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1. Blood pressure response to graded bicycle exercise in males and females across the age and fitness spectrum

Introduction

Hypertension is the strongest modifiable risk factor for cardiovascular disease (CVD), being responsible for over half of CVD deaths related to stroke and coronary artery disease.[1] A phenomenon known as 'masked hypertension' occurs in 10–15% of adults when resting office blood pressure (BP) measurements fail to identify individuals with hypertension that is evident during routine daily activities.[2–4] It has been suggested that an exaggerated BP response during graded exercise testing could predict latent[5–7] and masked hypertension irrespective of resting BP.[8–10]

The normal limits and clinical significance of an exaggerated BP response during exercise have not been clearly defined,[11] and there are differing recommendations for the diagnosis of masked hypertension.[12,13] Until recently, an exaggerated BP response was defined as a maximal systolic BP (SBP_{max}) during exercise of ≥210 mmHg in males and ≥190 mmHg in females.[14] However, SBP_{max} is directly related to aerobic fitness,[15–17] with higher SBP_{max} in fitter individuals, potentially secondary to heightened cardiac output during intensive exercise and not pathological hypertension. As a result, there has been increasing recognition that indexing SBP to exercise workload (W; a metric that is highly co-linear with cardiac output) may provide a greater insight into physiologic systemic vascular function and load.[11,18] Current studies that provide reference values for SBP indexed to W primarily involve individuals referred for clinical exercise testing[19] or small cohorts of athletic individuals.[20–22]

We aimed to validate previous findings relating to SBP indexed to exercise W in a large cohort of males and females across the age and fitness spectrum and assess associations with age, sex, and fitness. Furthermore, we extend this to include changes in diastolic BP (DBP) during exercise using a validated automated BP monitor.

In contrast to the doctrine that higher SBP at maximal exertion is associated with markers of adverse vascular health (defined by associations with older age and lower fitness), we hypothesized that higher SBP measured at peak exercise would paradoxically be associated with younger age and greater fitness. Systolic blood pressure indexed to W has the potential to address this paradox related to flow-associated pressure increases, and thus, we hypothesized that steeper SBP/W-slopes would be associated with markers of adverse vascular health.

Methods

This study includes data from three multicentre international prospective studies, specifically designed to determine the impact of high-volume endurance training on cardiovascular structure and function. The following studies shared the same protocol of incremental exercise to volitional fatigue with the same automated BP measurements: the Pro@Heart study, 'the prospective athlete heart study—elucidating genetic determinants of cardiac remodelling using exercise as an environmental stress' (trial registration number NCT05164328, ACTRN12618000716268); the ProAFHeart study, 'atrial remodelling and the risk of arrhythmias in endurance athletes' (ACTRN12618000711213); and the Master@Heart study (trial registration number NCT03711539). The full protocols for the Pro@Heart and Master@Heart study have been described elsewhere.[23,24] Research protocols received approval from the Human Research Ethics Committees at the various enrolment locations, the Alfred Hospital Ethics Committee, Melbourne,

Australia (333/15, 484/16), and the UZ/KU Leuven Research Ethics Committee, Belgium (S57241, S61336). All participants gave written informed consent.

Study participants

Enrolled participants were current or former endurance-trained athletes or non-athlete control participants (<3 h of endurance exercise per week). Participants were included in the current analysis if they underwent a cardiopulmonary exercise test with concurrent BP assessment between February 2018 and December 2023 at either the Baker Heart and Diabetes Institute, Melbourne, Australia, or UZ Leuven, Belgium. Participants were excluded if they had (i) diagnosed hypertension and were on antihypertensive treatment, (ii) an implanted cardiac device, (iii) permanent atrial fibrillation (AF) or in AF at the time of exercise testing, (iv) clinically diagnosed cardiomyopathy, or (v) missing BP measurement at maximal exertion.

Study protocol

Clinical information and anthropometry

A health and lifestyle questionnaire was administered to participants to establish cardiovascular risk factors, comorbidities, and medication use. Height and weight were measured to calculate body mass index.

Resting blood pressure measurement

Resting BP was assessed in the supine position after 5–10 min of rest, using a correctly sized cuff and digital automatic BP machine (Omron HEM-907XL Pro BP Monitor or Omron model M6W, Omron Healthcare, Kyoto, Japan).

Bicycle exercise test

The exercise test was conducted on an electronically braked bicycle ergometer (LODE Excalibur Sport, Groningen, The Netherlands, or the Avantronic Cyclus 2, Leipzig, Germany). Two minutes of passive resting data were obtained prior to commencing exercise. Following a 1 min warm-up at an initial resistance of 30–60 W, the W increased progressively until volitional fatigue, with the power output at volitional fatigue defined as maximal W (W_{max}). Peak heart rate (HR_{peak}) achieved during exercise was obtained from continuous 12-lead ECG monitoring (Vyntus^{TM} ECG 12-lead PC-ECG, Vyaire Medical, GmbH, Germany).

Blood pressure during exercise

The BP response during exercise was measured with an automated auscultatory BP device that incorporates R-wave gating from QRS complexes derived from a 3-lead ECG and a microphone for K-sound detection (Tango® M2 ECG-gated Automated BP Monitor, Suntech Medical Inc, NC, USA) which has been previously validated during exercise.[25] Measurements were performed seated on the ergometer prior to commencing exercise, at 2 min intervals throughout the test, at maximal exertion, and during recovery. Maximal SBP (SBP_{max}) was determined as the highest SBP achieved during exercise. Based on the prevailing definition,[14] a SBP_{max} ≥ 210 mmHg for males and ≥190 mmHg for females was defined as an exaggerated SBP_{max}. A non-exaggerated SBP_{max} was characterized as a 'normal' SBP_{max}. For each BP measurement, the corresponding W was recorded. The SBP or DBP W-slopes were derived from individual linear regression analyses of SBP and DBP against W with SBP/DBP as the dependent variable (see Supplementary material online, *Figure S1*).

Cardiorespiratory fitness

Gas exchange data were collected continuously throughout the test using a calibrated metabolic cart (Vyntus^{TM} CPX, Metabolic Cart, Vyaire Medical GmbH, or Cortex Metalyzer 3b, Leipzig, Germany) for the measurement of peak oxygen uptake (VO_{2peak}), calculated as the highest value from a 30 s rolling average using 5 s averaged breath-by-breath values.

Statistical analysis

Variables were assessed for normality using the Shapiro–Wilk test. Continuous data are presented as mean (± standard deviation; parametric) or median (interquartile range; non-parametric), and categorical variables as number and frequency or percentage. Where relevant, percentages (%) are reported within each cohort. A $P < 0.05$ (two-tailed) was considered statistically significant. The independent *t*- or Mann–Whitney *U*-tests were used to compare continuous variables and Pearson's x^2 test to compare categorical variables between sexes. Given the sexual dimorphism of BP,[26] we stratified all analyses by sex to account for potential sex-specific BP responses to exercise.

A linear regression was performed on multiple measures for each participant to determine the equation SBP = m × Watt + c and the correlation coefficient (r). A generalized linear mixed model analysis was used to determine the group regression for males and females, with individuals considered as a random effect, thereby accounting for inter-individual variability in baseline ($W = 0$) SBP values. The mean correlation coefficient was determined as the mean of all individual values.

Univariable linear regression analysis was used to assess the potential associations of clinical, demographic, and exercise testing variables with the SBP- and DBP/W-slope. To avoid violating the assumption of independence, SBP_{max} and W_{max} were excluded from the linear regression analysis. Variables

from the univariable analysis were included in a multivariable linear forward stepwise regression model to determine the primary predictors of the SBP- and DBP/W-slope. Due to the representation of weight and BMI in $VO_{2peak,}$ these variables were excluded for violating the assumption of independence. We tested for multicollinearity among predictor variables in the multivariable model using a variance inflation factor (VIF) analysis.

To determine the associations of age and sex (and their interaction) with SBP/W-slope, we used univariate linear regression with age as a co-variate and sex as a fixed factor with an interaction for age and sex on SBP/W-slope as the dependent variable. We explored the potential relevance of SBP_{max} and SBP/W-slope by dividing the cohort into four subgroups based on sex-specific cut-offs for an exaggerated SBP_{max} and SBP-slope values below or above the median. This resulted in the following groups: Group 1, normal SBP_{max} and below-median SBP/W-slope; Group 2, normal SBP_{max} and above-median SBP/W-slope; Group 3, exaggerated SBP_{max} and below-median SBP/W-slope; Group 4, exaggerated SBP_{max} and above-median SBP/W-slope. Demographics were compared across the four subgroups using a one-way ANOVA with a Bonferroni *post hoc* test. All data were analysed using SPSS for windows software version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants characteristics

Five hundred and eighty-nine participants (81% male) were included in the analysis (*Figure 1*). Participants were predominantly endurance-trained athletes (77%) with cycling (46%) being the most popular sport, followed by rowing (24%). *Table 1* presents the characteristics and sex comparisons of the entire cohort. Median resting SBP was higher in males than females [125 (117–134) mmHg vs. 116 (108–125) mmHg, $P < 0.001$]. Males had higher VO_{2peak} [48.0 (40.7–57.1) mL/kg/min vs. 44.8 (34.9–51.7) mL/kg/min, $P <$

0.001] and attained a higher W_{max} than females [360 (300–420) W vs. 293 (229–349) W, $P < 0.001$].

Figure 1

CONSORT diagram: number of participants assessed and excluded and final study sample for analysis stratified for sex.

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Table 1

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Baseline participant characteristics for the full cohort and sex comparison

Variable	All (*n* = 589)	Male (*n* = 480)	Female (*n* = 109)	*P*-value
Demographics and clinical characteristics				
Age (years)	46 (24–56)	48 (25–57)	29 (22–47)	<0.001
Height (cm)	178 ± 8	180 ± 7	171 ± 7	<0.001
Weight (kg)	74 (67–81)	76 (69–83)	66 (60–72)	<0.001
BMI (kg/m^2)	23.4 (21.7–25.1)	23.6 (21.9–25.3)	22.9 (21.1–24.1)	<0.001
Resting SBP (mmHg)	124 (115–132)	125 (117–134)	116 (108–125)	<0.001
Resting DBP (mmHg)	71 (65–78)	72 (66–79)	66 (61–73)	<0.001

Variable	All (*n* = 589)	Male (*n* = 480)	Female (*n* = 109)	*P*-value
Resting HR (b.p.m.)	54 (47–60)	54 (47–59)	53 (46–61)	0.748
Endurance athlete, *n* (%)	455 (77)	366 (76)	89 (82)	
Running, *n* (%)	70 (15)	56 (15)	14 (16)	0.920
Cycling, *n* (%)	211 (46)	199 (54)	12 (13)	<0.001
Rowing, *n* (%)	107 (24)	61 (17)	46 (52)	<0.001
Triathlon, *n* (%)	46 (10)	36 (10)	10 (11)	0.694
Other, *n* (%)	21 (5)	14 (4)	7 (8)	0.103
Non-athlete, *n* (%)	134 (23)	114 (24)	20 (18)	
Medications				
Beta-blocker, *n* (%)	6 (1)	5 (1)	1 (1)	0.907
Lipid-lowering drug, *n* (%)	8 (1)	7 (1)	1 (1)	0.660
Exercise testing and blood pressure response to exercise				
Maximal HR (b.p.m.)	176 (166–188)	176 (164–187)	181 (169–190)	0.041
Maximal workload	333 (282–	360 (300–	293 (229–	<0.001

Variable	All (*n* = 589)	Male (*n* = 480)	Female (*n* = 109)	*P*-value
(Watt)	407)	420)	349)	
VO_{2peak} (mL/kg/min)	47.9 (39.5–56.2)	48.0 (40.7–57.1)	44.8 (34.9–51.7)	<0.001
Exercise SBP_{max} (mmHg)	208 (188–228)	210 (190–230)	199 (183–212)	<0.001
Exaggerated SBP, *n* (%)	316 (54)	246 (51)	70 (64)	0.014
SBP/W-slope (mmHg/W)	0.25 ± 0.11	0.24 ± 0.10	0.27 ± 0.12	0.031
DBP/W-slope (mmHg/W)	0.000 (−0.026 to 0.029)	−0.005 (−0.030 to 0.023)	0.010 (−0.010 to 0.050)	<0.001

Values are median (IQR), mean ± SD, or *n* numbers (%). The *P*-value is for comparison between sexes.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate, VO_{2peak}, peak oxygen uptake, SBP_{max}, maximal SBP; W, workload.

Maximal blood pressure response

The median SBP_{max} for males and females approximated the cut-offs[14] for an exaggerated SBP response [210 (190–230) mmHg in males and 199 (183–212) mmHg in females, $P < 0.001$, for comparison]. Amongst the entire cohort, 51% of male and 64% of female participants had an exaggerated SBP_{max} (*P* =

0.014). This sex difference in SBP_{max} prevalence was primarily driven by the athlete subgroup, whereby an exaggerated SBP_{max} was more prevalent in female (72%) compared with male endurance athletes (58%, P = 0.014). In contrast, for non-athletes, the prevalence of an exaggerated SBP_{max} was similar between females (30%) and males (31%, P = 0.950).

Blood pressure responses indexed to workload

A strong association between SBP and W was observed with a mean R^2 = 0.85 ± 0.18 (P < 0.05). *Figure 2* shows the SBP indexed to W response (SBP/W-slope) for males and females in the full cohort and within the athlete and non-athlete subgroups. In the full cohort, the mean SBP/W-slope was lower in males compared with females (0.24 ± 0.10 mmHg/W vs. 0.27 ± 0.12 mmHg/W, P = 0.031). Subgroup analyses revealed that the sex differences in the SBP/W relationship may have been driven by the non-athlete participants (0.26 ± 0.13 mmHg/W in males vs. 0.36 ± 0.20 mmHg/W in females, P = 0.005). In contrast, there was no sex difference for the mean SBP/W-slope in the athlete subgroup (0.24 ± 0.10 mmHg/W vs. 0.25 ± 0.09 mmHg/W, P = 0.378) for males and females, respectively. The effect of sex on SBP/W-slope was significantly different according to athletic status (sex × athlete interaction, P = 0.02). The median DBP/W-slope was also lower in males vs. females [−0.005 (−0.030 to 0.023) mmHg/W vs. 0.010 (−0.010 to 0.050) mmHg/W, respectively, P < 0.001].

Figure 2

Scatterplot of multiple individual systolic blood pressure measurements during graded bicycle exercise testing with linear regression lines for systolic blood pressure indexed to workload in males (n = 480; blue colour) and females (n = 190; red colour) in *A*) the full cohort, *B*) athletes, and *C*) non-athletes. Overall, females have a steeper mean systolic blood pressure/workload-slope compared with males, 0.27 ± 0.12 mmHg/W vs. 0.24 ± 0.10 mmHg/W, respectively (P =

0.031). This was primarily due to sex differences in non-athletes (sex interaction, P = 0.005), whereas this difference was not apparent in athletes (sex interaction, P = 0.38).

Univariable and multivariable predictors of workload-indexed exercise blood pressure responses

There was a weak positive association between SBP/W-slope and both age (R^2 = 0.106, P < 0.001) and resting DBP (R^2 = 0.030, P < 0.001) for males but not females (*Table 2*). Weak negative associations were also observed between SBP/W-slope and height (R^2 = 0.035, P < 0.001), VO_{2peak} (R^2 = 0.088, P < 0.001), and HR_{peak} (R^2 = 0.072, P < 0.001) in males. Similarly, females had weak negative associations between SBP/W-slope and height (R^2 = 0.055, P = 0.015) and VO_{2peak} (R^2 = 0.084, P = 0.002), but no significant association was seen with HR_{peak}. Weight and resting SBP were not significantly associated with the SBP/W-slope in males or females.

Simple linear regression analysis of systolic blood pressure/workload-slope (mmHg/W) with clinical, demographic, and exercise variables in males and females

Variable	R^2	Unstandardized β	Unstandardized β 95% CI	Standardized β	*P*-value
Males					
Age (years)	0.106	0.002	0.001 to 0.003	0.325	<0.001
Height (cm)	0.035	−0.003	−0.004 to −0.001	−0.186	<0.001

Variable	R^2	Unstandardized β	Unstandardized β 95% CI	Standardized β	*P*-value
Weight (kg)	0.003	−0.001	−0.001 to 0.000	−0.052	0.251
BMI (kg/m^2)	0.005	0.003	−0.001 to 0.006	0.073	0.110
Resting SBP (mmHg)	0.002	0.000	0.000 to 0.001	0.046	0.319
Resting DBP (mmHg)	0.030	0.002	0.001 to 0.003	0.173	<0.001
VO_{2peak} (mL/kg/min)	0.088	−0.003	−0.003 to −0.002	−0.297	<0.001
HR_{peak} (bpm)	0.072	−0.002	−0.002 to −0.001	−0.268	<0.001
Females					
Age (years)	0.005	0.001	−0.001 to 0.002	0.074	0.445
Height (cm)	0.055	−0.004	−0.008 to −0.001	−0.234	0.015
Weight (kg)	0.011	−0.001	−0.004 to 0.001	−0.103	0.284

Variable	R^2	Unstandardized β	Unstandardized β 95% CI	Standardized β	*P*-value
BMI (kg/m^2)	0.000	0.001	−0.009 to 0.011	0.019	0.848
Resting SBP (mmHg)	0.004	−0.001	−0.002 to 0.001	−0.062	0.527
Resting DBP (mmHg)	0.001	0.000	−0.002 to 0.003	0.034	0.728
VO_{2peak} (mL/kg/min)	0.084	−0.003	−0.005 to −0.001	−0.290	0.002
HR_{peak} (b.p.m.)	0.007	−0.001	−0.003 to 0.001	−0.082	0.396

CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; W, workload; VO_{2peak}, peak oxygen uptake; HR_{peak}, peak heart rate.

