortic disease are lacking.

Thoracic aortic surgery remains an area in which a substantial opportunity exists for improving perioperative outcomes. Complex thoracic aortic surgery requiring hypothermic circulatory arrest (HCA) represents higher-risk surgery with a 20% to 30% adverse event rate for patients undergoing elective arch surgery and a 15% to 30% mortality rate for patients undergoing emergent acute type A aortic dissection repair.[10–13] A personalized approach to female and male patients may prove to be an important strategy for improving overall surgical outcomes.

Our objective was to investigate sex-related differences in patients undergoing thoracic aortic surgery involving circulatory arrest by comparing clinical presentation, surgical strategies, and patient outcomes, to identify potentially modifiable practices that may mitigate any sex-related disparities in outcome.

METHODS

Data, analytic methods, and study materials from this study will not be made available because the database used here is the subject of other ongoing studies by our group.

Study Population

The Canadian Thoracic Aortic Collaborative (CTAC), a network of aortic surgeons across Canada, retrospectively compiled a comprehensive database of consecutive cases of aortic surgery using circulatory arrest. All affiliated surgeons were invited to voluntarily contribute their data as long as they were able to provide consecutive cases with complete datasets. There were a total of 52 contributing surgeons from 10 centers, with the lowest-volume center contributing 34 cases and the highest-volume center submitting 394 cases. Each center obtained local ethics approval from their respective institutional review boards, and individual informed consent was waived at all centers. All extents of thoracic aortic surgery including hemiarch replacements, total arch reconstructions, distal arch, and descending thoracic aortic repairs were included if circulatory arrest was used with or without cerebral perfusion techniques. Elective and emergent cases were included, as were cases with concomitant surgery. Circulatory arrest cases for thoracoabdominal aortic repair, or for those not involving aortic repair (ie, congenital cases, tumor removal, etc), were excluded.

Primary Outcomes

Three major outcomes were evaluated: in-hospital mortality, in-hospital stroke, and a modified version of the Society of Thoracic Surgeons–defined composite end point for mortality or major morbidity (STS-COMP). This composite end point was defined as the occurrence of 1 or more of the following end points: in-hospital mortality, stroke, dialysis-dependent renal failure, deep sternal wound infection, reoperation, or prolonged ventilation of >40 hours.

Statistical Methods

Continuous variables were expressed as mean±SD or median (interquartile range), and were compared using *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as frequencies (%) and were compared using Pearson χ^2 test or Fisher exact test, as appropriate. Statistical significance was set at $\alpha = 0.05$.

Factors associated with the 3 major outcomes were identified through logistic regression models using least absolute shrinkage and selection operator selection methods to identify candidate variables. Variables assessed as potential risk factors included preoperative baseline characteristics (age, aortic valve disease, aortic diameter, presence of dissection or rupture, urgent status of surgery, and comorbidities), as well as operative data (extent of aortic reconstruction, concomitant surgeries, surgical times, HCA temperatures, HCA times, and

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cerebral protection strategies). For variables that were not normally distributed (eg, surgical times), a logarithmic transformation was used. To account for the effect of the individual centers, multivariable analyses using mixed effects regression models with logit link and a random effect of the center were then conducted using variables identified through least absolute shrinkage and selection operator methods. Variables were manually excluded in a backward selection process until all variables in the final model were significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

A total of 1653 patients were included in this study, of whom 1155 were males (69.9%) and 498 were females (30.1%). Table 1 summarizes the differences in baseline characteristics between women and men. Women were older (66±13 versus 61±13; *P*<0.001) with a higher rate of hypertension (*P*=0.001) and renal failure (*P*=0.03), whereas men had a higher rate of coronary artery disease (*P*=0.03), poor ventricular function (*P*<0.001), and previous cardiac surgery (*P*=0.01). Other medical history, including rates of previous neurological events (*P*=0.42) and rates of connective tissue disease (*P*=0.41), were similar between the 2 groups. Anatomically, women had a smaller body surface area (*P*<0.001), translating into greater indexed aortic diameters (*P*<0.001). In terms of valve anatomy, men had a greater proportion of bicuspid aortic valves (*P*<0.001) and a higher rate of aortic valve stenosis (*P*=0.04), but the rates of aortic insufficiency were similar (*P*=0.63). Twenty-five percent of women and 22% of men presented with acute aortic dissection or rupture (*P*=0.31), and similar proportions of both groups presented with an emergent or salvage status (*P*=0.51).

