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Cardiovascular disease in late survivors of tetralogy of Fallot: A tertiary care center experience

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Clinical Investigation

Cardiovascular Disease in Late Survivors of Tetralogy of Fallot

A Tertiary Care Center Experience

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Patients with tetralogy of Fallot can survive to late adulthood; however, there are few data on cardiovascular outcomes in this population. We conducted a single-center retrospective analysis of cardiovascular outcomes and risk factors in 208 patients with tetralogy of Fallot to better evaluate the burden of cardiovascular disease in this group. Descriptive statistics were used to determine the prevalence of relevant cardiovascular risk factors and outcomes, including a composite analysis of cardiovascular disease. Rates and mean values from the American Heart Association 2011 Heart Disease and Stroke Statistics Update were used as population estimates for comparison.

In tetralogy of Fallot patients, cardiovascular disease prevalence was not different from that found in the general population (40% vs 36%, P=0.3). However, there was significantly more cardiovascular disease in tetralogy of Fallot men aged 20 to 39 years (30% vs 14%, P <0.05) and in tetralogy of Fallot men aged 40 to 59 years (63% vs 29%, P <0.0001). This was due to higher prevalence of coronary disease (12% vs 7%, P <0.05) and heart failure (16% vs 2%, P <0.0001). In particular, the increased prevalence of heart failure (regardless of pulmonary valve disease) accounts for the frequency of cardiovascular disease in tetralogy of Fallot men aged 20 to 59 years.

These data support the need to routinely screen young adult male survivors of tetralogy of Fallot for asymptomatic heart failure. Further studies are needed to determine the incidence, severity, and long-term effects of cardiovascular disease in the adult congenital heart disease population. ***(Tex Heart Inst J 2013;40(4):418-23)***

Key words: *Cardiovascular disease; cardiovascular risk factors; congenital heart disease; heart failure; late outcomes; retrospective studies; tetralogy of Fallot*

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The population of adults living with congenital heart disease is rapidly expanding.[1,2] Patients with tetralogy of Fallot (TOF) form the largest group of adult patients born with cyanotic congenital heart disease. Medical and surgical advances have permitted prolonged survival in cases of TOF, which has been documented well into the 7th and 8th decades of life.[3,4] As this population ages, it is important for cardiologists to begin considering cardiovascular risk factors and cardiovascular outcomes traditionally associated with older age.[5,6] The objective of this study was to investigate the prevalence of traditional cardiovascular risk factors and outcomes in TOF patients at a tertiary care center, in comparison with the general population.

Patients and Methods

All adult patients with TOF (>18 years old) seen at the Center for Adults with Congenital Heart Disease at Washington University in St. Louis were included in the study. Clinical data on all patients were analyzed retrospectively (1998–2011) through the electronic medical record. A standardized data repository was used to extract the following: demographics, concomitant congenital heart disease, cause of death if applicable, systolic and diastolic blood pressure (BP), diagnosis of high BP or use of antihypertensive medications solely for the treatment of hypertension, history of cerebrovascular accident or transient ischemic attack, body mass index, presence of arteriosclerotic coronary artery disease (CAD) by coronary angiography, history of myocardial infarction, presence of obesity, history of heart failure, smoking status (current and past use), presence of hyperlipidemia or use of cholesterol-lowering medications, most recent lipid panel, most recent hemoglobin A_{1C}, fasting blood sugar level, history of prediabetes or diabetes mellitus, diagnosis of metabolic syndrome, and calculation of Framingham risk score.[7]