Weaker associations were seen for the above-mentioned variables and DBP/W-slope in males. For females, the DBP/W-slope did not reveal significant associations with any of the evaluated variables.

Univariable predictors were added into separate forward stepwise multivariable regression models (stratified for sex) to predict SBP/W-slope (*Table 3*). Age, height, and VO_{2peak} were significant predictors in males and explained 14% of the variance in SBP/W-slope. In females, VO_{2peak} and height were identified as significant predictors of the SBP/W-slope, explaining 10% of the variance. For the DBP/W-slope in males, the significant predictors were height, VO_{2peak}, and

HR_{peak} (adjusted R^2 = 0.072, P < 0.001; *Table 3*). For females, the model did not retain any variables.

Predictors of systolic blood pressure/workload-slope (mmHg/W) and diastolic blood pressure/workload-slope (mmHg/W) from stepwise forward multivariable regression

Sex	Predictor	Adjusted R^2	Unstandardized ß	Unstandardized β 95%CI	Standardized ß	*P*-value
SBP/W-slope (mmHg/W)						
Male	Age (years)	0.138	0.001	0.001–0.002	0.195	<0.001
	VO_{2peak} (mL/kg/min)		−0.002	−0.002 to −0.001	−0.180	0.001
	Height (cm)		−0.002	−0.003 to −0.001	−0.142	0.001
Female	VO_{2peak} (mL/kg/min)	0.101	−0.003	−0.005 to −0.001	−0.256	0.007
	Height (cm)		−0.003	−0.007 to 0.000	−0.187	0.047
DBP/W-slope (mmHg/W)						
Male	Height (cm)	0.072	−0.001	−0.002 to −0.001	−0.191	<0.001

Sex	Predictor	Adjusted R^2	Unstandardized ß	Unstandardized β 95%CI	Standardized ß	*P*-value
	VO_{2peak} (mL/kg/min)		−0.001	−0.001 to 0.000	−0.126	0.010
	HR_{peak} (b.p.m.)		0.000	−0.001 to 0.000	−0.098	0.045

SBP, systolic blood pressure; DBP, diastolic blood pressure; W, workload; CI, confidence interval; VO_{2peak}, peak oxygen uptake; HR_{peak}, peak heart rate.

Impact of age and sex on systolic blood pressure/workload-slope

When including age and sex (and their interaction) into a multivariable model, the overall model predicted 9% of the variance in SBP/W-slope ($P < 0.001$). Age ($P < 0.001$), sex ($P = 0.001$), and their interaction ($P = 0.047$) significantly influenced the SBP/W-slope (i.e. sex impacted the effect of age on SBP/W-slope and vice versa). For males, the SBP/W-slope showed a significant increase with age [β = 0.002, 95%CI (0.001–0.003), $P < 0.001$] although in females, there was no significant association ($P = 0.363$). When comparing the SBP/W-slope between sexes, males had a lower SBP/W-slope compared with females [β= −0.093, 95% CI (−0.147 to −0.039), $P = 0.001$].

Subgroup analysis based on maximal systolic blood pressure and systolic blood pressure- or diastolic blood pressure/workload-slope

Four subgroups consisting of normal and exaggerated SBP_{max} and those below- and above-median SBP/W-slope (0.23 mmHg/W for males and 0.25 mmHg/W for females) are characterized in *Table 4*. Individuals with an exaggerated SBP_{max} and low SBP/W-slope were younger with a higher VO_{2peak} compared with the other groups. Conversely, a normal SBP_{max} and high SBP/W-slope

were associated with the lowest VO_{2peak} and older age. The two groups with a normal SBP_{max} had a lower resting SBP compared with the two groups with an exaggerated SBP_{max} (118 ± 13 mmHg and 121 ± 12 mmHg for a normal SBP_{max} and above- or below-median SBP/W-slope, respectively, vs. 127 ± 15 mmHg and 128 ± 12 mmHg for an exaggerated SBP_{max} and above- or below-median SBP/W-slope, respectively, $P < 0.001$). When comparing individuals with values below or above the median DBP/W-slope, a lower DBP/W-slope was associated with younger age ($P = 0.001$) and higher VO_{2peak} ($P = 0.003$;

Participant characteristics stratified by sex-specific subgroups based on an exaggerated maximal systolic blood pressure response to exercise and above/below-median for systolic blood pressure/workload-slope (0.23 mmHg/W and 0.25 mmHg/W for males and females, respectively)

	Normal SBP_{max}		**Exaggerated SBP_{max}**		
Variables	**Low SBP/W-slope(*n* = 160)**	**High SBP/W-slope(*n* = 113)**	**Low SBP/W-slope(*n* = 137)**	**High SBP/W-slope(*n* = 179)**	***P*-value**
Age (years)	41 ± 16	48 ± 16*	34 ± 15*	46 ± 16*	<0.001
Height (cm)	179 ± 8	177 ± 8	180 ± 8	177 ± 7	0.003
Resting SBP (mmHg)	121 ± 12	118 ± 13	128 ± 12*	127 ± 15*	<0.001
Resting DBP (mmHg)	71 ± 10	72 ± 9	69 ± 11	73 ± 10	0.004
Exercise testing					

Variables	Normal SBP_{max}		Exaggerated SBP_{max}		*P*-value
	Low SBP/W-slope(*n* = 160)	**High SBP/W-slope(*n* = 113)**	**Low SBP/W-slope(*n* = 137)**	**High SBP/W-slope(*n* = 179)**	
Maximal HR (b.p.m.)	177 ± 17	172 ± 16	182 ± 14*	173 ± 15	<0.001
Maximal HR (% predicted)[a]	98 ± 7	98 ± 7	99 ± 6	99 ± 6	0.930
VO_{2peak} (mL/kg/min)	47.3 ± 9.9	42.1 ± 9.4*	55.4 ± 11.2*	47.0 ± 12.2	<0.001
VO_{2peak} (% predicted)[b]	118 ± 22	111 ± 24	133 ± 18*	125 ± 22*	<0.001

Values are mean ± SD.

SBP, systolic blood pressure; DBP, diastolic blood pressure; W, workload; HR, heart rate; VO_{2peak}, peak oxygen uptake.

[a]Predicted values based on the equation: 208 − 0.7 × age.[27]

[b]Predicted values based on the FRIEND VO_2 regression equation.[28]

Post hoc Bonferroni comparison: *$P < 0.05$ relative to normal SBP_{max} and low SBP/W-slope.

Discussion

The prevailing clinical paradigm is that an exaggerated SBP_{max} during exercise is indicative of vascular dysfunction and masked hypertension. However, in our large sample of apparently healthy males and females of varied age and fitness,

over 50% of participants had an exaggerated BP response to exercise that was paradoxically associated with higher cardiorespiratory fitness (CRF). In contrast, when SBP was expressed relative to exercise intensity, a higher SBP/W-slope was associated with older individuals with lower levels of fitness. The inverse association between SBP_{max}, age, and CRF suggests that SBP_{max} should not always be considered a valid indicator of vascular pathology. Rather, expressing SBP relative to W or measures of CRF may provide clinical insight into physiological vascular aging. When indexing the SBP during exercise to W, a higher SBP/W-slope was also observed in females compared with males, highlighting the importance of providing sex-specific reference values even for exercise BP responses.

We clearly demonstrate that healthy individuals frequently exceed conventional guidelines for exercise BP (peak SBP ≥ 210 mmHg in males and ≥190 mmHg in females). Thus, the specificity of absolute exercise BP cut-offs for possible identification of masked hypertension and vascular dysfunction needs to be questioned. Our data suggests that relying upon a single measure of SBP at peak exertion may be misleading if one seeks to identify vascular pathology. In ostensibly healthy individuals, we described a consistent linear relationship between SBP and W during incremental exercise, implying that if an individual is capable of exercising to a sufficient W, then a high SBP_{max} is virtually assured. This is illustrated by the fact that those with the highest SBP_{max} have the greatest CRF. Such findings are consistent with prior data suggesting that higher observed SBP_{max} recordings in athletes should lead to a reappraisal of what is considered the upper limits of normal.[17,29]

Evaluating SBP relative to exercise W via SBP/W-slope, has been proposed[11,16] as a method to account for CRF, and may be a better differentiator of physiological vs. pathological vascular function. Several studies have highlighted that all-cause mortality is better predicted when SBP is indexed to W.[18,30] However, there is significant variability in the normal

ranges of the relationship between SBP and W. Hedman *et al.*[19] evaluated age- and sex-specific reference values from 3839 adults undergoing clinical exercise testing and identified a mean SBP/W-slope of 0.41 ± 0.15 mmHg/W in males and 0.52 ± 0.21 mmHg/W in females. These values appear significantly higher compared with the mean SBP/W-slope observed in our cohort, a difference that may result from the fact that the cohort of Hedman *et al.*[19] was referred for clinical exercise testing and were less fit compared with our healthy, mostly athletic, population. However, our observed SBP/W-slopes were also lower than those reported in a study of young professional male handball and female soccer players.[20] In particular, our mean SBP/W-slope for females was approximately half of that derived from the small cohort (n = 25) of young females studied by Bauer *et al.*[20] (0.27 mmHg/W vs. 0.53 mmHg/W). On the other hand, our values are similar to those reported in two recent studies of young healthy endurance athletes.[21,22]

Consistent with our hypothesis, sub-divisions of our healthy cohort provided additional insights. We found that younger and aerobically fitter individuals had a higher SBP_{max} but lower SBP/W-slope and older, less-fit individuals had a lower SBP_{max} but steeper SBP/W-slope. The aforementioned findings support the superiority of exercise BP indexed to W as compared with SBP_{max} for the evaluation of vascular health. Our data provide sex-specific reference values for SBP- and DBP/W-slope across the age and fitness spectrum, facilitating the clinical assessment of BP response during graded exercise testing on a bicycle ergometer.

Sex differences

Despite females having a lower resting BP and SBP_{max} compared with males, we found that females have a higher SBP-slope relative to W, a finding similar to other studies.[20,22] Given that the increase in SBP during exercise is derived from a combination of changes in cardiac output and vascular resistance, this could indicate that females are generating a higher cardiac output for a certain

power output compared with males. Another possibility may be that females have less peripheral vasodilation compared with males during exercise. Nayor *et al.*[31] demonstrated that a higher SBP/W-slope was associated with greater arterial stiffness measured by carotid pulse wave velocity in both sexes, but that this relative stiffness was greater in females. A similar response has been observed in females with heart failure with preserved ejection fraction.[32] During exercise, for a similar stroke volume, female heart failure patients have increased arterial stiffness.[32] We were unable to determine the contribution of vascular stiffness to differential exercise BP responses seen in this study, but our data support the need for sex-specific diagnostic thresholds for BP response to exercise.

When evaluating sex differences in the SBP/W-slope within the athlete subgroup, no significant difference was observed. This finding could generate the hypothesis that exercise training minimizes the sex difference in the SBP/W-slope. It is important to note the issue of sample size, particularly the small number of female non-athletes, means that the results of the larger combined cohort can be considered more robust. Additionally, the term 'athlete' is not binary. Therefore, we propose that the effect of athletic conditioning on the SBP/W-slope can be more reliably assessed using CRF, as measured by VO_{2peak}, rather than athletic status. Nonetheless, the continuous and categorical athletic assessments proved complimentary in our data with greater VO_{2peak} and athletic status being associated with a lower SBP/W relationship.

Sex-specific nomograms

The group regressions for the relationship between SBP and exercise W, derived from a generalized linear mixed model that accounts for individual differences as a random effect, can be interpolated to provide some limits of normality. For example, we derived the following equation for healthy males: exercise SBP = 0.221 [95% CI (0.217–0.226)] × W + 135 [95% CI (133–137)]. Thus, at 200 W, less than 5% of the male population would be expected to have

a SBP ≥ 180 mmHg. For females, the equation—exercise SBP = 0.237 [95% CI (0.228–0.247)] × W + 133 [95% CI (129–136)]—predicts a slightly higher upper limit value of 182 mmHg at 200 W. Similarly, SBP cut-offs can be derived for lesser exercise Ws.

Limitations

We did not assess BP using gold standard 24 h ambulatory BP monitoring to confirm or exclude masked hypertension. Additionally, despite having a female cohort of endurance athletes comparably larger than prior studies, few were aged ≥50 years, limiting our ability to explore the effect of menopause on the SBP/W-slope. Lastly, the study population was primarily white; therefore, future research is needed across more ethnically diverse populations.

One of the strengths of this research is our methodology. Previous studies have relied upon a single measure of SBP obtained at peak exercise intensity or utilized auscultatory measures of BP during exercise, a technique that has seldom been validated against invasive standards. Accurate identification of the K-sounds at peak exercise can be extremely challenging, and it is impossible to blind the observer to context. We used an automated device that measures BP blind to the individuals age, sex, exercise intensity, and previous measures. We found that there was a high correlation for the individual relationships between SBP and W (mean r = 0.92), thereby providing a degree of internal validation.

Conclusions

To our knowledge, this is the largest study providing BP reference values for bicycle ergometer exercise across the age and fitness spectrum using an automated auscultatory BP device. We demonstrate that an exaggerated SBP_{max} is common and is associated with greater fitness. Indexing SBP to exercise W is a more informative metric than SBP_{max}; with higher slopes being associated with older, less-fit individuals and lower slopes with younger, fitter

individuals. Sex, age, exercise intensity, and cardiorespiratory fitness must be considered when evaluating BP response to exercise.

2.Just One in Five Grand Rounds Lectures Given by Women

Women are vastly underrepresented as speakers at grand rounds across the United States, delivering just one in five such lectures, new research shows.

Over a 25-year period, the proportion of female speakers increased by approximately 1% per year, with the representation growing the most for topics related to women's cardiovascular health but not changing for grand rounds with a focus on electrophysiology (EP) and basic/translational science.

"We found that women made up about 20% of the grand rounds lecturers, which is fairly equivalent to the proportion of women in cardiology," lead investigator Ersilia DeFilippis, MD (NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY), told TCTMD. "However, when we look at the talks these women were giving, they were more frequently talking about women's health topics, heart failure, and general cardiology. I think the fact that they were still relatively underrepresented as speakers in some of the procedural specialties shows there are areas for improvement."

Nosheen Reza, MD (Perelman School of Medicine at the University of Pennsylvania, Philadelphia), the study's senior author, said the unequal representation between sexes wasn't surprising, but she was gladdened to see things were improving.

"It was great to see that even though the marginal change is small—on average 1% per year—at least we are making forward progress," she told TCTMD. "For so long, across many metrics, things were stagnant in terms of number of women enrolling in medical school, proceeding to residency, proceeding to training in cardiology. Even if it is small, the percentage [of women given grand rounds talks] is increasing over time. These are good signs."

A grand rounds lecture in the traditional academic model is seen as a marker of expertise and career success, said Reza, but the talks also provide opportunities for further growth and development through clinical and research collaborations. They can also lead to opportunities to mentor younger cardiologists early in their career.

“From my personal experience, I can tell you the impact that it’s had downstream on trainees to see women . . . role models that may not exist at their own institution,” she said.

Cardiology’s Gender Gap

While more women apply to and graduate from medical school—54.6% of medical school students in 2023/2024 were women, according to the Association of American Medical Colleges—the gender gap in cardiology is well documented. The percentage of cardiology faculty at US medical schools is roughly 21%, but the percentage of practicing US cardiologists who are women ranges from 12% to 14%. That percentage is even lower in certain specialties, such as interventional cardiology and EP.

A similar trend is seen in studies looking into gender gaps across leadership positions. Study after study has shown women are less likely to appear as first and senior authors, to be made full professors, and to be assigned leadership positions for cardiovascular clinical trials. One recent analysis found that women made up only 10% of cardiovascular leadership committees of studies published in several high-impact journals.

The new study, which was published online December 23, 2024, in *JAMA Cardiology*, focused on grand rounds from 626 academic centers with internal medicine residency training programs between 1997 and 2022. In total, 3,806 lectures from 42 centers were included in the analysis. Of the talks, 799 (21%) were given by women and 3,007 (79%) by men. Female lecturers were more

likely to be assistant or associate professors, while men were more like to have full professor status.

During the study period, women gave 23.5% of the grand rounds focused on general cardiology, 14.6% of lectures on interventional cardiology, 12.8% on electrophysiology, 18.4% on multimodality imaging, 17.0% on heart failure, 15.0% on vascular medicine, 15.1% on valvular medicine, 17.7% on basic/translational research, 15.1% on cardiac critical care, and 19.5% on quality-improvement/innovation initiatives.

Proportions of women-led talks were higher for medical education (27.1%), adult congenital heart disease (55.6%), cardio-oncology (43.8%), and women's cardiovascular health (82.5%).

Over time, the proportion of female speakers giving general cardiology grand rounds increased by 2% each year, as did the proportion of female speakers for imaging, congenital heart disease, heart failure, and cardio-oncology lectures.