Operative Characteristics

Operative characteristics were compared between the 2 groups (Table 2). Female patients underwent less frequent complex proximal aortic operations including aortic root replacement, Ross procedure, or valve-sparing root replacement (29% versus 45%; *P*<0.001). The rates of total aortic arch repair were similar (*P*=0.08), as were the rates of concomitant surgeries (34% versus 38%; *P*=0.13).

In keeping with a higher rate of more complex root procedures, male patients experienced longer cardiopulmonary bypass times (*P*<0.001) and cross-clamp times (*P*<0.001). Absolute HCA time was marginally longer for women (21 [15–33] min versus 20 [14–31] min; *P*=0.009), but clinically relevant HCA time categories (≤30 min, 30–60 min, ≥60 min; *P*=0.44) and cerebral perfusion strategies (*P*=0.87) were similar in both groups, with 75% of all patients receiving antegrade cerebral perfusion. The lowest temperature achieved was also the same between the 2 groups (24 [20–26]°C versus 24 [20–26]°C; *P*=0.66).

Female patients experienced a higher intraoperative transfusion rate (74% versus 62%; *P*<0.001), and this was driven by packed red blood cell use.

Primary Outcomes

In-hospital mortality was higher in women than men (11% versus 7.4%; *P*=0.02). Similarly, the incidence of stroke was higher in women (8.8% versus 5.5%; *P*=0.01). The STS-COMP occurred in 31% of women in comparison with 27% of men (*P*=0.04). Additionally, women also experienced longer hospital lengths of stay (*P*<0.001) and increased rates of prolonged ventilation (0.02). These and other unadjusted early outcomes are summarized in Table 3.

Multivariable Analysis

Predictors of Mortality

Multivariable logistic regression identified female sex as an independent predictor of all 3 outcomes of interest (Figure). Female sex was associated with an increase in the risk of in-hospital mortality (odds ratio [OR], 1.81; 95% CI, 1.21–2.71). Other independent predictors of mortality included age (per 10-year increment, OR, 1.53; 95% CI, 1.24–1.89), acute aortic syndrome (OR, 5.49; 95% CI, 3.43–8.78), peripheral vascular disease (OR, 1.71; 95% CI, 1.18–2.47), and cardiopulmonary bypass time (log-transformed variable, OR, 8.54; 95% CI, 7.06–10.31). Furthermore, the use of HCA without cerebral perfusion was also an independent risk factor for mortality when compared with the use of antegrade cerebral perfusion (OR, 1.76; 95% CI, 1.19–2.60). In the subset of patients with tricuspid aortic valves, female sex remained an independent predictor of death (OR, 1.90; 95% CI, 1.28–2.83; *P*=0.001).

Predictors of Stroke

Female sex was also an independent predictor of postoperative stroke (OR, 1.90; 95% CI, 1.28–2.85). Acute aortic syndrome (OR, 2.07; 95% CI, 1.60–2.67) and cardiopulmonary bypass time (log-transformed variable, OR, 3.57; 95% CI, 2.22–5.73) were also identified as independent predictors of stroke. Predictably, increasing lengths of HCA time were associated with an increased stroke risk (30–60 min versus <30 min: OR, 1.60; 95% CI, 1.14–2.24; >60 min versus <30 min: OR, 1.96; 95% CI, 1.12–3.46). Interestingly, HCA without cerebral perfusion was not an independent risk factor. In the subset of patients with tricuspid aortic valves, female sex was no longer an independent predictor of stroke, but this may be secondary to a low event rate and limited power in this subgroup (87 events in 1157 patients).