The prevalence of these cardiovascular risk factors and outcomes was compared to population-level data recently released by the American Heart Association (AHA).[8] These population-level data are derived from a cohort of agencies, including the Centers for Disease Control and Prevention's National Center for Health Statistics; the National Heart, Lung, and Blood Institute; and the National Institute of Neurological Disorders and Stroke, among others. Sources of these data include several surveys, such as the National Health and Nutrition Examination Survey and The National Health Interview Survey, as well as reported data from the World Health Organization and National Vital Statistics System. All sources are listed in the annual report.[8] In many cases, population-level data were limited to percentages, which dictated the format of our statistics. To enable direct comparison of our data with the most recent AHA population-level data, composite endpoints were generated where appropriate. This included cardiovascular disease (CVD), which was defined as any of the following: high BP, stroke, CAD, or heart failure. The 2nd composite, coronary heart disease, included a history of myocardial infarction, angina, or CAD as evidenced by more than mild atherosclerosis on angiography. The presence of heart failure was determined by the review of records wherein a clinical diagnosis of heart failure had been made (that is, discharge summaries or clinic notes that specifically discuss the presence of heart failure), and not on the basis of diagnostic testing, such as review of echocardiograms or nuclear-perfusion studies. High BP was defined as one or more of the following: systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or the use of antihypertensive medication solely to treat hypertension. A medication originally prescribed for treatment of heart failure, albeit with BP-lowering properties, was not considered diagnostic of high BP in this study group unless concomitant high BP was documented in the chart. In the original AHA data, high BP was also defined as "being told ≥2 times by a health professional that BP was high"—a definition that could not be used in our study because of the retrospective nature of our data analysis. Hyperlipidemia was diagnosed if the total cholesterol level was ≥240 mg/dL, the low-density-lipoprotein (LDL) cholesterol level was ≥160 mg/dL, or a cholesterol-lowering medication was prescribed. Patients were deemed overweight if the body mass index was ≥25 kg/m^2 and obese if the body mass index was ≥30 kg/m^2. Prediabetes was defined as a fasting blood sugar level of 100–125 mg/dL, and diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL, a hemoglobin A_{1c} level ≥6.5%, or a random plasma glucose level ≥200 mg/dL with signs or symptoms of hyperglycemia.[9] Metabolic syndrome was defined as 3 or more of 5 metabolic indicators as described by the Adult Treatment Panel III.[10] All data arising from physical examination criteria, such as body mass index, were collected at the most recent clinic visit. Blood pressure was taken at each clinic visit, with a minimum review of at least 3 previous clinic-visit BP readings to determine if high BP was present. Lipid levels, fasting blood sugar levels, and hemoglobin A_{1c} levels were included in the analysis if they were drawn within the previous 5 years.

The data were analyzed with use of SAS software version 9.3 (SAS Institute Inc.; Cary, NC). Descriptive statistics were generated and study prevalence rates were determined and compared with population rates by using exact tests for a binomial distribution. Exact 95% confidence intervals (CIs) were also created for study prevalence rates. A P value of <0.05 was considered significant. Patients consented to ongoing retrospective studies at The Center for Adults with Congenital Heart Disease. This study was performed in compliance with the human-studies guidelines at Washington University, and the institutional review board approved this study.

Results

A total of 208 patients with TOF were seen at our center and consented to have their data used for research during the study period. Men comprised 53% (n=110) of the patients analyzed, and 47% (n=97) were women. The mean age was 39 years, and ages ranged from 18 to 81 years. All patients had undergone previous definitive repair of TOF. One patient had a residual ventricular septal defect and associated cyanosis secondary to Eisenmenger syndrome.

Descriptive Characteristics

Seventeen patients (9%) had complex TOF anatomy; pulmonary atresia was the most common complicating diagnosis (n=10; 5%). Thirteen patients were dead at the time of data collection (6%); endocarditis was the most common cause of death (n=3) in this cohort. However, because the data were gathered by retrospective chart review, any out-of-hospital death—and particularly any sudden cardiac death—could not be accurately evaluated. Additional descriptive statistics are listed in Table I.

Prevalence of Cardiovascular Disease

There was no significant difference in overall composite CVD in this TOF population (40% vs 36%, P=0.3). However, subgroup analysis (on the basis of sex and age) showed that there was significantly more CVD in TOF men aged 20 to 39 years (30% vs 14%, $P<0.05$) and in TOF men aged 40 to 59 years (63% vs 29%, $P<0.0001$). We analyzed the components of this composite endpoint to identify the conditions that were responsible for the observed difference and found that high BP was less prevalent overall in TOF (23% vs