For talks on medical education and quality improvement/innovation, the percentage of female lecturers increased 3% each year, while there was a 6% annual increase in female speakers on women's cardiovascular health. Grand rounds on interventional/valvular/vascular cardiology topics given by women increased 1% year over year, with no change in EP and basic science.

Importance of Diverse Speakers

To TCTMD, DeFilippis emphasized the importance of diversity when selecting grand rounds lecturers. The choice of speaker, as well as the people chosen for other more visible roles, such as leading a clinical trial or presenting from the podium at a major medical meeting, are important for young investigators and trainees "to really see what's possible," she said.

“I think visibility goes a long way in academic cardiology,” said DeFilippis. “A lot of us, whether you’re a woman or man, you spend time at your desk, oftentimes in our little silos, doing your work and taking care of patients, but it’s the people you see along the way who can really make a big difference. Seeing people who look like you on the main stage can be very inspiring.”

The 25-year study period included the COVID-19 pandemic, a time when many hospitals resorted to virtual lectures for grand rounds, she noted. This format, said DeFilippis, may help facilitate diversity of speakers by allowing women who might not be able to travel due to caregiver responsibilities at home to speak.

Seeing people who look like you on the main stage can be very inspiring. Ersilia DeFilippis

In terms of increasing the proportion of women delivering grand rounds lectures, DeFilippis encouraged those in charge of selection to be mindful of including a diverse range of voices.

“I’ve often felt as an early-career professional that cardiology grand rounds are only for the most accomplished professors who are late in their career,” she said. “Maybe it’s time to shift that paradigm a little bit.” Increasing the proportion of women, as well as mixing in younger doctors from diverse backgrounds, “can open our eyes and bring us new perspectives about illness and disease and health,” added DeFilippis.

Reza, who founded and directs the Penn Women in Cardiology program, said that when she served on the grand rounds committee, a look back through the years showed that women made up just 10% of speakers. With that knowledge, the committee made a concerted effort to diversify the list of nominations submitted to the chair and chief of cardiology.

“Within really a short period of time, just a couple of years, more than half of our grand rounds speakers were women for a couple consecutive years pre-COVID and during COVID,” said Reza. “It really didn’t take that much effort. It boiled down to somebody realizing the disparity and taking the time to search and nominate outstanding, well-deserving women who should be giving grand rounds but perhaps had just never been nominated or sponsored or saw that sort of opportunity.”

3.Posttraumatic Stress Disorder Is Associated With Endothelial Dysfunction in Women With HIV

Background

HIV induced endothelial dysfunction (ED) contributes to cardiovascular disease (CVD) in women with HIV (WWH). Although psychosocial stress has been implicated in the development of CVD in HIV, its impact on ED in WWH remains unknown.

Objectives

The authors hypothesized that posttraumatic stress disorder (PTSD) and HIV interact to contribute to ED in WWH.

Methods

We enrolled 87 women from the Women’s Interagency HIV Study in Atlanta, Georgia, who reported previous trauma and completed the PTSD Checklist: Civilian Version (PCL-C), which assesses PTSD symptom severity (PCL-C score) and PTSD status (PCL-C >44). Brachial artery flow-mediated dilation (FMD) was measured to assess endothelial function. The impact of PTSD, HIV, and their interaction on endothelial function was evaluated using linear regression

models adjusted for demographics, CVD risk factors, depressive symptoms, and statin use.

Results

Overall, 55 (63.2%) had HIV, 24 (27.5%) had PTSD, and 13 (14.9%) had both. Those with PTSD were more likely to smoke (18 [75%] vs 28 [44.4%], $P = 0.02$) and have depressive symptoms (14 [58.3%] vs 18 [28.6%], $P = 0.02$) than those without PTSD. In adjusted models, the HIV-PTSD (severity and status) interaction effect on FMD was significant ($P = 0.01$). Both PTSD severity (β per 10-point increase: −0.72% [95% CI: −1.22 to −0.21], $P = 0.01$) and PTSD status (β: −2.51% [95% CI: −4.21 to −0.77], $P = 0.01$) were independently associated with lower FMD in WWH but not in those without HIV.

Conclusions

PTSD is independently associated with ED in WWH. Whether treatment for PTSD improves ED and CVD in WWH needs further study.

Introduction

HIV has persisted as a prevalent, highly morbid pathogen for several decades—affecting over 38 million people.[1] By decreasing mortality rates, the advent and advancement of antiretroviral therapy (ART) have made HIV infection more prevalent and a chronic condition, thereby increasing individual susceptibility to other chronic conditions, including cardiovascular disease (CVD).[1,2] Recent studies have demonstrated a 1.4- to 2-fold increased risk of myocardial infarction (MI) and coronary heart disease in people with HIV (PWH) compared to people without HIV.[2-7] Importantly, the increased risk of cardiac morbidity, including MI, is more pronounced in women with HIV (WWH) compared to women without HIV (WWoH), who are estimated to have a 3-fold increased risk of MI.[5-9] Endothelial dysfunction (ED)—a precursor to atherosclerotic disease

and predictor of adverse cardiovascular outcomes—has been implicated as a mechanism by which HIV may induce CVD.[10-12]

Proposed etiologies of ED in PWH include chronic inflammation, ART side effects, and a high prevalence of traditional CVD risk factors.[13,14] Recent studies have highlighted the critical impact of interactions between HIV, stress exposure, and stress-related psychopathology, including depression, on clinical and subclinical CVD risk.[15-8] In male veterans and women with type 2 diabetes without HIV, posttraumatic stress disorder (PTSD) is associated with macrovascular ED.[19,20] PTSD is prevalent in WWH—with 30% of WWH experiencing recent PTSD—but whether it contributes to ED in WWH is unknown.[21,22] An association between PTSD and ED in WWH may identify PTSD as a therapeutic target to improve ED and the subsequent risk of CVD in this population.[21,23-25] In the current study, we examined how the interaction between PTSD and HIV is associated with endothelial function in women, with the hypothesis that PTSD will be associated with ED in WWH.

Methods

Study design

The current study was a cross-sectional secondary analysis of the BBH (Bone, Brain, and Heart) study, an Emory University substudy of the Atlanta WIHS (Women's Interagency HIV Study) conducted from 2019 to 2023.[26,27] BBH is a prospective cohort study investigating age-related end-organ changes in WWH. The BBH includes WWH with well-controlled HIV, defined as having HIV-1 RNA level <50 copies/mL and on ART for >2 years, and WWoH controls with similar socioeconomic demographics. Cis-gender women <30 years old, those who were pregnant or breastfeeding, nonambulatory, had a history of organ transplantation, bone disorders, autoimmune disorders, cancer, chronic liver disease, chronic kidney disease, CAD, acute coronary syndrome history, heart failure, or stroke were excluded from the BBH study.

We utilized social and demographic characteristics, medication history, health history, blood chemistry, and lipid panels from the Atlanta WIHS parent study for consented patients who were ultimately enrolled in BBH. Additionally, per BBH protocol, we supplemented the above data by conducting health and physical exams, obtaining anthropometric measurements, administering questionnaires, obtaining blood work, and conducting project-specific imaging at BBH entry visits. These entry visits included the collection of the Trauma Experiences Inventory, an inventory that determines exposure to different types of traumatic events, the PTSD Checklist: Civilian Version (PCL-C), and the Patient Health Questionnaire 9.[28] Of the 152 individuals enrolled in BBH at the time of this analysis, we included 87 participants who indicated they experienced trauma on the Trauma Experiences Inventory, completed the PCL-C, and completed endothelial testing through flow-mediated dilation (FMD) in this study. The BBH study was approved by the Institutional Review Board at Emory University, and all participants signed informed consent.[27]

PTSD data collection

We obtained PTSD data via the PCL-C for DSM IV, a 17-item measure of PTSD symptoms (avoidance, hyperarousal, and re-experiencing), with scores ranging from 1 to 5 for each item.[29,30] The total PCL-C score was calculated by aggregating scores of the 17 questions, resulting in a minimum score of 17 and a maximum score of 85. We utilized the raw PCL-C score as a continuous variable to approximate PTSD symptom severity, with higher scores indicating more severity. We also developed a binary PTSD status variable—presence or absence of PTSD—using a cutoff score of 44, which has adequate sensitivity and specificity in diagnosing probable PTSD.[30,31]

Vascular endothelial testing

Following established methodology, we utilized an Acuson 10-MHz linear-array transducer and an Acuson Aspen ultrasound system (Acuson) to measure

FMD.[32] Participants refrained from smoking 24 hours before testing. We obtained longitudinal B-mode ultrasound images of the right brachial artery 2 to 10 cm above the antecubital crease at the end of diastole during rest and hyperemia. At the start of the evaluation, a resting brachial artery diameter was assessed. After obtaining resting measurements, we induced hyperemia by inflating a blood pressure cuff on the patient's right forearm to 200 mm Hg for 5 minutes, then rapidly deflated the cuff. Hyperemic measurements were obtained 1 minute after deflation. An ultrasound technician, blinded to the patient's HIV and PTSD status, measured resting and hyperemia arterial diameters with customized software (Medical Imaging Applications, Inc), and images were digitized online. FMD was defined as the percent change in the brachial arterial diameter during hyperemia compared to rest.[32] There was minimal intraobserver variability in measuring FMD, with a mean difference of 0.82% ± 0.48% and correlation r = 0.97 in 11 participants who underwent FMD measurements twice over an average of 8 days.[33]

Statistical analysis

We present nonnormal continuous variables as median (IQR), normal continuous variables as mean ± SD, and categorical variables as frequencies and percentages. We used independent *t*-tests and Wilcoxon rank-sum tests to compare normal and nonnormal continuous variables across PTSD and HIV groups. We employed Fisher-exact and chi-square testing to compare categorical variables by PTSD and HIV status. Spearman rho test was used to assess correlations between 2 continuous variables. A multivariable linear regression model with cardiovascular and psychiatric risk factors, including age, body mass index, depressive symptoms (Patient Health Questionnaire 9 >4), serum creatinine levels, HIV status, self-reported diabetes, smoking, hypertension, hyperlipidemia, and statin use history, was used to assess PTSD's (score and binary) relationship with FMD and whether HIV-PTSD's interaction was associated with FMD. The interaction between HIV and PTSD

was deemed to be significantly associated with FMD at *P* values <0.05, and significant interactions were investigated by performing the above analysis after stratifying the sample by HIV status. All regression models involving FMD as the outcome variable were allometrically corrected and adjusted for baseline brachial artery diameter.[34] Statistical analyses were performed on R 4.2.0 (the R Foundation).

Results

Sample characteristics

In our sample of 87 individuals, the median age was 49 (IQR: 41-56) years, 89.7% identified as Black, and 63.2% had HIV (**Table 1**). Overall, the median PCL-C score was 31 (IQR: 22.5-45.5), 24 women (27.6%) had PTSD (PCL-C score >44), and 13 participants (14.9%) had concomitant HIV and PTSD. Women with PTSD were more likely to smoke and have depressive symptoms than their counterparts without PTSD, but the remaining clinical and risk factor profiles were similar between the 2 groups (**Table 1**). Sample characteristics did not significantly differ across HIV status.

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
Demographic factors				
Age (y)	49 (41-56)	49 (41-57)	49 (43.8-55)	0.70
Race				
Black non-Hispanic	78 (89.7)	57 (90.5)	21 (87.5)	0.40
White non-Hispanic	5 (5.7)	4 (6.3)	1 (4.2)	

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
Hispanic	1 (1.1)	0 (0.0)	1 (4.2)	
Other non-Hispanic	3 (3.4)	2 (3.2)	1 (4.2)	
Social determinants of health				
Marital status				0.60
Married/partner	26 (29.9)	21 (33.3)	5 (20.8)	
Divorced/widowed/separated	28 (32.2)	19 (30.2)	9 (37.5)	
Never married/other	32 (36.8)	22 (34.9)	10 (41.7)	
Education, terminal degree				0.90
<High school degree	28 (32.2)	20 (31.7)	8 (33.3)	
High school degree	24 (27.6)	17 (27)	7 (29.2)	
Above high school degree	35 (40.2)	26 (41.3)	9 (37.5)	
Lifestyle factors, psychiatric, and medical cardiovascular risk factors				
Body mass index (kg/m^2	33.4 ±6.7	33.7 ± 7.3	32.7 ± 6.1	0.60
Hyperlipidemia	11 (12.6)	7 (11.1)	4 (16.7)	0.70
Hypertension	36 (41.4)	29 (46)	7 (29.2)	0.20
Diabetes	12 (13.8)	9 (14.3)	3 (12.5)	1.00
Smoking	46 (52.9)	28 (44.4)	18 (75)	0.02
Creatinine (mg/dL)	0.8 (0.7-1)	0.9 (0.7-10)	0.8 (0.7-0.9)	0.40
Depressive symptoms (PHQ9>4)	32 (36.8)	18 (28.6)	14 (58.3)	0.02

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
PCL-C score	31 (22.5-45.5)	26 (18-32)	55 (49.3-61.5)	<0.001
HIV-related risk factors				
With HIV	55 (63.2)	42 (66.7)	13 (54.2)	0.40
CD4 cells/cubic (mm)	848.1 (341)	878.7 (351.4)	749.6 (295.9)	0.20
CD4 percent	35.4 ± 9.4	36.02 ± 9.45	33.38 ± 9.31	0.40
Medications				
Cholesterol medication	14 (16.1%)	10 (15.9)	4 (16.7)	1.00

Values are median (Q1,Q3), n (%), or mean ± SD. Overall sample characteristics stratified by PTSD status. *P* values were calculated using 2-sample *t*-tests, Wilcoxon rank sum, Fisher-exact and chi-square tests—significant *P* values <0.05.

PTSD = posttraumatic stress disorder.

Associations between endothelial function and PTSD/HIV in the overall sample

The median FMD for all participants was 4.32% [IQR: 2.56%-5.9%]. In unadjusted analyses, those with PTSD trended towards having lower median FMD than those without PTSD (3.41% [IQR: 1.87%-4.86%] vs 4.49% [IQR: 3.01%-6.48%], *P* = 0.052) (**Central Illustration A**); however, PTSD symptom

severity was not correlated with FMD ($\dot{\rho}$ = −0.16, *P* = 0.14) (**Central Illustration B**). In the adjusted model, those with PTSD (PTSD Status β: −1.06% [95% CI: −2.13 to 0.02], adjusted R^2: 0.22, *P* = 0.06) and those with more severe PTSD symptoms (PCL-C β per 10-point increase: −0.29% [95% CI: −0.63 to 0.06], adjusted R^2: 0.21, *P* = 0.10) had lower FMD than those without PTSD and less severe PTSD symptoms but these associations were not statistically significant (**Figure 1**). FMD was nearly identical between WWH and WWoH (4.16% [IQR: 3%-5.43%] vs 4.39% [IQR: 2.32%-5.9%], *P* = 0.90).

Posttraumatic Stress Disorder and Endothelial Dysfunction in Women With and Without HIV

(A to F) Unadjusted associations between flow-mediated dilation and posttraumatic stress disorder status (PCL-C >44) and posttraumatic stress disorder symptom severity (PCL-C score) in the overall sample (A, B), women with HIV (C, D), and women without HIV (E, F) assessed via Wilcoxon Rank Sum test and Spearman rho test, respectively. Lines with 95% CIs were added to visualize the direction of the relationship between posttraumatic stress disorder symptom severity and flow-mediated dilation in the overall sample (B), women with HIV (D), and women without HIV (F). PTSD = posttraumatic stress disorder.

Adjusted Associations Between Endothelial Function and Posttraumatic Stress Disorder Status or Symptom Severity in the Overall Cohort and HIV Subgroups

The multivariable linear model that calculated adjusted associations included age, body mass index, depressive symptoms (Patient Health Questionnaire 9 >4), serum creatinine levels, HIV status, self-reported diabetes, smoking, hypertension, hyperlipidemia, and statin use history. Negative posttraumatic stress disorder (PCL-C ≤44) was the reference in models with posttraumatic

stress disorder status. PTSD = posttraumatic stress disorder; WWH = women with HIV; WWoH = women without HIV.

PTSD and endothelial function by HIV status

The prevalence of PTSD was high in both HIV groups, with 13 WWH (23.6%) and 11 WWoH (34.4%) having PTSD. In adjusted models, HIV significantly modified the effect of both PTSD symptom severity and PTSD status on FMD (adjusted R^2: 0.28, *P* for interaction: 0.01 for both). In unadjusted analyses stratified by HIV, PTSD was negatively associated with FMD in WWH but not in WWoH. PTSD symptom severity had a significant negative correlation with FMD ($\dot{\rho}$ = −0.29, *P* = 0.034) in WWH but not in WWoH ($\dot{\rho}$ = 0.13, *P* = 0.48) (**Central Illustration D and F**). Correspondingly, PTSD status was associated with significantly lower FMD compared to those without PTSD (1.94% [IQR: 1.66%-3.6%] vs 4.68% [IQR: 3.19%-6.52%], *P* = 0.005) in WWH, a difference that was not present in WWoH (4.52% [IQR: 3.46%-5.44%) vs 3.77% [IQR: 2.97%-5.21%], *P* = 0.53) (**Central Illustration C and E**).