Table 1. Baseline Characteristics

Variable	Overall N=1653	Female n=498	Male n=1155	*P* Value
Risk factors				
Age, y	62±13	66±13	61±13	<0.001
Hypertension	1160 (70)	379 (76)	781 (68)	<0.001
Connective tissue disorder				0.41
None	1577 (96)	470 (95)	1107 (96)	
Confirmed	61 (3.7)	23 (4.7)	38 (3.3)	
Suspected	4 (0.24)	1 (0.20)	3 (0.26)	
Diabetes mellitus	202 (12)	72 (14)	130 (11)	0.07
Dyslipidemia	799 (49)	239 (49)	560 (49)	0.93
Renal failure	181 (11)	67 (13)	114 (10)	0.03
Cerebrovascular disease	176 (11)	58 (12)	118 (10)	0.39
Peripheral vascular disease	209 (13)	58 (12)	151 (13)	0.42
Smoker	715 (43)	198 (40)	517 (45)	0.06
Chronic obstructive pulmonary disease	209 (13)	74 (15)	135 (12)	0.08
Previous Cardiac Surgery	266 (16)	65 (13)	201 (17)	0.03
Atrial fibrillation	221 (14)	57 (12)	164 (15)	0.18
Coronary artery disease	371 (22)	95 (19)	276 (24)	0.03
Left ventricular ejection fraction				0.006
LVEF > 60%	1306 (79)	414 (83)	892 (77)	
LVEF 40% to 60%	249 (15)	69 (14)	180 (16)	
LVEF 20% to 40%	81 (4.9)	13 (2.6)	68 (5.9)	
LVEF < 20%	17 (1.0)	2 (0.4)	15 (1.3)	
Anatomy				
Body surface area, m^2	1.9±0.2	1.7±0.2	2.0±0.2	<0.001
Maximum aortic diameter, mm	53±17	53±12	53±19	0.96
Maximum indexed aortic diameter, mm/m^2	28±9	31±8	27±9	<0.001
Aortic valve anatomy				<0.001
Tricuspid valve	1118 (70)	380 (79)	738 (66)	
Bicuspid valve	467 (29)	99 (21)	368 (33)	
Unicuspid valve	12 (0.75)	1 (0.21)	11 (1)	
Aortic stenosis	440 (27)	116 (23)	324 (28)	0.04
Aortic insufficiency	848 (51)	260 (52)	588 (51)	0.63
Presentation				
Acute dissection or rupture	382 (23)	123 (25)	259 (22)	0.31
Dissection	530 (32)	157 (32)	373 (32)	0.75
Rupture	87 (5.3)	31 (6.2)	56 (4.8)	0.25
Urgency status				0.92
Elective	1091 (66)	325 (65)	766 (66)	
Urgent	158 (10)	46 (9.2)	112 (10)	
Emergent (<6 h)	368 (22)	116 (23)	252 (22)	
Salvage	36 (2.2)	11 (2.2)	25 (2.2)	
Emergent or salvage	404 (24)	127 (26)	277 (24)	0.51

Values are n (%) or mean±SD. LVEF indicates left ventricular ejection fraction.

Predictors of Mortality and Morbidity

The STS-COMP provided a global assessment of mortality and morbidity. Once more, female sex was an independent predictor (OR, 1.40; 95% CI, 1.16–1.69). A number of other factors were identified as independent predictors of STS-COMP, such as age, acute dissection