TABLE I. Descriptive Characteristics of the 208 Study-Group Patients

Variable	Available Sample (n)	Mean ± SD or Frequency (%)
Age (yr)	208	39 ± 12
Female sex	97	97 (47)
Systolic blood pressure (mmHg)	182	117 ± 15
Diastolic blood pressure (mmHg)	182	73 ± 10
Body mass index (kg/m²)	163	27 ± 7
Total cholesterol (mg/dL)	110	164 ± 48
LDL cholesterol (mg/dL)	107	95 ± 36
HDL cholesterol (mg/dL)	108	45 ± 17
Triglycerides (mg/dL)	109	126 ± 93
Fasting blood sugar (mg/dL)	146	97 ± 24
Hemoglobin A_{1c} (%)	32	6 ± 1
Framingham Risk Score	98	3.9 ± 3.6
Myocardial infarction	182	3 (2)
Coronary artery disease	162	8 (5)
High blood pressure	183	41 (22)
Stroke	182	12 (7)
Overweight	171	83 (49)
Obese	171	45 (26)
Heart failure	182	29 (16)
History of tobacco use	177	29 (16)
Current tobacco use	177	13 (7)
Dyslipidemia	142	26 (18)
Prediabetes	156	34 (22)
Diabetes mellitus	156	14 (9)
Metabolic syndrome	148	24 (16)

HDL = high-density-lipoprotein; LDL = low-density-lipoprotein; n = sample size available for given value

Data are presented as mean ± SD or as number and percentage.

34%, $P<0.05$). However, heart failure was significantly more common in TOF, both overall (16% vs 2%, $P<0.0001$), and specifically in men aged 20 to 39 years (15% vs 0.2%, $P<0.0001$) and in men aged 40 to 59 years (23% vs 2%, $P<0.0001$). Heart failure was also more common in women with TOF aged 20 to 39 years (11% vs 0.3%, $P<0.0001$) and 40 to 59 years (12% vs 1%, $P<0.05$). Coronary disease was observed more frequently in TOF (12% vs 7%, $P<0.05$), with the greatest difference seen in men aged 40 to 59 years (21% vs 6%, $P<0.05$) and in women aged 40 to 59 years (21% vs 6%, $P<0.05$). However, the rates of myocardial infarction were not statistically different between the study cohort and the general population (1.7% vs 3.1%, $P=0.3$). The final component of composite CVD, cerebrovascular disease, was also more common in TOF (7% vs 3%, $P<0.05$), particularly in men and women aged 40 to 59 years (Fig. 1).

To further define the origin of the increased risk of heart failure in TOF, we performed a descriptive subgroup analysis. This analysis showed that of the 29 patients with heart failure, 45% (n=13) were due to biventricular failure, 41% (n=12) were due to right ventricular failure, and 14% (n=4) were due to left ventricular (LV) failure. Of the 12 with right-sided heart failure, all but 2 had severe pulmonic insufficiency; the remaining 2 had severe pulmonic stenosis or Eisenmenger syndrome from a ventricular septal defect. Of those with biventricular failure, 62% (n=8) had concomitant moderate-to-severe pulmonic insufficiency. Patients with heart failure secondary to severe pulmonary valve disease (insufficiency or stenosis) were excluded to better judge whether heart failure was more common in TOF regardless of pulmonary valve disease. In the absence of such disease, there remained a trend toward increased prevalence of heart failure (4.9% vs 2.4%, $P=0.07$).

Lipids, Metabolism, and Smoking

There was a nonsignificant trend toward lower total cholesterol levels in patients with TOF. Eight percent of patients had a total cholesterol level ≥240 mg/dL versus 15% of the general population ($P=0.05$). High LDL cholesterol levels (≥130 mg/dL) were less common in TOF patients as well (15% vs 32%, $P<0.0001$). The average LDL cholesterol level in this cohort was 95 mg/dL (95% CI, 88–102), versus the population mean of 115 mg/dL ($P<0.0001$). However, HDL cholesterol ≤40 mg/dL was seen more frequently in TOF (44% vs 19%, $P<0.0001$); and the average HDL cholesterol level in TOF patients was 45 mg/dL (95% CI, 41–48) compared with 53 mg/dL in the general population ($P<0.0001$). There was no statistically significant difference in the prevalence of overweight patients; however, TOF patients were less severely overweight, with fewer classified as obese (26% vs 34%, $P<0.05$). Prediabetes was less common in TOF patients (22% vs 37%, $P<0.0001$), and there was no difference in diabetes mellitus between groups. Metabolic syndrome was also less prevalent in TOF (16% vs 35%, $P<0.0001$), as was smoking (7% vs 21%, $P<0.0001$).