Results were consistent after adjustment for demographics, traditional cardiovascular risk factors, depressive symptoms, statin use, and baseline brachial artery diameter. PTSD status (β: −2.51% [95% CI: −4.21 to −0.77], adjusted R^2: 0.34, *P* = 0.01) and PTSD symptom severity (β per 10-point increase: −0.72% [95% CI: −1.22 to −0.21], adjusted R^2: 0.34, *P* = 0.01) were both independently associated with lower FMD only in WWH and not in WWoH (PTSD status β: 0.49% [95% CI: −1.15 to 2.17], adjusted R^2: −0.01, *P* = 0.54; PTSD symptom severity β per 10-point increase: 0.3% [95% CI: −0.27 to 0.88], adjusted R^2: −0.05, *P* = 0.29) (**Figure 1**).

Discussion

We demonstrate that PTSD is associated with ED, a precursor of clinical CVD, in a cohort of predominantly Black women with well-controlled HIV.[10] Both the

presence and severity of PTSD are independently associated with worse endothelial function in WWH but not in WWoH.

Prior investigations have shown that other forms of psychological stress, such as depression, interact with HIV to affect subclinical and clinical cardiovascular health in different populations adversely.[16,17] In a predominately White and male cohort of U.S. veterans with HIV, the incidence of heart failure events was highest in those with concomitant depression and HIV compared to individuals with either depression, HIV, or no risk factors.[16] Other investigations leveraging data from the WIHS found that more severe depressive symptoms were associated with prevalent carotid plaque in WWH but not WWoH.[17] We saw a similar interaction between HIV and psychological comorbidity on subclinical CVD in this cohort, whereby PTSD was associated with ED after controlling for CVD risk factors, demographics, and depressive symptoms in WWH but not in WWoH.

Our results are particularly relevant to Black women, the predominant demographic studied, who are known to have reduced endothelial vasodilator function and a higher prevalence of PTSD compared to non-Black women and men.[35-39] These sex and race-based differences in endothelial function may explain differences between our findings, which showed no association between PTSD and ED in WWoH, compared to those reported in a Veteran's study, which showed an association between PTSD and ED in men without HIV.[20] Furthermore, the high prevalence of smoking, a major contributor to ED, among those without HIV in our sample could have made it difficult to measure a significant association between PTSD and ED in this subgroup.[40] Our findings and a previous study showing an association between PTSD and ED in Black WWoH with type 2 diabetes demonstrate how comorbidities, such as diabetes or HIV, may influence the relationship between PTSD and vascular function in this group.[19]

The association between PTSD and endothelial function in WWH within our cohort was independent of traditional cardiovascular factors, including smoking. Thus, mechanisms such as the potentiation of inflammation in women with concomitant HIV and PTSD may underscore our findings of increased ED in this subgroup. Through glucocorticoid resistance via alterations in neuroendocrine networks, nuclear factor kappa-B signaling, and increased activation of the sympathetic nervous system, PTSD induces a proinflammatory state with elevated interleukin 6 (IL-6) levels.[41-44] Similarly, HIV increases inflammation through residual viral replication, alteration in gut permeability, and reduction of T-regulatory cells.[45,46] In vitro studies in human endothelial cells have shown that IL-6 interferes with endothelial vasodilatory function by reducing NO synthase activity by inhibiting site-specific phosphorylation and increasing inhibitory caveolin-1 levels, thereby reducing nitric oxide (NO) bioavailability.[47] Therefore, IL-6-mediated inflammation might partly explain the interaction effect between PTSD and HIV on endothelial function in women and should be explored in future studies.

Besides inflammatory-mediated mechanisms, neurohormonal changes and amino acid availability could also contribute to our findings. PTSD-induced glucocorticoid resistance contributes to metabolic syndrome-like physiology, characterized by lipogenesis, hyperleptinemia, and insulin resistance, which harm endothelial function.[48] Finally, individuals with PTSD may also have reduced arginine bioavailability, a precursor to NO, possibly due to increased arginase activity.[49]

Our results suggest that the residual risk for ED in WWH may be partly due to stress-related disorders, such as PTSD. There are effective pharmacologic and counseling management options to mitigate PTSD.[24,25] Thus, timely recognition of these psychological comorbidities through early trauma screening could lead to counseling or therapy that improves endothelial function and subsequently prevents adverse cardiovascular outcomes in this at-risk population. As a

result, future investigations that directly investigate the impact of PTSD therapy on endothelial function and cardiovascular outcomes in WWH would be illuminating.

Study Limitation

Our study did not include men with HIV and was primarily composed of Black WWH, so associations found in our study may not apply to PWH with different demographic characteristics. More work must be done to examine whether trends in our research are seen in PWH cohorts with uncontrolled HIV and other demographic or socioeconomic backgrounds. The lack of association between PTSD and WWoH in our study could be partly attributable to our small sample size, so larger studies with women are needed to confirm our study's findings. These more extensive studies could measure inflammatory biomarkers to directly assess whether the interaction we see is mediated through inflammation, and these studies could examine whether the PTSD-HIV interaction is associated with ED measured through other means, such as reactive hyperemia index or coronary flow reserve. We also relied on self-reported history of cardiovascular risk factors, which could have introduced recall bias and misclassification in our models. Finally, since our study was conducted during the COVID-19 pandemic and COVID-19 has been identified as a cause of ED, these results may have been confounded by unmeasured COVID-19 infections.[50]

Conclusions

PTSD is associated with worse ED in a predominately Black cohort of women with well-controlled HIV, independent of CVD risk factors. Our findings suggest that PTSD is potentially one modifiable risk factor for CVD and that screening for and intervening on PTSD may reduce cardiovascular risk in WWH. Consequently, future studies investigating whether treatment of PTSD will improve ED and CVD risk in WWH are necessary.

4.Congenital Heart Disease Fetuses Have Decreased Mid-Gestational Placental Flow, Placental Malperfusion Defects, and Impaired Growth

Background

Placental health may impact the development and outcomes of congenital heart disease (CHD). CHD fetuses have been shown retrospectively to have decreased placental blood flow.

Objectives

The purpose of this study was to determine if CHD fetuses with decreased placental blood flow have placental pathology at birth and if there is a relationship between placental blood flow, placental pathology, and outcomes.

Methods

We performed a prospective case-control study of 38 CHD fetuses, including 28 with single ventricle physiology and 36 controls. Demographic, clinical, and postnatal biometric data were collected. Umbilical venous volume flow (UVVF) was measured from 2nd trimester fetal echocardiograms. Placentas underwent standardized pathological analysis. Standard descriptive statistics and regression analyses were performed to analyze the relationship between UVVF, placental defects, and outcomes.

Results

CHD fetuses had a 15% decrease in mid-gestational UVVF indexed to fetal weight ($P < 0.01$), and a 27% reduction in UVVF as a proportion of fetal cardiac output ($P < 0.01$) compared to controls. CHD fetuses had increased placental maternal vascular malperfusion (MVM) lesions (44% vs 18%, $P < 0.05$), especially high-grade MVM (39% vs 9.1%, $P = 0.05$), and a trend toward

increased placental fetal vascular malperfusion lesions (42% vs 23%, $P = 0.10$). Placental MVM but not fetal vascular malperfusion lesions were associated with decreased birth weight in CHD fetuses ($P < 0.001$). There was no association between UVVF and placental pathologic findings or fetal growth.

Conclusions

CHD (particularly single ventricle) fetuses have decreased mid-gestational placental blood flow, increased placental malperfusion defects, and impaired fetal growth. Placental MVM may influence impaired fetal growth in CHD.

Introduction

The majority of congenital heart disease (CHD) remains unexplained by currently identified genetic or environmental factors. The maternal-fetal environment may impact the development of, and outcomes associated with, CHD.[1-3] Our understanding of the role of the placenta, despite its critical place in the uterine environment, is quite limited.

The fetal heart and placenta develop concurrently and share several key developmental pathways.[1] Placental and umbilical cord abnormalities are associated with an increased risk of fetal CHD.[4-6] Likewise, there is a known association between maternal hypertensive disorders of pregnancy and fetal CHD.[7,8] Specifically, abnormal vascular development and an imbalance between circulating angiogenic and antiangiogenic factors is implicated in the pathophysiology of both placental abnormalities and CHD.[9,10]

Our limited understanding of the placenta in CHD is in part due to the challenges of assessing the organ in utero. In CHD, traditional Doppler indices of placental blood flow such as umbilical artery (UA) flow and the cerebroplacental ratio (CPR) can vary considerably[6,11,12] and are often normal.[13,14] Umbilical venous volume flow (UVVF) is a validated noninvasive Doppler-derived method to directly assess blood flow from placenta to

fetus.[15] UVVF measurements are highly reproducible; however, additional studies are required to standardize the methodology.[16] UVVF is an early indicator of fetal growth restriction and uniquely reflects characteristics of the placenta rather than the fetus.[17,18] We previously demonstrated decreased mid-gestational UVVF parameters in CHD fetuses compared to controls.[19] In this work, we sought to determine whether CHD fetuses with impaired placental blood flow demonstrate distinct pathological features of the placenta at birth and explore their relationship with adverse clinical outcomes.

Methods

Study design

This was a single-center prospective case-control study performed in the Children's Hospital of Philadelphia's (CHOP) Fetal Heart Program and approved by the CHOP Institutional Review Board (IRB# 17-014630). Patients were consecutively enrolled from February 2018 to October 2019. Maternal-fetal dyads who obtained a fetal echocardiogram at CHOP's Fetal Heart Program either for clinically indicated screening or follow-up for CHD were eligible to participate in the study. Inclusion criteria for controls were fetal gestational age of 18 to 28 weeks, no structural heart disease on fetal echocardiogram, and consent to transfer the placenta to CHOP after delivery. Exclusion criteria for all subjects were multiple gestation, major extracardiac congenital abnormalities (such as congenital diaphragmatic hernia), significant fetal arrhythmia, hydrops fetalis, and the presence of hemodynamically significant maternal CHD (moderate or greater complexity).[20] All eligible dyads were approached for study participation. Enrolled fetuses with CHD included those with single ventricle (SV) CHD (n = 28), tetralogy of Fallot (n = 9), and D-transposition of the great arteries (n = 1). Thirty-six control fetuses were enrolled. Mothers of 11 cases were simultaneously enrolled in a prospective randomized clinical trial of vaginal natural progesterone therapy vs placebo (**NCT02133573**) to evaluate the effect on neurodevelopment for fetuses with

CHD. Placebo or progesterone was administered twice daily between 28 and 39 weeks gestation. Randomization of overlapping study subjects remained blinded to this study's investigators.

The majority of SV CHD were single right ventricle lesions, including hypoplastic left heart syndrome (n = 24) and its variants, such as double outlet right ventricle with mitral atresia (n = 2), and severely right-dominant unbalanced complete atrioventricular canal defects (n = 1). One patient with tricuspid atresia and unobstructed normally related great arteries was included in the SV category. All cases underwent prenatal and/or postnatal genetic evaluation.

Fetal echocardiograms were performed via standard protocol which included assessment of fetal biometry, umbilical vein and artery Doppler tracings, and cardiac rhythm and anatomy. Echocardiographic findings from 2nd trimester studies were compared between cases and controls, however all follow-up fetal echocardiograms performed for cases were included to evaluate longitudinal changes in UVVF. Measurements determined to be inaccurate due to inadequate 2nd trimester image quality were excluded. Controls had single studies performed with no follow-up. Other requisite data collection prior to delivery occurred via medical record review and no additional prenatal visits were required. Medical record review included maternal demographics, fetal gestational age and sex, pregnancy history, maternal medical history, and any known fetal genetic diagnoses. All cases were delivered in either the Special Delivery Unit at CHOP or at the University of Pennsylvania, and placentas were collected at delivery. Control subjects were provided shipment supplies for return of their placentas from delivery hospitals. Postnatal information was obtained from the medical record, or for controls, from a delivery information sheet with delivery course and neonatal biometrics filled out by the mother's obstetrician. A fraction of controls were lost to follow-up and did not return

their placentas and/or provide postnatal medical information. Controls received compensation of $25 for participation in and completion of the study.

UVVF and combined cardiac output measurements

UVVF was calculated as previously published.[19] Briefly, the umbilical vein was visualized in a free loop in the longitudinal plane and 3 measurements of the diameter of the vessel were averaged. Spectral Doppler of the umbilical vein was obtained at an angle of insonation of <20°. Due to the laminar flow pattern in the umbilical vein, the mean velocity is equal to half the maximum velocity. The cross-sectional area of the umbilical vein multiplied by the mean velocity of flow yields the rate of blood flow, UVVF, in mL/min. Interobserver reliability for UVVF measurements by this study's investigators was previously reported as high,[19] and these measurements are included in the standard fetal echocardiogram protocol at CHOP. Measurements were obtained at the time of the study but reviewed for adequacy and accuracy by R.J., D.Y.H., and Z.T.

Combined cardiac output (CCO) was assessed by multiplying the calculated area of both outflow tracts by the velocity-time integral determined by spectral Doppler for both the right and left ventricles and combining the values. In the case of single outflow tracts, only that value was used.

Placental pathology and analysis

All placentas were examined in the pathology department at CHOP utilizing a systematic protocol, including recording the trimmed placental weight, membrane insertion, gross appearance, dimensions of the placental disc, and umbilical cord characteristics. Histologic samples included sections of membranes, umbilical cord, and at least 3 full-thickness sections of nonlesion placental parenchyma. Macroscopic and microscopic lesions were described according to the 2016 Amsterdam Placental Workshop Group[21] and Freedman et al placental phenotypic classification systems[22] (**Supplemental Table 1**).

Microscopic examination was performed by a single perinatal pathologist for all placentas (R.L.), blinded to CHD type, UVVF values, and outcomes.

Statistical analysis

Continuous variables are presented as median (IQR). Categorical parameters are described as frequency (N) and percentage (%). Controls were compared to all CHD and SV cases using chi-squared/Fisher's tests and *t*-test/Wilcoxon tests depending on the variable type and distribution. $P \leq 0.05$ was considered statistically significant. Linear and logistic regressions were performed to analyze the relationship between UVVF indexed to fetal weight (UVVF/Wt), placental defects, and outcomes. Following the exclusion of one patient with an outlier UVVF/Wt measurement, quantile regression was applied to: 1) assess the relationship between UVVF/Wt and gestational age; and 2) evaluate deviation from a healthy reference population. The optimal model for this study population was based on the Akaike information criterion and included both linear and quadratic terms.

All statistical analyses were conducted using R software, version 4.2.3 (R Development Core Team). R package rms was used for quantile regression and R package ggplot2 was used for figure generation.

Results

Subjects

A total of 38 fetal cases, the majority with SV CHD, as well as 36 fetal controls were included. The characteristics of the study population are shown in **Table 1**. The median gestational age of the cases was slightly higher than those of the controls (23 weeks vs 21 weeks; $P < 0.001$). Maternal age was slightly lower in cases compared to controls. There was no difference in the distribution of maternal race, comorbidities, medication exposure, or fetal sex between cases and controls. While only present in few subjects, there was no difference in

prevalence of maternal hypertension, preeclampsia, or maternal aspirin use between groups. Simple, or class I maternal CHD[20] was present in 4 controls (1 small VSD s/p spontaneous closure in childhood, 1 VSD s/p repair in childhood with no residual disease, 1 mild mitral valve prolapse, and 1 double aortic arch s/p neonatal repair), and in 1 case (small VSD s/p spontaneous closure). There was an increased prevalence of maternal diabetes in the control group, which may be due to diabetes being an indication for surveillance fetal echocardiography. One case was diagnosed postnatally with Rubinstein-Taybi syndrome. No other genetic anomalies were identified in cases or controls at the time of medical record review.

Table 1Characteristics of the Study Population

	Controls (n = 36)	All CHD (n = 38)	*P* Value[a]	Single Ventricle (n = 28)	*P* Value[b]
Fetal gestational age (wk)	21.0 (20.0-22.0)	23.0 (22.3-26.8)[c]	**<0.001**	23.0 (22.8-25.0)[d]	**<0.001**
Maternal age (y)	32.0 (29.8-35.0)	30.0 (26.0-33.0)[e]	**0.022**	31.0 (27.0-34.0)	0.209
Maternal race			0.565		0.507
African American	3 (8.3%)	1/31 (3.2%)		0/22 (0%)	
Asian	3 (8.3%)	6/31 (19%)		4/22 (18%)	
Caucasian	28 (78%)	21/31 (68%)		16/22 (73%)	
Hispanic	1 (2.8%)	2/31		1/22 (4.5%)	

Table 1Characteristics of the Study Population

	Controls (n = 36)	All CHD (n = 38)	*P* Value[a]	Single Ventricle (n = 28)	*P* Value[b]
		(6.5%)			
Other	1 (2.8%)	1/31 (3.2%)		1/22 (4.5%)	
Fetal sex			0.532		0.539
Female	7/17 (41%)	12/37 (32%)		9 (32%)	
Male	10/17 (59%)	25/37 (68%)		19 (68%)	
Maternal comorbidity	19 (53%)	15 (39%)	0.251	12 (43%)	0.431
Chronic hypertension	3 (8.3%)	2 (5.3%)	0.670	2 (7.1%)	>0.999
Preeclampsia/Gestational hypertension	1 (2.8%)	3 (7.9%)	0.615	2 (7.1%)	0.577
Diabetes	10 (28%)	1 (2.6%)	**0.002**	0 (0%)	**0.003**
Autoimmune disease	0 (0%)	2 (5.3%)	0.494	2 (7.1%)	0.188
Maternal CHD	4 (11%)	1 (2.6%)	0.194	1 (3.6%)	0.375
Obesity	0 (0%)	2 (5.3%)	0.494	2 (7.1%)	0.188
Renal disease	0 (0%)	0 (0%)		0 (0%)	
Smoker	0 (0%)	0 (0%)		0 (0%)	
Aspirin use	5 (14%)	3 (7.9%)	0.474	2 (7.1%)	0.454
Antihypertensive medication use	0 (0%)	1 (2.6%)	>0.999	1 (3.6%)	0.438

CHD = congenital heart disease.