Table 2. Intraoperative Differences Between Female and Male Patients

Variable	Overall N=1698	Female n=506	Male n=1192	*P* Value
Aortic replacement				
Ascending aorta	1468 (89)	456 (92)	1012 (88)	0.02
Arch replacement				
Hemiarch replacement	1364 (83)	401 (81)	963 (83)	0.16
Total arch replacement	288 (17)	99 (20)	189 (16)	0.08
Elephant trunk repair	153 (9.3)	54 (11)	99 (8.6)	0.14
Aortic valve or root surgery				
Aortic valve replacement	308 (19)	112 (22)	196 (17)	0.008
Bentall procedure	473 (29)	103 (21)	370 (32)	<0.001
Ross procedure	34 (2.1)	4 (0.80)	30 (2.6)	0.02
Valve-sparing root replacement	153 (9.3)	37 (7.4)	116 (10)	0.09
Concomitant surgery				
Any concomitant surgery	609 (37)	170 (34)	439 (38)	0.13
Mitral valve replacement	41 (2.5)	12 (2.4)	29 (2.5)	0.90
Mitral valve repair	25 (1.5)	9 (1.8)	16 (1.4)	0.52
Coronary artery bypass grafting	330 (20)	86 (17)	244 (21)	0.07
ASD or VSD closure	26 (1.6)	6 (1.2)	20 (1.7)	0.43
Head or neck vessel surgery	237 (14)	76 (15)	161 (14)	0.48
Other	173 (10)	51 (10)	122 (11)	0.84
Perfusion				
Cardiopulmonary bypass time, min	174 (134, 228)	161 (118, 213)	181 (139, 234)	<0.001
Crossclamp time, min	109 (70, 153)	95 (64, 137)	117 (78, 163)	<0.001
Hypothermic circulatory arrest time, min	20 (14, 31)	21 (15, 33)	20 (14, 31)	0.009
Hypothermic circulatory arrest time categories				0.44
30 min or less	1216 (74)	357 (72)	859 (75)	
Between 30 and 60 min	299 (18)	97 (19)	202 (18)	
60 min or more	133 (8.1)	44 (8.8)	89 (7.7)	
Lowest temperature, °C	24 (20, 26)	24 (20, 26)	24 (20, 26)	0.66
Cerebral perfusion strategy				0.87
No cerebral perfusion	340 (21)	106 (21)	234 (20)	
Antegrade cerebral perfusion	1233 (75)	369 (74)	864 (75)	
Retrograde cerebral perfusion	80 (4.8)	23 (4.6)	57 (4.9)	
Cerebral perfusion time	18 (10, 27)	18 (11, 28)	17 (10, 27)	0.21
Cerebral ischemia time	0 (0, 8)	0 (0, 10)	0 (0, 8)	0.04
Cerebral ischemia time 30 mins or more	60 (3.6)	21 (4.2)	39 (3.4)	0.40
Transfusion				
Any transfusion	1091 (66)	370 (74)	721 (62)	<0.001
Any pRBC used	718 (43)	301 (60)	417 (36)	<0.001
Units of pRBC in transfused patients	4.0 (2.0, 6)	3.0 (2.0, 6)	4.0 (2.0, 6)	0.99
Any FFP used	859 (53)	265 (53)	594 (51)	0.52
Units of FFP in transfused patients	4.0 (2.0, 8)	4.0 (2.0, 7)	4.0 (2.0, 8)	0.09
Any platelet used	882 (53)	280 (56)	602 (52)	0.89
Units of platelet in transfused patients	8.0 (2.0, 12)	8.0 (2.0, 12)	8.0 (2.0, 12)	0.89
Any factor VII used	131 (8.2)	36 (7.6)	95 (8.5)	0.54

Values are n (%) or median (IQR). ASD indicates atrial septal defect; FFP, fresh frozen plasma; IQR, interquartile range; pRBC, packed red blood cell; and VSD, ventricular septal defect

Table 3. Outcome Differences Between the Sexes

Variable	Overall (%) N=1698	Female (%) n=506	Male (%) n=1192	*P* Value
In-hospital mortality	139 (8.4)	54 (11)	85 (7.4)	0.02
Cerebrovascular accident	108 (6.5)	44 (8.8)	64 (5.5)	0.01
STS modified composite end point for mortality and major morbidity	452 (27)	153 (31)	299 (27)	0.04
Cardiac reoperation	139 (8.4)	39 (7.8)	100 (8.7)	0.58
Need for intra-aortic balloon pump	3 (0.18)	1 (0.2)	2 (0.17)	0.90
Prolonged ventilation (>40h)	248 (15)	92 (18)	156 (14)	0.009
Atrial fibrillation	610 (38)	196 (40)	414 (36)	0.12
Postoperative myocardial infarction	18 (1.2)	6 (1.3)	12 (1.1)	0.73
Cardiac arrest	55 (3.5)	16 (3.2)	39 (3.4)	0.86
Dialysis-dependent renal failure	85 (5.1)	24 (4.8)	61 (5.3)	0.70
Septicemia	20 (1.4)	4 (0.9)	16 (1.6)	0.33
Deep sternal wound infection	5 (0.3)	1 (0.2)	4 (0.35)	0.62
Sternal dehiscence	13 (0.79)	3 (0.60)	10 (0.87)	0.58
Temporary neurological dysfunction	38 (2.6)	15 (3.5)	23 (2.3)	0.19
Delirium	324 (20)	97 (20)	227 (20)	0.96
Spinal cord injury	16 (1.0)	4 (0.8)	12 (1.0)	0.66
ICU length of stay, days	2.0 (1.0, 5)	2.7 (1.0, 5)	2.0 (1.0, 4)	0.02
Hospital length of stay, days	8 (6, 13)	9 (6, 14)	8 (6, 12)	<0.001

Values are n (%) or median (IQR). ICU indicates intensive care unit; and STS, Society of Thoracic Surgeons.

or rupture, redo-surgery, and cardiopulmonary bypass time (Table I in the online-only Data Supplement). In the subset of patients with tricuspid aortic valves, female sex remained an independent predictor of STS-COMP (OR, 1.46; 95% CI, 1.16–1.84; *P*=0.001).