Discussion

Adults with congenital heart disease are living longer, and many with TOF have a near-normal life expectancy.[11] Two previous studies have looked at the presence of CAD in adult congenital heart disease populations[5,6] and have found, not surprisingly, that CAD was present in middle-aged adults with congenital heart disease who had other cardiovascular risk factors, such as high

BP and high cholesterol. The present study is the first analysis of cardiovascular risk factors and outcomes that focuses specifically on the TOF population.

Our data indicate that CVD is more prevalent in TOF men aged 20 to 59 years and appears to be attributable predominantly to higher rates of heart failure, coronary heart disease, and stroke. Of these, the greatest difference was seen in the prevalence of heart failure. Nearly all patients with isolated right ventricular failure, and more than half of TOF patients with biventricular failure, had moderate-to-severe pulmonic insufficiency, which accounts for the increase in heart failure witnessed in our TOF population. However, the remaining 31% of patients (n=9) had isolated LV failure or biventricular failure without pulmonic insufficiency, which remains almost double the current prevalence in the general population. This finding is consistent with recently published data, and indicates that there may be a trend toward higher rates of heart failure even in TOF patients who do not have pulmonary valve disease.[12] Similar findings have previously been published: as early as 2002, it was shown that right ventricular ejection fraction was the most significant predictor of degree of LV dysfunction in late survivors of TOF.[13] The duration of arterial shunt palliation and the regurgitant fraction of aortic insufficiency (if present) were also predictors of LV function, although less significant.[13] This right ventricular–LV interaction was manifest again in a United States cohort in 2004.[14] The mechanism by which a ventricular–ventricular interaction exists is not well understood and has been postulated to be due to septal fibrosis, akinesis of the septum secondary to patching, altered patterns of septal motion, or possibly demand ischemia. Earlier work has focused on the possibility of an anatomic link, the so-called Torrent-Guasp band: a helical ventricular myocardial band connecting the right and left ventricles.[15,16] However, as in the case of most hypotheses, data to the contrary also exist.[17]

Despite the difference in prevalence of CVD in TOF men aged 20 to 59 years, modifiable risk factors such