Values are median (IQR) or n (%). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 31 for fetal gestational age for all CHD subjects.

d n = 24 for fetal gestational age for single ventricle subjects.

e n = 37 for maternal age for all CHD subjects.

Placental blood flow

On manual review, 7 cases lacked adequate image quality for an accurate calculation of second trimester UVVF. At the time of fetal echocardiography, the median fetal weight for cases was higher than controls, in the setting of slightly higher median gestational age (**Table 2**). Accordingly, absolute UVVF was not different between cases and controls. When UVVF was indexed to fetal weight (UVVF/Wt), it was significantly decreased in all cases, as well as the SV subgroup, compared to controls. UVVF as a proportion of cardiac output (UVVF/CCO), reflecting the proportion of fetal circulation returning to the placenta, was significantly decreased in all cases, as well as the SV subgroup, compared to controls. While still within the normal range, there was an increased mean UA pulsatility index (UA PI), and a decreased mean uterine artery PI (UtA PI) in cases compared to controls. The middle cerebral artery PI (MCA PI) and CPR were not different (**Table 2**). UVVF/Wt slowly declined throughout the late 2nd trimester and 3rd trimester in cases who underwent at least one follow-up study (n = 23) (**Figure 1**). Compared to published norms,[23] average UVVF/Wt values for cases were decreased compared to the

50th percentile for healthy fetuses in the 2nd trimester, however continued to trend slightly lower than normal in later gestation.

Table 2Placental Blood Flow Characteristics

	Controls (n = 36)	All CHD (n = 31)	*P* Value [a]	Single Ventricle (n = 24)	*P* Value [b]
Fetal weight (g)	437 (340-546)	629 (530-756)	**<0.001**	646 (528-830)	**<0.001**
CCO (mL/min/kg)	394 (345-472)[c]	442 (321-542)	0.574	371 (321-471)	0.555
UVVF (mL/min)	51 (38-68)	61 (47-84)	0.147	59 (44-80)	0.333
UVVF/Wt (mL/min/kg)	113 (98-145)	96 (79-115)	**0.007**	87 (74-108)	**0.001**
UVVF/CCO (%)	30 (24-39)[c]	22 (18-30)	**0.006**	23 (20-31)	**0.045**
MCA PI	1.67 (1.55-1.79)[c]	1.78 (1.55-1.93)	0.261	1.77 (1.49-1.89)	0.660
UA PI	1.23 (1.16-1.36)	1.36 (1.27-1.48)	**0.020**	1.33 (1.28-1.39)	0.091
UTA PI	0.96 (0.78-1.24)	0.78 (0.66-1.00)	**0.017**	0.80 (0.67-0.99)	**0.038**
CPR	1.36 (1.17-1.52)[c]	1.29 (1.10-1.50)	0.404	1.30 (1.14-1.46)	0.413

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

CCO = combined cardiac output; CPR = cerebroplacental ratio (MCA/UA); MCA = middle cerebral artery; PI = pulsatility index; UA = umbilical artery; UTA = uterine artery; UVVF = umbilical venous volume flow; other abbreviation as in **Table 1**.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 35 for CCO, UVVF/CCO, MCA PI, and CPR for controls.

Umbilical Venous Volume Flow/Wt Throughout Gestation in Congenital Heart Disease Fetuses

UVVF/Wt (ml/min/kg) was measured from serial fetal echocardiograms across gestational age (GA) in CHD fetuses. 95% (p95), 50% (p50), and 5% (p5) are represented by solid lines using a quantile regression with linear and quadratic terms. p5 = 9.35* GA - 0.20* GA^2 - 44.54. p50 = 14.68* GA – 0.27* GA^2 - 100.97. p95 = 6.14* GA – 0.15* GA^2 +83.73. Gray shading represents 95% confidence interval of the p50. Gray dashed lines represent the previously published 5% (p5 [ref]), 50% (p50 [ref]), and 95% (p95 [ref]) regression model of UVVF/Wt over gestation in healthy fetuses.[23] Average UVVF/Wt for cases was decreased compared to the reference 50th percentile for healthy fetuses in the 2nd trimester, however continued to trend slightly lower than normal in later gestation. CHD = congenital heart disease; UVVF = umbilical venous volume flow.

Placental pathology

Thirty-nine percent of control subjects were lost to follow-up and did not provide their placenta or postnatal data for analysis. Placentas from 2 cases who delivered at an outside institution were not available for analysis. In those analyzed, there was no significant difference between placental weight in cases compared to controls (**Table 3**). There was also no difference in the ratio of placental weight to birth weight (PW:BW), an indicator of placental efficiency. Notably, 44% of all cases and 41% of SV cases had lesions associated with maternal vascular malperfusion (MVM) compared to 18% of controls (*P* = 0.041, *P* = 0.088). In particular, cases had significantly more high-grade MVM

lesions compared to controls (39% cases vs 9.1% controls, $P = 0.049$). Lesions associated with fetal vascular malperfusion (FVM) were found in 42% of total cases, and 41% of SV cases, compared to 23% of controls, however this finding was not statistically significant ($P = 0.141$, $P = 0.181$). There was no difference in the prevalence of other placental abnormalities between groups, including umbilical cord abnormalities, chronic inflammation, increased villous vascularity, or other significant pathology (massive perivillous fibrin deposition, delayed villous maturation, or chorangiosis). There was a nonsignificant trend toward an increased prevalence of acute inflammatory lesions in the control placentas ($P = 0.055$).

Table 3Placental Pathology in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value [a]	Single Ventricle (n = 27)	*P* Value [b]
Placenta weight (g)	442 (428-473)	426 (332-490)	0.332	412 (335-493)	0.300
PW:BW	0.13 (0.12-0.14)[c]	0.13 (0.11-0.15)	0.820	0.12 (0.11-0.15)	0.574
Cord abnormality	6 (27%)	11 (31%)	0.790	5 (19%)	0.510
Acute inflammation (AI)	13 (59%)	12 (33%)	0.055	11 (41%)	0.201
AI grade			0.115		0.376
0	9 (41%)	24 (67%)		16 (59%)	
1	11 (50%)	9 (25%)		8 (30%)	
2	2 (9.1%)	3 (8.3%)		3 (11%)	
Chronic inflammation	10 (45%)	23 (64%)	0.169	17 (63%)	0.220

Table 3Placental Pathology in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value[a]	Single Ventricle (n = 27)	*P* Value[b]
(CI)					
CI grade			0.382		0.444
0	12 (55%)	13 (36%)		10 (37%)	
1	6 (27%)	13 (36%)		9 (33%)	
2	4 (18%)	10 (28%)		8 (30%)	
Maternal vascular malperfusion (MVM)	4 (18%)	16 (44%)	**0.041**	11 (41%)	0.088
MVM grade			**0.049**		0.063
0	18 (82%)	20 (56%)		16 (59%)	
1	2 (9.1%)	2 (5.6%)		1 (3.7%)	
2	2 (9.1%)	14 (39%)		10 (37%)	
Fetal vascular malperfusion (FVM)	5 (23%)	15 (42%)	0.141	11 (41%)	0.181
FVM grade			0.295		0.449
0	17 (77%)	21 (58%)		16 (59%)	
1	3 (14%)	11 (31%)		8 (30%)	
2	2 (9.1%)	4 (11%)		3 (11%)	
Increased villous vascularity	3 (14%)	6 (17%)	>0.999	5 (19%)	0.715
Other pathologies[d]	7 (32%)	14 (39%)	0.587	13 (48%)	0.247

PW:BW = placental weight: birth weight ratio; other abbreviation as in **Table 1**.

Values are median (IQR) or n (%). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 18 for PW:BW for controls samples.

d Other pathologies include presence of hemosiderosis, massive perivillous fibrin deposition, delayed villous maturation, chorangiosis, or isolated small for gestational age placenta (<10th percentile).

Clinical outcomes

There was no difference in birth gestational age between cases and controls (**Table 4**). All cases, as well as the SV subgroup, demonstrated significantly decreased birth weight compared to controls (*P* = 0.026 for all CHD, *P* = 0.050 for SV). Birth length was also decreased in cases however there was significant attrition (75%) due to loss to follow-up in controls for this outcome (**Table 4**). There was 1 intrauterine fetal demise at term in a case. All other cases survived to 30 days if inpatient or index hospital discharge, whichever came first.

Table 4Clinical Outcomes in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value [a]	Single Ventricle (n = 27)	*P* Value [b]
Gestational age at delivery (wk)	39.2 (38.5-39.6)[c]	38.9 (38.3-39.6)	0.236	39.0 (38.3-39.7)	0.437
Birth weight (g)	3,358 (3,165-3,742)[c]	3,145 (2,873-3,462)	**0.026**	3,160 (2,905-3,502)	**0.050**
Birth length (cm)	51.4 (49.5-52.5)[c]	48.4 (47.1-50.0)[d]	0.012	48.9 (48.0-51.0)[e]	0.048

Table 4Clinical Outcomes in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value [a]	Single Ventricle (n = 27)	*P* Value [b]
Head circumference (cm)	35.0 (33.8-35.5)[c]	33.5 (32.5-34.5)[d]	0.086	33.5 (32.5-34.5)[e]	0.177

Abbreviation as in **Table 1**.

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c Controls: n = 18 for gestational age at delivery and birth weight. n = 9 for birth length. n = 8 for head circumference.

d All CHD: n = 34 for birth length. n = 33 for head circumference.

e Single ventricle: n = 25 for birth length and head circumference.

When comparing fetuses with evidence of either MVM or FVM to those without, there was no significant difference in the mid-gestational UVVF/Wt of cases or controls (**Table 5**). However, there was significantly decreased birth weight in cases with evidence of either MVM or FVM compared to cases without, which was not present in the control group, though in the setting of 39% attrition of controls for this outcome. Univariable linear regression demonstrated that for cases, the presence of either MVM or FVM lesions was associated with a 382g decrease in birth weight ($P = 0.029$), a relationship not seen in the control group ($P = 0.692$) (**Table 6**). Decreased birth weight in cases compared to controls appeared to be related to MVM lesions in particular but was

independent of the presence of FVM lesions (**Figure 2**). Accordingly, the presence of MVM lesions was associated with a 531g decrease in birth weight for all CHD ($P < 0.001$), and 403g decrease in birth weight for SV cases ($P = 0.017$). There was no significant relationship between MVM lesions and birth weight in the control group, or between FVM lesions and birth weight for any subjects (**Table 6**). There was no significant difference in median intensive care unit length of stay (ICU LOS) in cases with evidence of either MVM or FVM compared to cases without (**Table 5**). Regression analyses did not demonstrate a significant relationship between mid-gestational UVVF/Wt and clinical outcomes (data not shown).

Table 5The Influence of Placental Malperfusion Defects on UVVF and Outcomes

	Controls			**All CHD**		
	MVM/FVM Absent	**MVM/FVM Present**	***P* Value**	**MVM/FVM Absent**	**MVM/FVM Present**	***P* Value**
	(n = 11)	**(n = 9)**		**(n = 11)**	**(n = 18)**	
UVVF/Wt (ml/min/kg)	99.7 (93.2-133.5)	119.1 (113.1-161.7)	0.056	88.2 (83.4-106.9)	96.7 (71.3-118.2)	0.982
	(n = 12)	**(n = 6)**		**(n = 12)**	**(n = 24)**	
Birth weight (g)	3,402 (3,110-3,726)	3,282 (3,206-3,891)	0.750	3,480 (3,064-3,749)	3,130 (2,766-3,258)	**0.039**
				(n = 12)	**(n = 23)**	
ICU LOS (d)				14.5 (10.0-20.5)	17 (10.3-30.0)	0.444

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

FVM = fetal vascular malperfusion; ICU LOS = index hospitalization ICU length of stay; MVM = maternal vascular malperfusion; other abbreviations as in **Tables 1** and **2**.

Table 6Univariable Linear Regression Modeling of the Association Between Presence of Placental Malperfusion Lesions and Birth Weight (g)

	Controls (n = 18)	*P* Value	All CHD (n = 36)	*P* Value	Single Ventricle (n = 27)	*P* Value
Predictor						
MVM/FVM	81.42 (−346.70 to 509.53)	0.692	−381.75 (−726.59 to −36.91)	**0.031**	−230.00 (−599.73 to 139.73)	0.212
MVM	−14.87 (−559.08 to 529.35)	0.955	−531.56 (−829.27 to −233.85)	**<0.001**	−403.47 (−729.76 to −77.17)	**0.017**
FVM	145.13 (−393.67 to 683.94)	0.576	62.34 (−290.41 to 415.10)	0.722	189.46 (−168.31 to 547.23)	0.286

Values are beta coefficient and (95% CI). Three separate univariable linear regressions were applied to each patient population. The independent variable was presence of MVM/FVM lesions, presence of MVM lesions, or presence of FVM lesions. For all models, birth weight (g) was the dependent variable. **Bold** text indicates $P \leq 0.05$.

Abbreviations as in **Tables 1** and **5**.

Impaired Fetal Growth in Congenital Heart Disease Occurs Exclusively With Maternal Vascular Malperfusion Lesions

(A) CHD fetuses but not controls demonstrate significantly decreased birth weight (3,480 g vs 3,130 g; $P = 0.04$) in the presence of PMP lesions. Decreased birth weight in CHD fetuses is seen only in the presence of MVM lesions (3,340 g vs 2,905 g; $P < 0.001$) (B), and not FVM lesions (3,140 g vs 3,160 g; $P = 0.7$) (C). FVM = fetal vascular malperfusion; MVM = maternal vascular malperfusion; PMP = placental malperfusion; other abbreviation as in **Figure 1**.

Discussion

We previously demonstrated in a retrospective study that fetuses with CHD have decreased mid-gestational placental blood flow, however correlation with placental pathology could not be performed.[19] In this prospective cohort, we demonstrate that CHD fetuses, specifically those with SV physiology, have decreased mid-gestational placental blood flow, a high prevalence of placental malperfusion (PMP) defects, and impaired fetal growth resulting in lower birth weight at similar gestational age compared to normal fetuses (see **Central Illustration**). CHD fetuses had on average only 22%, rather than the normal 30%, of fetal CCO returning from the placenta, which we hypothesize, may be due to increased placental resistance. The effect of redistribution of fetal blood flow is unclear, as cerebral blood flow reflected by absolute mid-gestational CPR was not different. Assessment of middle cerebral artery PI and CPR *z*-scores may better reflect the distribution of fetal blood flow given varying fetal gestational ages. The increased mid-gestational UA PI in cases may also reflect increased placental resistance, however decreased flow through the UA despite increased placental resistance may normalize the UA PI, and thus UVVF may be a more reliable indicator of placental flow. The significance of decreased UtA PI in cases is unclear but suggests that placental resistance was not sufficiently elevated at mid-gestation to result in elevated UtA Doppler parameters. Our work confirms that abnormal placental blood flow in fetuses with CHD can be detected as early as mid-gestation.

Placental Malperfusion in Fetal Congenital Heart Disease

Fetuses with CHD have decreased blood flow from the placenta to fetus through the umbilical vein, as measured in second trimester fetal echocardiograms by umbilical venous volume flow. In the setting of unchanged cardiac output, decreased umbilical flow is suggestive of increased placental resistance. These fetuses have a higher incidence of placental malperfusion lesions at birth. Placental maternal vascular malperfusion lesions, in particular, are associated with decreased fetal growth in CHD. Abbreviation as in **Figure 1**.