DISCUSSION

In the most comprehensive analysis to date, we observed female sex to be an independent risk factor for death, stroke, and the composite end point of mortality and major morbidity in patients undergoing thoracic aortic surgery involving circulatory arrest. This study adds clarity to the current literature, which has been inconsistent in terms of sex-related differences after thoracic aortic surgery. Multiple single-center studies evaluating various techniques of hemiarch and arch replacement have reported similar outcomes between women and men, although 1 study focused on ascending aortic surgery did identify a marginal difference favoring men.[10,14–17] For acute aortic dissections, the International Registry of Acute Aortic Dissection (IRAD) reported that women presented later in the course of disease, with more coma/altered mental status, hypotension, and tamponade, and had significantly higher in-hospital mortality.[18] On the other hand, GERAADA, the German Registry of Acute Aortic Dissections Type A, and a single-center Japanese study, did not identify female sex as an independent predictor of mortality.[11,19] The large all-comers design of our study may have allowed a better assessment of sex-related outcome disparity.

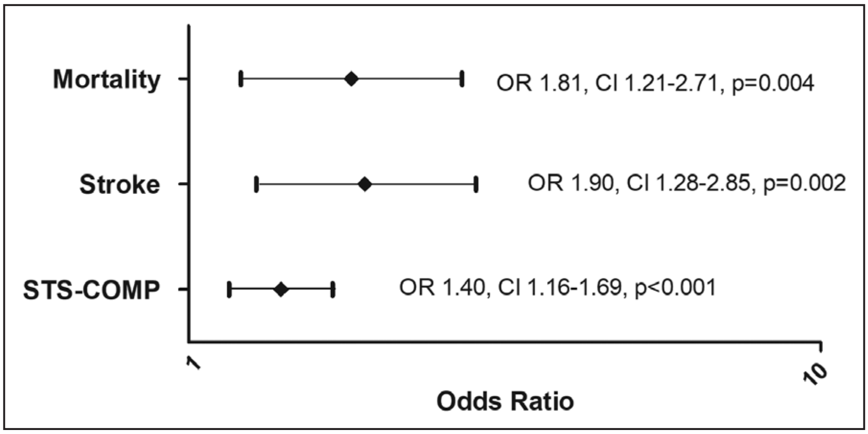

Figure. The effect of female sex on outcomes after multivariable analysis. Diamonds represent the odds ratios (ORs), and ticks represent the 95% CIs. STS-COMP indicates modified Society of Thoracic Surgeons–defined composite end point for mortality and major morbidity.

Several potential explanations for differences in cardiovascular disease management and outcomes have been proposed. First, women tend to present later in the disease process and with more comorbidities. This pattern has been repeatedly demonstrated in coronary surgery, mechanical circulatory support, mitral valve surgery, combined valve and coronary surgery, and ruptured abdominal aortic aneurysm surgery.[5,6,20–22] In our study, female patients were older with larger indexed aortic sizes but had less coronary disease and reduced left ventricular ejection fraction than their male counterparts. Second, the underlying pathology may differ between women and men.[23] In aneurysmal disease, there is evidence that women exhibit increased extracellular matrix breakdown through increased matrix metalloproteinases 2 and 9 expression and decreased tissue inhibitors of metalloproteinases 1 and 2 expression, resulting in greater aortic wall stiffness and perhaps faster aortic growth rates.[24–26] Finally, women may receive less optimal medical and surgical management, as previously shown for coronary disease, mitral valve disease, and ruptured abdominal aortic aneurysms.[5,9,22,23,27] We observed that although women presented with larger indexed aortic sizes, they underwent less complex and potentially less comprehensive root repair than men.

Taken together, our data suggest that aortic surgery is being performed on female patients later in the disease process, which may present technical challenges resulting from smaller body size and increased tissue fragility. Such technical factors may explain the outcome gap as well as the more limited repairs in women we have demonstrated. This hypothesis is supported by literature on abdominal aortic aneurysm repair, where women also encounter higher early mortality rates.[28] Earlier repair at a lower size threshold for women is suggested by Society for Vascular Surgery practice guidelines to improve suitability for endovascular repair, overcome technical barriers, and therefore equalize outcome between women and men.[29,30] It remains a hypothesis whether this approach may also benefit women undergoing open thoracic aortic surgery.