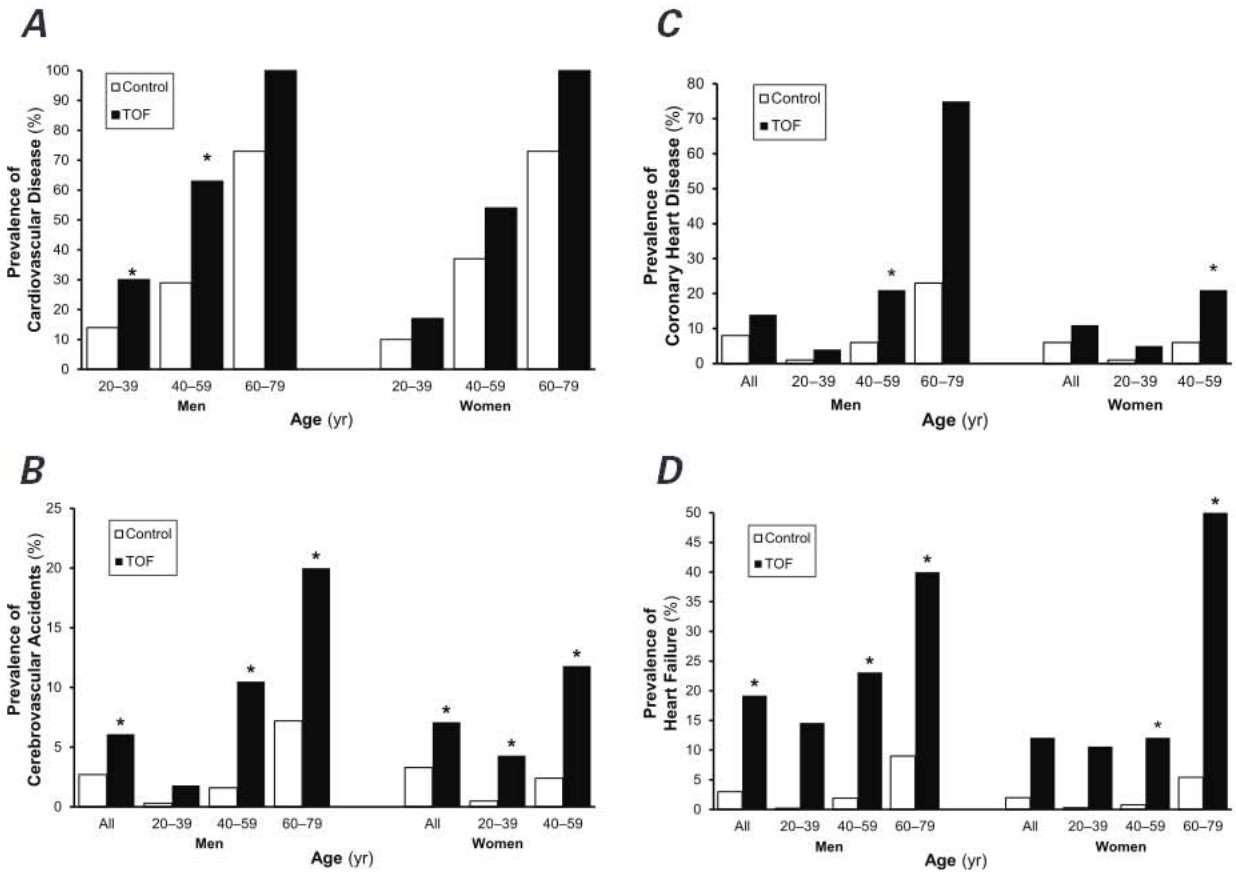

Fig. 1 *Prevalence of **A**) cardiovascular disease, **B**) cerebrovascular accidents, **C**) coronary heart disease, and **D**) heart failure in the control group and tetralogy of Fallot (TOF) patients by sex and age. Cardiovascular disease was significantly more prevalent among men with TOF aged 20 to 39 and 40 to 59 years. Cerebrovascular disease was more prevalent in TOF men over age 40 and in TOF women over age 20. Coronary heart disease was more prevalent in middle-aged and older TOF patients, and the age-adjusted prevalence of heart failure was higher in all TOF patients aged 40 to 79 years than in the comparable general population cohort. Control group data are drawn from the general population.*

*P <0.05

as abnormal lipid profile, obesity, and smoking were less common in the TOF population. A simple explanation could be that the mean age of the TOF group was lower than the mean age of the general population, thereby tending toward better metabolic numbers; or these results could arise from the ongoing medical care and routine screening and counseling that TOF patients receive over their lifetimes.

There have been data regarding CVD in geriatric congenital heart patients, in whom mortality rates appear to be driven by acquired disease and not by congenital disease.[18] Of those included in that report, only 82 patients were classified as having severe lesions, and TOF was included in that subset. Our study is the first to quantify CVD in a large, single-center group of TOF patients with age-stratified outcomes.

Limitations

In common with many other studies of the adult congenital heart disease population, this study is retrospective, and therefore the findings are imperfect in their ability to predict prospective events. These data were generated from our tertiary care center's database; referral bias might therefore be present. Many patients with TOF undergo coronary angiography at a substantially younger age than the general population for reasons unrelated to suspicion of coronary vascular disease. This could lead to earlier identification of CAD in younger, asymptomatic individuals and to the increased prevalence of coronary heart disease identified in our study population. In addition, patients with TOF are more likely to have undergone multiple operations that require cardiopulmonary bypass, which quite possibly account for the increased prevalence of stroke. Finally, rates and mean estimates taken from the AHA 2011 Heart Disease and Stroke Statistics Update were treated as known, fixed population values. Tests to evaluate TOF study-sample differences did not take into account any variability associated with these population estimates.

Conclusions

Cardiovascular disease is more common in TOF men 20 to 59 years old than in age-matched men from the general population, due to an increased prevalence of heart failure. Most heart failure seen in patients with TOF (of all ages) is mediated, at least in part, by pulmonic insufficiency. Nevertheless, there is a trend toward increased numbers of TOF patients developing biventricular or left-sided heart failure in the absence of significant pulmonic valve dysfunction. The trend toward increased coronary disease in TOF patients, particularly in men and women aged 40 to 59 years, is probably attributable to more aggressive follow-up than to an increased incidence of atherosclerosis. These data emphasize the importance of routine clinical screening of young adult male survivors of TOF for asymptomatic heart failure. Monitoring would enable earlier treatment when indicated. On the basis of our results, we believe that cardiovascular risk factor screening in the TOF population should not differ from such screening in the general population. There is a need for large-scale studies to define the incidence, severity, and long-term effects of CVD in the adult congenital heart disease population.

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