We have undertaken a rigorous analysis of placental pathology in CHD based on standardized placental phenotypic classification systems.[21,22] An increased frequency of MVM and FVM defects has been reported in CHD.[24-26] The frequency of our placental findings in CHD is similar to published reports,[26,27] however reported frequencies vary widely due to variable patient and control populations, and criteria for placental pathologic diagnosis. FVM can occur secondary to umbilical cord obstruction or flow alterations in CHD which could result in decreased placental blood flow and stasis.[28] MVM is due to defective placental implantation in early pregnancy resulting in inadequate maternal spiral artery remodeling and disrupted intervillous flow.[25] We did not find a significant difference in umbilical cord abnormalities, as has been previously reported in CHD,[29,30] or in the frequency of chronic inflammatory lesions, which when severe, can be a cause of FVM.[21] The trend toward increased low-grade acute inflammation in controls likely reflects induction of most CHD mothers prior to the onset of natural labor, while most control mothers labored naturally.[31]

Interestingly, decreased birth weight in cases compared to controls was only observed in the presence of MVM lesions but was independent of FVM lesions. MVM lesions in controls were not associated with decreased birth weight in our cohort though the number of control samples with MVM was small, suggesting a possible multifactorial etiology for decreased birth weight in CHD. No change

in birth weight was seen in the setting of FVM lesions for cases or controls. MVM and FVM lesions are associated with intrauterine growth restriction,[25,28] a common finding in CHD.[24-27,32] Some retrospective studies lacking control groups have not implicated other placental pathologies in low birth weight in CHD,[33,34] however low placental weight *z*-score at birth and low placental volume by magnetic resonance imaging have been associated with decreased fetal growth in CHD in other studies.[5,35] A direct association specifically between PMP and birth weight in CHD is rarely interrogated.[33,36,37] Our data suggest that the mechanisms underlying MVM may act in synergy with the impaired fetal hemodynamics and/or alterations in systemic oxygenation in fetal CHD to impair fetal growth. While we had hypothesized that UVVF might be a mid-gestational marker of PMP, our analyses revealed no significant association between mid-gestational UVVF and placental pathologic findings or measures of fetal growth. Nevertheless, we demonstrate tangible evidence of altered fetal-placental circulation in CHD. Better understanding of the role of abnormal placental blood flow in CHD could inform the future use of therapeutic agents in utero such as aspirin, known to improve placental perfusion in maternal preeclampsia.[38]

There are several limitations to this study. The small sample size resulted in the study likely being underpowered to achieve statistical significance where clinically meaningful differences may exist. The study may have been underpowered to determine the nature of the relationship between UVVF, placental abnormalities, and many of our study outcomes. Due to technical issues or loss to follow-up, some data were not available for all subjects. High rates of attrition for control subjects' placental and outcomes data could introduce bias, affecting the validity of these outcomes. As UVVF was measured at mid-gestation, there may be additional factors not accounted for that affect placental development between mid-gestation and delivery. Our study demonstrated several significant findings despite a number of factors which may have biased this study toward the null hypothesis. Control subjects were

recruited from referrals due to clinical indications for screening fetal echocardiograms, and thus do not fully represent low risk, normal pregnancies. Eleven cases may have received vaginal progesterone (randomization was blinded) as part of an unrelated clinical trial evaluating the effect of progesterone on neurodevelopment in CHD, an outcome not analyzed in our study. Vaginal progesterone has been associated with vasodilation and improved Doppler flow parameters in utero,[39] which could have biased our results toward the null hypothesis with regard to UVVF. Its impact on PMP lesions at birth is unknown. The frequency of placental abnormalities in our prospective control population may be higher than in more commonly used retrospective control populations, as several indications for fetal echocardiography (ie, diabetes) may increase the risk of abnormal placental pathology. Similarly, the presence of maternal CHD, present in 4 controls and 1 case, has been associated with PMP and decreased birth weight. However, when stratified based on CHD severity according to the 2018 American Heart Association/American College of Cardiology guidelines,[20] several studies have not found a robust association between "simple" maternal CHD, similar to that found in our study subjects, and PMP or impaired fetal growth.[40,41] Comparison of our control subjects with and without both maternal diabetes and CHD revealed no significant differences in maternal or fetal characteristics, placental blood flow, placental pathology, or outcomes (**Supplemental Tables 2 to 5**). Any predisposition to placental defects or poor growth due to maternal diabetes or CHD would most likely bias our results toward the null hypothesis; however, we were able to detect meaningful comparative increases in placental pathology in our cohort. Our findings are most relevant to fetuses with SV CHD and may not be generalizable to other CHD subgroups. Future work comparing placental blood flow and pathology between right and left-sided obstructive lesions will be of great interest, as the degree of fetal brain and placental hypoxia varies.[42] Additional studies in a larger cohort are necessary to determine the relationship between abnormal UVVF parameters and placental pathology at birth, and whether they are

associated with additional outcomes of interest such as abnormal neurodevelopment and increased mortality, which have been associated with placental abnormalities in CHD.[2,43]

Conclusions

In this prospective study, we demonstrate that fetuses with CHD, specifically SV CHD, have decreased mid-gestational placental blood flow, increased frequency of PMP defects, and impaired fetal growth. In addition, a rigorous and systematic evaluation of the placenta in fetal CHD demonstrates an association between decreased fetal growth and the presence of placental MVM lesions but not FVM lesions. Our study did not demonstrate significant associations between impaired mid-gestational UVVF and placental pathologic findings. Despite this, decreased UVVF reflects tangible evidence of abnormal in utero fetal placental blood flow in CHD. There remain significant unknowns regarding the abnormal fetal circulation, its relationship to placental abnormalities in CHD, and how they may contribute to outcome disparities which warrant future investigation. Understanding the mechanism underlying PMP in CHD is of great interest and could inform novel therapeutic targets.

5.Influence of age and sex on the diagnostic yield of inherited cardiac conditions in sudden arrhythmic death syndrome decedents

Introduction

Sudden arrhythmic death syndrome (SADS) refers to a sudden death,[1,2] which remains unexplained despite comprehensive post-mortem examination and a toxicological screen.[3–5] Contemporary studies suggest that SADS may account for up to 40% of sudden deaths in young (<35 years) individuals.[5] Familial clinical evaluation (FE) and post-mortem genetic testing [‘molecular autopsy’ (MA)], have the potential to identify an inherited cardiac condition (ICC) in a significant proportion of decedents, with most diagnoses attributed to inherited

arrhythmia syndromes, including long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT).[1]

The potential to identify underlying ICCs in asymptomatic family members, who may also be at risk of fatal arrhythmias, has led to updated guidelines recommending FE of first-degree relatives of the decedent and MA, following a SADS death, to prevent further tragic sudden deaths in a family.[6,7] Proposed clinical protocols and gene panels have differed between studies historically, leading to disparities in the reported diagnostic yield and the conditions identified in the decedents.[5,8,9] Irrespective of the decedent's demographics and circumstances of death, most families undergo a similar clinical evaluation for underlying ICCs. Though there are some studies reporting differences in baseline demographics for individuals with ICCs, such as a higher prevalence of CPVT in younger patients, no studies to date have reviewed the differences between yield of underlying diagnosis for SADS deaths, according to the age and sex of the decedent. A more personalized approach to the evaluation of SADS families may be more clinically applicable.

We investigated two consecutive cohorts of SADS decedents and their families who were referred to our clinic for evaluation. The objective of this study was to assess the impact of age and sex of the decedents on the diagnostic yield and underlying aetiology of SADS deaths using FE in first degree family members and MA in post-mortem deoxyribonucleic acid (DNA). The diagnostic yield for the combined approach was evaluated in a smaller subset of these cohorts who had undergone both diagnostic methods.

Methods

Case selection

SADS cases were defined as: (i) an unexplained death, (ii) in an individual aged 1–64 years, (iii) with no known prior cardiovascular disease, (iv) who died within 1 h of symptom onset, or an unwitnessed death with the decedent having been seen in good health within 24 h of death, (v) with no cause of death identifiable on comprehensive coronial and/or cardiac autopsy, and (vi) negative toxicology.[3,5,10] This retrospective cohort study included two different cohorts: (i) consecutive referrals for FE at the St George's and Lewisham Hospitals, United Kingdom, tertiary referral Cardiogenetics clinics between 2009 and 2017 and (ii) consecutive referrals for autopsy at the Cardiac Risk in the Young (CRY) Centre for Cardiac Pathology at Royal Brompton Hospital (2007–11) and St George's, University of London (2012–17) with DNA suitable for MA. Cases where cardiac autopsy identified a structural heart disease, such as cardiomyopathy or those with non-specific structural changes on cardiac autopsy, such as idiopathic left ventricular hypertrophy or idiopathic fibrosis were excluded from the study. Consent was obtained from decedent next of kin. The study was approved by St George's University of London ethics (#10/H0803/121, #17/LO/0747).

Familial evaluation

First-degree family members of SADS cases were assessed using a uniform investigation protocol to identify underlying ICCs as previously described.[10] Clinical history, physical examination, baseline electrocardiogram (ECG) with standard (4th intercostal space), and high-lead (2nd and 3rd intercostal space) placement, echocardiogram and 24-h Holter monitoring were offered to all relatives. Exercise testing was performed in relatives over the age of 16 years, and where possible in younger patients at a paediatric unit. If there was suspicion of underlying structural heart disease, cardiac magnetic

resonance imaging was performed. If no diagnosis was established family members were offered drug provocation testing using a class I antiarrhythmic agent [Ajmaline 1 mg/kg (maximum 100 mg) over 5 min]. Further investigations were undertaken at the respective physician's discretion.[11] Standard clinical diagnostic criteria for ICCs were used.[1,12,13] Brugada syndrome diagnoses were also stratified according to the Shanghai consensus diagnostic scoring system.[14] Decedents were allocated the highest score available in their family: definite/probable BrS (score ≥3.5); possible BrS (score 2–3); and low probability (<2).

Molecular autopsy

SADS decedents with appropriate post-mortem DNA samples (in most cases fresh spleen tissue) available were sequenced using next-generation sequencing. Sequencing was performed using the SureSelect system (Aligent Technologies, Santa Clara, CA, USA) or Illumina TruSight Cardio system (Illumina, San Diego, CA, USA). Variants were restricted to those with minor allele frequency <0.001 in genome aggregation database (gnomAD) and non-truncating variants in *TTN* were excluded. Rare variants in 36 major channelopathy and cardiomyopathy genes (see Supplementary material online, *Table S1*) validated to be associated with ICCs and available in the CardioClassifier software (http://www.cardioclassifier.org) were reviewed and manually curated (B.G.) for pathogenicity using the American College of Medical Genetics and Genomics (ACMG) criteria.[15–17] A pathogenic or likely pathogenic variant was deemed diagnostic of the cause of death. Loss of function *SCN5A* variants were deemed diagnostic of BrS.

Statistical analysis

All the variables in the final dataset were explored using graphics, summarized according to their nature and by diagnostic method in *Table 1*. The two cohorts (FE and MA) were analysed separately. There were 407 participants evaluated

by FE, and 424 evaluated by MA. A subset of 71 was tested through both diagnostic methods and therefore was part of both cohorts in the analysis.

Table 1

Cohort characteristics

Demographic	Overall (*n* = 760)	FE cohort (*n* = 336)	MA cohort (*n* = 353)	Combined MA + FE cohort (*n* = 71)	
Sex					*P* = 0.61
Male	505 (66)	228 (68)	233 (66)	44 (62)	
Female	249 (32)	108 (32)	120 (34)	27 (38)	
Missing	6	4 (1)	2 (1)	–	
Age overall mean	31 ± 12	29 (12)[a] 27(20, 36)[b] (1,64)[c]	33(12)[a] 31(23, 41)[b] (1, 64)[c]	30 (12)[a] 29 (22, 37)[b] (1, 52)[c]	*P* < 0.001
1–10 years	20 (3)	10	6	4	
11–20 years	154 (20)	86	56	12	

Demographic	Overall (*n* = 760)	FE cohort (*n* = 336)	MA cohort (*n* = 353)	Combined MA + FE cohort (*n* = 71)	
21–30 years	226 (30)	99	105	23	
31–40 years	192 (25)	83	91	18	
41–50 years	109 (14)	32	65	12	
51–64 years	52 (7)	19	30	3	
Missing	7 (0.9)	7	–	–	
Symptoms prior to death	182 (24)				n/a
Palpitations	58 (8)	33	17	8	
Syncope	83 (11)	42	33	8	
Chest pain	45 (6)	17	21	7	
Unknown-missing	97 (13)	–	–	–	
Family history of sudden death	111 (18)	60 (17)	42 (12)	9	n/a

Demographic	Overall (*n* = 760)	FE cohort (*n* = 336)	MA cohort (*n* = 353)	Combined MA + FE cohort (*n* = 71)	
Unknown-missing	141 (19)	–	–	–	
Number of first degree relatives evaluated	3 (2)[a]	2.9 (1.9)[a]	–	3.7 (1.6)	
Number of relatives with a diagnosis	0.6 (1)[a]	0.6 (1)[a]	–	0.6 (1)[a]	
Final cause of death					
Unexplained	578 (76)	215 (64)	324 (92)	39 (55)	*P* < 0.0001
Brugada syndrome	109 (14)	86 (26)	6 (1.6)	17 (24)	*P* < 0.0001
Long QT syndrome	41 (5)	22 (6.5)	12 (3.4)	7 (9.8)	*P* = 0.04
CPVT	13 (2)	5 (1.5)	6 (1.6)	2 (2.8)	*P* = 0.73
Cardiomyopathy	19 (3)	8 (2)	5 (1.4)	6 (8.4)	*P* = 0.002

FE, familial evaluation; MA, molecular autopsy; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Data shown as mean (%) except: [a]mean (SD); [b]median (IQR); [c]range.

The outcome of a diagnosis by FE was defined as unexplained, or 'explained', consisting of either BrS, LQTS, CPVT, or cardiomyopathy, in families subjected to FE only, or by FE ± MA in the 71-patient subset subjected to both. The outcome of a diagnosis by MA was defined similarly in decedents subjected to MA only, *or* by MA ± FE in the same 71-patient subset. These outcomes denoted the cause of death in SADS decedents. Continuous and categorical baseline characteristics were analysed using one way ANOVA and x^2, respectively.

The analytical strategies evaluated the overall yield of FE- and MA-diagnoses using multinomial logistic models on an outcome defined by the cause of death by FE or MA assuming that the group that remained unexplained represented a clinical category. The yields were then investigated for the effects of sex and age, and then by both simultaneously. Circumstances of death were also assessed but incomplete data prevented meaningful analysis and are not presented. The analysis produced age and sex-dependent specific risks of each diagnosis for FE or MA. We opted for a Bayesian framework for statistical inference (non-informative priors were used throughout) using Markov chain Monte Carlo estimation methods which allowed estimation of the posterior distribution of the relative risk ratios (RRR) for the effect of age, sex, or both on the risk of one cause of death vs. another.

The posterior distribution of the estimates has been summarized by their means and their uncertainties were assessed by their corresponding 95% credible intervals (CIs). In the Bayesian framework, a 95% CI associated with a RRR which did not contain 1, was considered a significant result. This approach accommodated missing responses in the data under missing at random assumption. We also derived cause-specific predicted probabilities of a specific diagnosis and all collated 'explained' diagnoses and presented them overall, by age, sex and by both in tables and graphically. Age dependent FE-

and MA-estimated yields and their uncertainty were plotted against the corresponding observed proportions in 10 year groups. Elementary data processing, summaries and appropriate tests have been executed using Stata 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX, USA: StataCorp LLC) but the core of the modelling work has been implemented in OpenBUGS (https://www.mrc-bsu.cam.ac.uk/software/bugs/).

Results

Cohort characteristics

Demographic and clinical characteristics for the SADS cohort are detailed in *Table 1*. A total of 760 SADS decedents were included in the study. There were 407 participants in the FE cohort, 424 in the MA cohort, and 71 in both cohorts. The majority were male (67% FE and 65% MA) with a mean age at death of 29 years in FE cohort and 32 years in MA cohort. The diagnostic flowchart of the study cohort is shown in *Figure 1*. The cohort's breakdown is shown in Supplementary material online, *Figure S1*.

Diagnostic yield and underlying cause of death

The estimated yield of explained FE-diagnoses is 37% (32 and 42%) based on the 407 patients who underwent FE and 149 receiving an explicit cause of death. The estimated yield of explained MA-diagnoses is 8.8% (6 and 12%) based on 424 patients who underwent MA and 35 receiving an explicit cause of death (*Figure 1*). There were 35 pathogenic and likely pathogenic variants (see Supplementary material online, *Table S2*) and 145 variants of uncertain significance identified in the cohort (see Supplementary material online, *Table S3*).

In the 71 decedents, who were evaluated with both the FE and MA modalities, a diagnosis was established in 32 equating to a diagnostic yield of 45% (95% CI; 38%, 61%); 26 (36.6%) diagnosed by *FE only*, 4 (5.6%) diagnosed *by MA*

only and 2 (2.8%) diagnosed *by both modalities*. Sensitivity analysis showed no bias attributed to the combined cohort.

Impact of sex on the diagnostic yield of inherited cardiac conditions

An underlying diagnosis of an ICC was more likely to be identified in female SADS decedents compared with males by both FE [40% (34–45%) vs. 36% (31–41)], and MA [15% (10–20) vs. 6% (3–8%)] (*Figure 2A* and *B*). The increased likelihood of a diagnosis in female decedents was present across most ICCs (see Supplementary material online, *Table S4*) and was most evident with the diagnostic yield of LQTS on MA [8.1% (4.1–13.4%) vs. 1.2% (0.2–2.7%)].

Figure 2

Likelihood of a sudden arrhythmic death syndrome death remaining unexplained is greater in males across all ages by familial evaluation (*A*) and by molecular autopsy (*B*).

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Impact of age on the diagnostic yield of inherited cardiac conditions

The yield of an ICC diagnosis by FE was highest in the youngest decedents (*Figure 3A*), with an observed 50% yield in 0–10 years group. The yield of an ICC diagnosis by MA was also highest in the youngest decedents (*Figure 3B*), with an observed 30% yield in 0–10 years group. Both age-specific diagnostic yields had a decreasing trend with age with the yield of FE being 40% in 11–20 year olds and ~ 30% in >20 year olds and the MA yield being around 10% in those >10 year old. For each year increase in age, the relative risk ratio of an ICC diagnosis declined by 11% [RRR 0.89 (0.81–0.97)] for FE and by 12% [RRR 0.88 (0.81–0.94)] for MA.