This study has certain limitations. Despite considering a wide array of clinical predictors in our analyses, our study was observational in nature, thus allowing for bias from unmeasured confounders. Furthermore, despite the comprehensive nature of our database, we did not capture several variables that may explain the variation in sex-related outcomes, such as medication use and perioperative care. Additionally, it is difficult using our methodology to tease out the effect of variables highly correlated with sex, such as total blood volume and blood transfusions. Nevertheless, this study provides valuable data that have been lacking regarding sex-related differences in outcome after thoracic aortic surgery.

A striking outcome gap between the women and men undergoing thoracic aortic surgery was demonstrated in this large multicenter study. Surgical repair later in the disease process for women may contribute to this disparity. Further investigation into this and other factors is warranted to ensure continued progress toward eliminating excess risk in different patient groups.

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Correspondence

Michael W. A. Chu, MD, FRCSC, 339 Windermere Rd, B6-106 University Hospital, London, ON N6A 5A5, Canada. Email michael.chu@lhsc.on.ca

Affiliations

University of Toronto, Canada (J.C., M.O., M.D.P.). University of Montreal, Canada (L.-M.S., I.E.-H., I.B.). Laval University, Quebec, Canada (F.D., A.C.). University of Ottawa, Canada (M.B., M.G.). University of British Columbia, Victoria, Canada (J.B.). University of Manitoba, Winnipeg, Canada (M.H.Y., C.L.). Health Sciences North, Sudbury, Canada (R.A., B.B.). Queen's University, Kingston, Canada (D.P.). University of Western Ontario, London, Canada (C.T., M.W.A.C.).

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APPENDIX

List of members of Canadian Thoracic Aortic Collaborative: Chu, Michael W.A., Western University, London, ON Adams, Corey, Memorial University, St. John's, NL Atoui, Rony, Northern Ontario School of Medicine (NOSM), Sudbury, ON Appoo, Jehangir, University of Calgary, Calgary, AB Bittira, Bindu, Sudbury Regional Hospital-Memorial Site, Sudbury, ON Boodhwani, Munir, University of Ottawa, Ottawa, ON Bouhout, Ismail, University of Montreal, Montreal, QC Bozinovski, John, Royal Jubilee Hospital, Victoria, BC Cartier, Raymond, University of Montreal, Montreal, QC Chung, Jennifer, University of Toronto, Toronto, ON Cutrara, Charles, University of Toronto (Trillium), Mississauga, ON Dagenais, Francois, Laval University, Quebec City, QC Demers, Phillipe, University of Montreal, Montreal, QC Dumont, Eric, Laval University, Quebec City, QC El-Hamamsy, Ismail, University of Montreal, Montreal, QC Fedak, Paul, University of Calgary, Calgary, AB Ghoneim, Aly, McGill University, Montreal, QC Guo, Ray, Western University, London, ON Hassan, Ansar, Saint John Regional Hospital, St. John, NB Herman, Christine, Dalhousie University, Halifax, NS Kumar, Kanwal, University of Manitoba, Winnipeg, MB Lachapelle, Kevin, McGill University, Montreal, QC Lodewyks, Carly, University of Manitoba, Winnipeg, MB MacArthur, Roderick, University of Alberta, Edmonton, AB Mazine, Amine, University of Toronto, Toronto, ON McClure, Scott, University of Calgary, Calgary, AB Moon, Michael, University of Alberta, Edmonton, AB Ouzounian, Maral, University of Toronto, Toronto, ON Payne, Darrin, Queens University, Kingston, ON Peterson, Mark, University of Toronto, Toronto, ON Poirier, Nancy, University of Montreal, Montreal, QC Poostizadeh, Ahmad, University of British Columbia, Kelowna, BC Pozeg, Zlatko, Saint John Regional Hospital, St. John, NB Salasidis, Gary, St. Mary's Hospital, Kitchener-Waterloo, ON Stevens, Louis-Mathieu, University of Montreal, Montreal, QC Tarola, Chris, Western University, London, ON Tsang, John, University of Saskatchewan, Regina, SK Valdis, Matt, Western University, London, ON Whitlock, Richard, McMaster University, Hamilton, ON Wong, Daniel, University of British Columbia, Vancouver, BC Wood, Jeremy, Dalhousie University, Halifax, NS Yamashita, Michael, University of Manitoba, Winnipeg, MB

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