Figure 3

Overall diagnostic yield for sudden arrhythmic death syndrome deaths remaining unexplained after investigation, reduces with increased age at time of sudden death in both familial evaluation cohort (*A*) and molecular autopsy cohort (*B*).

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There was an inverse age-related association for the overall diagnostic yield of LQTS (10% for ages 0–10, 7% for ages 11–20, and ~ 5% for >20 years). This was due to reduced probability of a LQTS diagnosis by FE, with the relative risk ratio declining by 5.6% [RRR 0.94 (0.91–0.98)] for each year increase in age. The relative risk of LQTS diagnosis with MA was similar across age groups (*Figure 4A* and *B*). There was also an inverse age-related association for the overall diagnostic yield of CPVT, which was consistent across both FE and MA. For each year increase in age, the relative risk of a CPVT diagnosis declined by 11% [RRR 0.89 (0.81–0.97)] for FE and by 12% [RRR 0.88 (0.81–0.94)] for MA (*Figure 4C* and *D*, see Supplementary material online, *Table S5*).

Figure 4

The age-dependent yield of the diagnosis by familial evaluation (*A* and *C*); and by molecular autopsy (*B* and *D*) for the diagnosis of long QT syndrome (*A* and *B*) and catecholaminergic polymorphic ventricular tachycardia (*C* and *D*) (data shown with 95% CI).

When adjusting for the combined effect of age and sex, results remained similar with a reduction of the diagnostic yield of LQTS (from FE) and CPVT (from both MA and FE) with advancing age.

Diagnosis of Brugada syndrome and the significance of the Shanghai score

The diagnosis of BrS was similar across all age groups of decedents. When the BrS diagnoses were stratified according to the relatives' highest Shanghai score, 16 were identified with definite/probable BrS (score ≥ 3.5), 45 with possible BrS (score 2–3) and 48 with a low likelihood of BrS. The probability of diagnosing BrS by Shanghai score was associated with advanced age, with a relative risk ratio increase of 7.8% (2.5–14%) for every year for possible vs. low likelihood, and a relative risk ratio increase of 11% (4–19%) for every year for definite vs. low likelihood (*Figure 5*).

Discussion

This study explored the largest cohort of autopsy negative sudden unexplained deaths (SADS) to date, incorporating 760 decedents aged between 1 and 64 years and showed an overall diagnostic yield of an underlying ICC of up to 45% by a combined approach of FE and MA. The yield was 37% by FE alone and 9% by MA alone. Inherited arrhythmia syndromes formed the bulk of the diagnoses with both approaches. Brugada syndrome accounted for 70% of the ICC diagnoses by FE, with LQTS, CPVT, and BrS all identified fairly evenly in the MA cohort. Importantly, our study indicates that a targeted approach to the evaluation of SADS decedents is possible as both age and sex of the decedent had a significant influence on the diagnostic yield by both FE and MA. Younger decedents were more likely to receive a diagnosis of LQTS or CPVT and female sex was associated with a higher diagnostic yield of ICCs, particularly LQTS.

A key finding of this study is that our combined approach of FE + MA provides a diagnostic yield of up to 45% following sudden death in the young. This

diagnostic yield is higher than has been suggested in previous studies highlighting the importance of the targeted combined approach. Hayashi *et al.*[18] have reviewed the spectrum of epidemiology of sudden death with their quoted yield up to 29%. They also highlight the age variation with increased yield of ICC in young sudden deaths, and lower yield in sudden death over 35, due to the rapid rise of coronary artery disease associated deaths in this age group. Our study showed a significant inverse association between the age of death and a diagnosis of CPVT or LQTS. This is congruent with patient cohorts where a higher risk of arrhythmic events were observed in younger probands of CPVT.[19,20] Indeed, the relative risk of CPVT diagnosis reduced by 11–12% for each year increase of age and the yield of CPVT diagnosis by either FE or MA was minimal for decedents of both sexes over the age of 25 years. Similarly, the relative risk of LQTS diagnosis by FE reduced by 5.6% for each year increase of age and a diagnosis of LQTS was rare for deaths occurring over the age of 40 years. Whilst CPVT is known to have a higher prevalence in children and adolescent sudden deaths, this is the first study to our knowledge, which shows increased age over 40 years leads to a lower likelihood of a death being due to LQTS.

Our data indicate that after a SADS death there is a greater likelihood of identifying an ICC in women rather than men. This was the case across both investigative approaches and all conditions. The sex discrepancy was more evident in the MA arm where female decedents were three-fold more likely (15.3 vs. 5.5%) to exhibit a pathogenic or likely pathogenic variant. The difference was particularly striking for the presence of pathogenic or likely pathogenic variants related to LQTS with a seven-fold difference in females (8.1%) compared with males (1.2%). Our results mirror findings from a large cohort of over 1700 LQTS patients where female sex was an independent risk factor for life-threatening arrhythmias with a hazard ratio of 1.7 compared with male patients.[21] Our results do not support the findings of Priori *et al.*[22] who showed that males with *RYR2* variants were more likely to experience events

than females but the numbers in the CPVT group were small and results should be interpreted with caution. Our data suggests that MA is an important part of the diagnostic armamentarium following a SADS death in a female decedent given the higher diagnostic yield of up to 15.3% in our cohort.

These results also reflect the larger size and higher frequency of overall unexplained deaths in the male sub-group of SADS decedents. Aetiologies for these unexplained SADS cases where male sex predominates, remain to be defined, including any yield of genetically and clinically inscrutable forms of idiopathic ventricular fibrillation, early repolarization syndrome and short-coupled Torsades-de-Pointes and non-cardiac disorders such as sudden unexpected death in epilepsy (SUDEP).[23–25]

Employing the proposed Shanghai diagnostic scoring system in relatives of SADS decedents diagnosed with a type 1 Brugada pattern resulted in the downgrading of most diagnoses to possible or low likelihood. This is due to the impact of systematic Ajmaline provocation testing on the clinical yield of BrS, as reported in our earlier study.[10] There were, however, no differences in associated decedent characteristics across the three main diagnostic probability groups, other than a younger mean decedent age in the low likelihood sub-group. This may reflect that more severe cases presenting at a younger age are more likely to have greater polygenic or oligogenic susceptiblity,[26] and suggests that adjustments to the Shanghai scoring system will be necessary in order to diagnose and manage these families correctly. Furthermore, given the similar proportion of BrS diagnoses in younger and older age groups, greater recognition of the potential risk of paediatric BrS is required although the absolute numbers of paediatric deaths due to BrS is much lower than in adults.[27]

Our results indicate when the autopsy is unexplained; there is a role for a targeted approach in the evaluation of SADS decedents. Our study adds to the previous literature in unexplained sudden death by providing greater into the

underlying cause based on the demographics of the decedent. This data also highlights the relative importance of incorporating a precision medicine approach following a young unexplained sudden death with age and gender targeted investigations a consideration. All but very few cases of CPVT and LQTS diagnoses were in the younger age group (<40 years), with BrS accounting for 14% of the diagnostic yield in decedents ≥40 years. This underscores the importance of high lead ECGs and provocation testing as the main diagnostic tool for BrS in the older age group and suggests that in centres where these tests are not performed there is likely to be limited diagnostic yield for FE in decedents ≥40 years.

The diagnostic yield of MA was 8.8% in our cohort. The value of MA was greatest in younger decedents and in females, largely due to the identification of pathogenic variants related to CPVT and LQTS. This is important when one considers the diagnostic challenges of both conditions and the potential for evidence-based interventions to reduce arrhythmic risk including initiation of beta-blockers. Moreover, especially in CPVT where a significant proportion may be due to *de novo* variants, where first degree family members are unlikely to be at risk, MA provides the opportunity for some degree of psychological closure for other family members.[13,28,29] Thus it is appropriate that MA is now recommended in SADS cases <40 years.[6,7] In countries where post-mortem genetic testing is not readily available, our study suggests the highest diagnostic yield to be in those decedents who are younger, and therefore this study can help guide appropriate resource allocation.

Sadly, in our cohort, 111 (18%) decedents had a family history of sudden death, prior to their own deaths. ICCs are inherited typically in an autosomal dominant manner with first-degree family members having a 50% risk of the same condition. Our results show that with the combined approach of MA and FE the diagnostic yield can be as high as 45%. We therefore hope that this high prevalence of a prior family history of sudden death decreases as families are

referred on and investigated appropriately following a first sudden death in their family using our approach.[3,4,8,9]

Limitations

The study is limited by the small numbers of decedents (n = 71) who were comprehensively assessed with both MA and FE, the most informative subset. Ideally confirmatory genetic testing would have been performed in relatives diagnosed with a phenotype on FE to provide more evidence to the underlying molecular diagnosis in the deceased. In addition, the low diagnostic yield of MA and the low absolute numbers of decedents with a diagnosis of CPVT limit the overall power of the study despite the large cohort size. Nonetheless, CPVT is a rare condition with a prevalence of 1:10 000 and the prevalence is striking within our cohort of 760 decedents. The number of genes included in our panel was restricted by the availability of contemporaneous sequencing data and the Cardioclassifier software. The addition of more genes may have increased yield of rare variants, but given that many of these would be less definite in their role in SADS, we would not have expected a significant change in yield from that currently reported.

Conclusions

After a SADS death, the diagnostic yield of comprehensive FE and MA in an expert setting can be up to 45% using a combined approach. Younger age of death is associated with greater likelihood of LQTS and CPVT diagnosis with the highest yield in children and adolescents. Female sex in SADS decedents is associated with a higher yield of LQTS in MA. Targeted post-mortem testing can be considered as both age and sex have a significant influence on the diagnostic yield of FE and MA. Based on these data, there was no evidence to suggest an effect of age on the diagnosis of BrS by either FE or MA methods. The incremental value of MA in diagnosing CPVT and LQTS in younger decedents supports routine MA in SADS cases <40 years.

6.Genes May Help Explain Link Between Adverse Pregnancy Outcomes, Later CVD

Preeclampsia, gestational hypertension, and other adverse pregnancy outcomes (APOs) are known predictors of worse cardiovascular health later in life, but a new mendelian randomization study suggests that it's not the events themselves—but rather, shared genetic underpinnings—that explain the added risk.

The results were published as a research letter in *Circulation*.

"There is a very strong link between adverse pregnancy outcomes and maternal future risk of cardiovascular diseases, and this is something that clinicians and women also are increasingly aware of," investigator Tormod Rogne, MD, PhD (University of Oslo, Norway), told TCTMD.

He said the big question is: "Does this only serve for predictive purposes, or is it actually a causal effect? Would the same cardiovascular disease in the future have happened if the adverse pregnancy outcome did not occur?"

The field is approaching the question of APOs and cardiovascular disease from various angles, including what biological changes happen at a vascular level after a female patient experiences one of these pregnancy-related conditions, said Rogne.

It may be that some aspects of the relationship are causative and some are not. He also cautioned that while their new data suggest the link isn't causal, the analysis also does not definitively rule out that possibility and future studies may provide contradictory results.

"In epidemiology, we have this idea that for anything to be interesting it has to be causal. But that's not really true," he specified. "In a clinical setting, it doesn't really matter that much whether the preterm birth or the preeclampsia

are causally linked to future cardiovascular disease risk. It has happened, [so] the question is: what do we do about it now? The point is that it still has a very important predictive function."

Rachel Bond, MD (Dignity Health, Gilbert, AZ), who didn't take part in the study, told TCTMD it drives home the idea that when women have an APO, "it could potentially reflect an underlining susceptibility to CAD, but doesn't necessarily mean that you materially can alter their actual risk."

The data suggest a shared mechanism, she agreed. "Is that mechanism potentially genetic or metabolic or vascular? The likelihood is it's probably all of the above, if not more."

Irrespective of the mechanism, the knowledge that APOs can signal higher CVD risk over a female patient's lifetime can inspire closer monitoring and attention to other risk factors, Bond and Rogne said.

The study results, too, don't dramatically shift the approach to these patients, since APOs signal a high-risk phenotype, Bond noted.

"We would still be recommending that we screen aggressively and do appropriate risk stratification. . . . We need to identify and manage these preexisting risk factors, the ones that we could modify," she said, citing high blood pressure, high cholesterol, and diabetes. "Not only are we doing cardiodiagnostic testing a little bit earlier because they have a history of adverse pregnancy outcomes, but sometimes we're even more aggressive when it comes to their management."

APOs are considered "risk enhancers" in current guidelines, she added, but with this new report, clinicians may be inspired to think about the conditions as independent risk factors that, in and of themselves, merit attention.

In a clinical setting, it doesn't really matter that much whether the preterm birth or the preeclampsia are causally linked to future cardiovascular disease risk. Tormod Rogne

Rogne and co-author Dipender Gill, BMBCh, PhD (Imperial College London, England), used a unique tactic to get at the mechanisms driving the relationship: a comparison of both female and male individuals. The idea was that while the two sexes could share genetic characteristics predisposing them to CAD, only females could become pregnant and thus develop APOs.

Male, Female Risks in Parallel

Rogne pointed out that even the 2021 American Heart Association scientific statement on the topic has wording that implies causation by specifying that seven specific APOs "increase" both CVD risk factors and incidence—hypertensive disorders of pregnancy, preterm delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss.

The researchers evaluated these same APOs in their study. First, using a genome-wide association study in a population with European ancestry, they identified single nucleotide polymorphisms (SNPs) linked to each APO yet independent from one another. They also, from a different genome-wide association study, extracted sex-specific SNPs linked to coronary artery disease.

Their mendelian randomization analysis confirmed that, for females, genetic propensity to gestational diabetes, gestational hypertension, and preeclampsia was significantly associated with higher risk of CAD, with odds ratios ranging from 1.03 to 1.15. Preterm birth showed a trend, but no links were seen for miscarriage or placental abruption.

Strikingly, though, these associations were similar for women and men regardless of the occurrence of APOs, which suggests the links between the pregnancy- and CV-related risks are driven by shared genetic liabilities, the

authors write. “In other words, our study suggests that experiencing an APO may reveal a person’s underlying susceptibility to future risk of CAD, but experiencing an APO may not materially change that risk,” they explain.

As a “stress test” for their methods, Rogne said, the researchers also looked from the opposite perspective: at whether CAD foretold APO risk, a counterintuitive notion since few women would have CAD at such a young age prior to pregnancy. These bidirectional analyses similarly showed that genetic liability to CAD was closely tied to gestational hypertension, preeclampsia, and preterm birth, with a trend toward higher risk of gestational diabetes.

This may change how we approach CVD risk stratification in people who were born from pregnancies complicated with APOs. Josephine Chou

Josephine Chou, MD (Denver, CO), who commented on the study for TCTMD, noted that its concept of shared genetic liability dovetails with earlier evidence showing a link between APOs in women and CVD risk in their offspring. “While not definitively causative, the results are intriguing and hypothesis-generating,” she said.

“Currently, most of the focus on APO and future CVD has focused on the lifelong risk for the mother, and the need for intensive maternal CVD risk screening and treatment,” Chou wrote in an email. “However, if there is a significant genetic etiology that can be passed down to her offspring, this may change how we approach CVD risk stratification in people who were born from pregnancies complicated with APOs.”

What Next?

One thing that limits the generalizability of the study is “we have only evaluated women of European ancestry. . . . It might be that in other contexts in other countries, you would find different things,” Rogne acknowledged. “These sorts of gene-environment interactions are always difficult to tease out.”

Chou, for her part, stressed that it's critically important to do a similar study in other populations, such as Black women, who are known to be especially at risk during pregnancy. "It would also be interesting to see if strategies to reduce the burden of APOs"—for example, aspirin for preeclampsia prevention—might "reduce the risk of, or attenuate the genetic susceptibility of, offspring CVD," she said.

A promising path for future research, Rogne suggested, would be to analyze data from existing randomized trials that were designed to prevent APOs. Those trials tend to stop after birth, but 10-year follow-up could reveal new insights about whether the interventions they tested in fact reduced long-term CV risks.

Bond also highlighted the many possible directions for research. In particular, "future studies really do need to continue to explore the shared genetic and maybe even molecular pathways that help us to improve these early risk identifiers," she suggested, noting that this knowledge might allow for precision medicine in female patients.

7.Is Assisted Reproductive Technology Associated With CV Risk?

Carlo Andrea Pivato, MD, et al., conducted a systematic review and meta-analysis of 7,298 articles on randomized, cohort or case-control studies through MEDLINE. Studies were included in the final meta-analysis if they reported on the association between ART and cardiovascular outcomes (adjusted for confounding factors including age), there was a control group and at least one year of follow-up. The study protocol was registered on PROSPERO.

ART was defined as both in vitro fertilization (IVF)-based and non–IVF-based approaches, including ovarian stimulation drugs (gonadotropin-releasing hormone agonist or antagonist), clomiphene citrate and ovulation induction drugs such as letrozole.

In the 10 studies included in the meta-analysis, 500,664 women underwent ART. They were likely to be older, have more ovulatory disorders such as polycystic ovary syndrome, and have more cardiovascular risk factors except for smoking. They were also more likely to have pregnancy-related complications. Women were included in the comparison group regardless of baseline fertility or whether they had ever been pregnant.

Results showed that ART did not appear to be significantly associated with increased risk of cardiovascular diseases in women over a median follow-up of 10 years after adjusting for confounders, including the likelihood of major adverse cardiac events (MACE) (effect size [ES], 1.04), coronary heart disease (ES, 0.88), stroke (ES, 1.21), venous thromboembolism (ES, 0.95), hypertension (ES, 1.08) or diabetes (ES, 1.03).

ART was also associated with a lower risk of heart failure (ES, 0.75), which could be impacted by ART type, lifestyle or socioeconomic factors.

However, studies with shorter follow-up periods reported more elevated risk of cardiovascular and cerebrovascular events following ART.

"Any initial risk signal may become diluted as more events occur due to other causes, rendering the association undetectable at 10 years," write the authors. "This interpretation suggests that ART could indeed increase short-term MACE incidence, an effect we cannot presently exclude."

8.Men at Higher Lifetime Risk of Developing HFrEF While Women at Higher Risk of HFpEF

The lifetime risk of developing heart failure with reduced ejection fraction (HFrEF) is greater in men, while women are at greater risk of developing HF with preserved EF (HFpEF), according to 25-year results from the PREVEND study published Dec. 30 in the *European Heart Journal*.

The current study is an extension of the PREVEND community-based European cohort, which previously investigated risk factors for HFrEF and HFpEF development. Investigators looked at lifetime risk of developing HF, HFpEF and HFrEF as well as eight population-attributable fraction of potentially modifiable risk factors on the development of HF. The eight risk factors studied were hypertension, hypercholesterolemia, obesity, smoking, atrial fibrillation, chronic kidney disease, myocardial infarction and diabetes.

The study sample included 4,268 men and 4,290 women from the PREVEND cohort followed from 1997 to 2022. During a median follow-up of 23.4 years, 534 (6.2%) patients developed HFrEF, 270 (3.2%) developed HFpEF, and 1,657 died before they developed HF. The mean age at baseline was 50 years for men and 47 years for women, while mean age at onset of HF was 72.1 years and 74.2 years, respectively.

Results showed a similar overall lifetime risk of developing HF: 24.5% in men compared to 23.3% in women. For HFrEF, lifetime risk was lower in women vs. men (11.9% vs. 18.1%). For HFpEF, lifetime risk was higher in women vs. men (11.5% vs. 6.4%). In women, 71% of incident HFrEF cases were attributable to the eight risk factors vs. 60% in men. Additionally, in women, 64% of incident HFpEF cases were attributable to the risk factors vs. 46% in men. Specifically, hypertension and hypercholesterolemia were the strongest risk factors for developing HFrEF, whereas hypertension and obesity were the strongest risk factors for developing HFpEF.

The authors note the present results "convey a positive message, namely that the prevention and treatment of well-known risk factors may have the potential to substantially reduce cases of incident HF…in particular in women."

9.Sex Differences in the Safety and Efficacy of Different Durations of DAPT After PCI

Background

Randomized controlled trials (RCTs) have examined the clinical impact of abbreviating the duration of dual antiplatelet therapy (DAPT) and have reported outcomes in men and women.

Objectives

The authors examined the safety and efficacy of different durations of DAPT following percutaneous coronary intervention (PCI) in men and women.

Methods

We searched Cochrane, Embase, MEDLINE, PubMed, Scopus, and Web of Science databases for RCTs that compared any 2 of 1, 3, 6, or 12 months of DAPT after PCI and reported outcomes in men and women. We performed a systematic review and network meta-analysis to examine sex-based differences in net adverse clinical events (NACE), major adverse cardiovascular events (MACE), and bleeding.

Results

Fifteen RCTs were included, comprising 44,610 men (74.7%) and 15,132 women (25.3%). No difference in NACE or MACE was observed between 1, 3, 6, or 12 months of DAPT in both sexes. In both men and women, 1 and 3 months of DAPT were each associated with lower risk of bleeding compared with 12 months of DAPT. In women, 3 months of DAPT was associated with a lower risk of bleeding compared with 6 months. Similar results were found in sensitivity analysis of acute coronary syndrome-only trials.

Conclusions

No significant sex-based differences in NACE or MACE were observed with different durations of DAPT after PCI, while a lower bleeding risk was observed with shorter DAPT (1-3 months) among both sexes. This suggests that shorter DAPT may be preferred in both sexes following PCI, especially in those with high bleeding risk.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a purinergic receptor P2Y, G-protein coupled, 12 protein (P2Y12) inhibitor is recommended after percutaneous coronary intervention (PCI) to reduce the risk of thrombotic events. However, the optimal duration of this therapy continues to be a subject of debate, especially among patients with acute coronary syndrome (ACS) vs chronic coronary syndrome.[1,2] Women are known to have poorer outcomes after cardiovascular events, as well as an increased risk of bleeding after PCI.[3,4] Female sex has been identified as an independent predictor of major bleeding in some studies,[3,5] though risk scores used to predict bleeding after PCI do not include sex in the risk model.[6,7] Early DAPT cessation has also been shown to be more common among women compared to men.[5] It remains unknown if there are sex-based differences in the safety and efficacy of different durations of DAPT following PCI.

Prolonged DAPT using potent P2Y12 inhibitors increases the risk of bleeding, while shorter durations raise concerns regarding efficacy in preventing potential recurrent ischemic events.[8] Prior studies evaluating sex differences in DAPT duration have demonstrated discordant results. For example, the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) trial [9] showed similar 2-year bleeding and ischemic outcomes among men and women with 6 months vs 24 months of DAPT after PCI, whereas the TICO trial [10] demonstrated a higher risk of net adverse

clinical events (NACE) and major bleeding among women even after multivariable adjustment. Moreover, women remain underrepresented in cardiovascular trials evaluating optimal DAPT duration after PCI.[11-13] As such, individual studies are underpowered to examine the safety and efficacy of different durations of DAPT among women.

In order to clarify whether sex differences exist in the optimal duration of DAPT following PCI, we conducted a sex-specific systematic review and meta-analysis of randomized controlled trials (RCTs) to examine if there were sex-based differences in the safety and efficacy of different DAPT durations in patients who have undergone PCI for stable angina or ACS.

Methods

This systematic review was implemented in accordance with a previously documented protocol at the Open Science Framework (DOI: 10.17605/OSF.IO/CGF76) and compliance with the reporting standards provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis group (**Supplemental Table 1**).[14] Our study was exempt by the Yale Institutional Review Board as we utilized data from previously published sources exclusively.

Search strategy and inclusion criteria

Two authors (D.P. and S.M.) carried out a thorough literature search across the Cochrane Library, Ovid Embase, Ovid MEDLINE, PubMed, Scopus, and the Web of Science Core Collection. The search encompassed articles from the inception of these databases up until June 4, 2024. This search was constructed using carefully selected terminology and keywords, along with synonyms related to topics such as DAPT, treatment duration, PCI, and RCT, mirroring the approach taken in a prior study.[15] The complete search strategies for all databases can be found in **Supplemental Table 2**. Upon compiling

relevant studies, the reference lists of each study were cross-referenced to identify additional pertinent literature. Citations from the initial search were imported into EndNote 20 software to eliminate duplicate studies. The screening process included evaluating titles, abstracts, full manuscripts, and supplementary material to determine eligibility. The selected studies underwent a careful re-evaluation for accuracy, which was superintended by the corresponding author (M.N.). Any disagreements were settled through team discussions under the corresponding author's guidance.

Studies with the following criteria were included: 1) RCT; 2) comparison between any 2 of 1, 3, 6, or 12 months of DAPT; 3) reporting of outcomes associated with men and women; 4) follow-up duration ≥9 months from the index PCI; and 5) written in the English language. When ≥2 studies on the same RCT data were found, the earlier original paper was prioritized. DAPT was defined as the concomitant administration of aspirin and a P2Y12 inhibitor. For each included trial, we applied the Cochrane Collaboration's tool to appraise the risk of bias, and for each pooled outcome, we used the GRADE system to assess its quality.[16,17]

Data acquisition and outcomes of interest

From each individual trial, we collected details including the trial's acronym, year(s) of enrollment, the country where the study took place, the proportion of patients with ACS, the agent for single antiplatelet therapy (SAPT) used in the experimental (abbreviated DAPT) groups, the type of stents employed, and the number of men and women included. Moreover, we organized baseline patient characteristics to facilitate study-level comparisons. The primary outcome of interest was NACE. Secondary outcomes comprised major adverse cardiovascular events (MACE) and bleeding. The definitions of the outcomes were based on the individual trial, and each of the outcomes reported in each trial can be found in **Supplemental Table 3**.

Statistical analysis

To ensure uniformity across all studies, we computed risk ratios (RRs) comparing different durations of DAPT from the selected RCTs. Zero-cell correction was unnecessary since all the outcomes had at least 1 occurrence in all the studies. After we collected the outcomes from each trial, we performed a frequentist network meta-analysis with random effects model to determine pooled estimates by alternating the reference groups. Briefly, we compared the risk of our primary and secondary outcomes after 1 vs 3, 6, and 12 months of DAPT; 3 vs 6 and 12 months of DAPT; and 6 vs 12 months of DAPT. Pooled RRs with their respective 95% CI were generated. *P* values <0.05 were considered statistically significant, and *P* values <0.10 but >0.05 were considered marginally significant for hypothesis-generating purposes. Assumptions inherent in network meta-analysis were made, including transitivity, consistency, homogeneity, sufficiency of evidence, and additivity of treatment effects.[18] We evaluated inconsistencies between direct and indirect estimates by node-splitting analysis. We assessed the level of heterogeneity and incoherence in the network models by using the magnitude of the between-study variance Tau-squared and the I^2 statistic for incoherence. In each outcome, we computed P-scores for each duration of DAPT. P-scores indicate the level of certainty that a particular duration of DAPT is superior to others, weighted equally across all denominators.[19] A P-score of 0 signifies the poorest duration of DAPT, while a score of 1 represents the best duration of DAPT. The technical underpinnings of the frequentist network meta-analysis model we used have been previously described.[20] The statistical model specifications used can be found in **Supplemental Table 4**.

A sensitivity analysis was performed for the subset of trials that reported major bleeding, as defined by Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding or TIMI major bleeding. Two more sensitivity analyses were performed for the subset of trials that exclusively enrolled patients with ACS

and those that used ticagrelor as the single antiplatelet agent. Finally, we performed a conventional pairwise meta-analysis based on the DerSimonian and Laird method to compare women and men who underwent a shortened duration of DAPT using a selection of trials that published post-hoc analysis on sex differences.[10,21-23] Because the baseline characteristics of women and men differed, we adjusted the outcomes for select covariates (hypertension, diabetes mellitus, dyslipidemia, and ACS) using multivariable Poisson regression and used the adjusted RRs for supplementary meta-analysis. All statistical analyses were performed using SAS, version 9.4 (SAS Institute) and R version 4.2.3 (R Foundation for Statistical Computing).

Results

Fifteen RCTs with a total sample size of 59,742, including 44,610 men (74.7%) and 15,132 women (25.3%), were included in our study (**Figure 1**).[11-13,24-35] 7 trials, which included 16,024 men (35.9%) and 5,855 women (38.7%), compared 3 months with 12 months of DAPT (**Figure 2**).[13,24,27,28,31-33] 4 trials, which included 7,474 men (16.8%) and 2,467 women (16.3%), compared 6 months with 12 months of DAPT.[26,29,30,34] 3 trials, which included 17,941 men (40.2%) and 5,402 (35.7%) women, compared 1 month with 12 months of DAPT.[12,25,35] One trial, which included 3,171 men (7.1%) and 1,408 women (9.3%), compared 1 month with 6 months of DAPT.[11] The number of patients in each duration of DAPT is summarized in **Supplemental Table 5**. Two trials recruited participants with high risk of bleeding.[11,33] Years of recruitment ranged from 2008 to 2022 (**Table 1**). From the 15 selected trials, 8 were carried out in Asia, with 6 of them conducted in South Korea. One trial took place in Brazil. The remaining 6 trials were multinational collaborations that encompassed various countries spanning the Americas, Europe, and Asia. The proportion of ACS cases within the chosen trials ranged from 32.0% to 100%, with an unadjusted mean of 70.0%. When adjusted for sample size of each of the trials, ACS constituted 71.2% of the total trial population. Five trials

exclusively enrolled patients with ACS.[12,24,26,31,35] Aspirin was the SAPT agent used in 7 trials, followed by 4 trials that administered ticagrelor and 2 trials that protocolized clopidogrel. One trial utilized both aspirin and clopidogrel, while another provided the prescribing physician with discretion over which antiplatelet agent to use. The stents deployed, and the baseline patient characteristics were variable among the trials (**Supplemental Table 6**). Of note, these characteristics represent all the patients, both men and women combined, in each trial, as attributes stratified to men and women were unavailable in all but 3 trials. The definitions of NACE, MACE, and bleeding also differed from one trial to another (**Supplemental Table 3**).

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Network Plot of the Included Randomized Controlled Trials

The network plot illustrates the number of trials that compared 1 month, 3 months, 6 months, and 12 months of dual antiplatelet therapy among (A) men and (B) women. The size of the circles and lines are proportional to the total sample size of men or women patients and the number of relevant trials, respectively.

Table 1Main Characteristics of the Included Trials

Trial	Year[a]	Country	ACS[b]	SAPT	Stent	Experimental			Control		
						Men	Women	DAPT	Men	Women	DAPT
ULTIMATE DAPT	2019-2022	Multinational	100%	Ticagrelor	SES, ZES, others	1,264	436	1 mo	1,257	443	12 mo
HOST-	201	South	55.2	Any[c]	SES	731	271	3	756	255	12

Table 1Main Characteristics of the Included Trials

Trial	Year[a]	Country	ACS[b]	SAPT	Stent	Experimental			Control		
						Men	Women	DAPT	Men	Women	DAPT
IDEA	6-2021	Korea	%					mo[d]			mo
MASTER DAPT	2017-2019	Multinational	48.3%	Clopidogrel, aspirin	SES	1,590	705	1 mo	1,581	703	6 mo
TICO	2015-2018	South Korea	100%	Ticagrelor	SES	1,204	323	3 mo	1,224	305	12 mo
SMART CHOICE	2014-2017	South Korea	58.2%	Clopidogrel	EES, SES	6,040	1,839	3 mo	6,100	1,828	12 mo
TWILIGHT	2015-2017	Multinational	64.8%	Ticagrelor	Second-generation DES[e]	1,087	408	3 mo	1,111	387	12 mo
STOPDAPT-2 ACS	2015-2017	Japan	100%	Clopidogrel	Cobalt-chromium EES	2,709	846	1 mo	2,712	852	12 mo
REDUCE	201	Multinatio	100	Aspirin	CD34+	1,63	427	3	1,6	429	12

Table 1Main Characteristics of the Included Trials

Trial	Year[a]	Country	ACS[b]	SAPT	Stent	Experimental			Control		
						Men	Women	DAPT	Men	Women	DAPT
	4-2016	nal	%		antibody-coated SES	1		mo	49		mo
GLOBAL LEADERS	2013-2015	Multinational	50.6%	Ticagrelor	BES	602	127	1 mo	567	166	12 mo
SMART-DATE	2012-2015	South Korea	100%	Aspirin	ZES, EES, BES	1,016	341	6 mo	1,028	327	12 mo
IVUS-XPL	2010-2014	South Korea	49.0%	Aspirin	EES	611	298	6 mo	632	288	12 mo
ISAR-SAFE	2008-2014	Multinational	40.7%	Aspirin	EES, SES, ZES, BES, PES	470	229	6 mo	494	207	12 mo
I-LOVE-IT 2	2012-201	China	81.8%	Aspirin	SES	1,611	386	6 mo	1,612	391	12 mo

Table 1Main Characteristics of the Included Trials

Trial	Year[a]	Country	ACS	SAPT[b]	Stent	Experimental			Control		
						Men	Women	DAPT	Men	Women	DAPT
OPTIMIZE	2010-2012	Brazil	32.0 %	Aspirin	ZES	992	571	3 mo	982	574	12 mo
RESET	2009-2010	South Korea	54.6 %	Aspirin	ZES	682	377	3 mo	665	393	12 mo

ACS = acute coronary syndrome; BES = biolimus-eluting stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; GLOBAL LEADERS = Global Leaders Strategy With the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus 2-Month Dual Antiplatelet Therapy in Patients Undergoing PCI; HOST-IDEA = Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Coronary Intervention With Next-Generation Drug-Eluting Stent Platforms and Abbreviated Dual Antiplatelet Therapy; I-LOVE-IT 2 = Is There a Life for DES After Discontinuation of Clopidogrel: Multicenter Study of the Endeavor Zotarolimus-Eluting Stent in Uncertain DES Candidates; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment–Study; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions; MASTER DAPT = MAnagement of high-bleeding-risk pATients post bioresorbable polymer coated stent implantation with an Abbreviated versus prolonged DAPT regimen; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment

With the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice; PES = paclitaxel-eluting stent; SAPT = single antiplatelet therapy; SES = sirolimus-eluting stent; SMART CHOICE = Comparison between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents; SMART-DATE = Smart Angioplasty Research Team: Safety of 6-mo Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes; STOPDAPT-2 = Short and optimal duration of dual antiplatelet after everolimus-eluting cobalt-chromium stent: a randomized multicenter trial; RESET = REal Safety and Efficacy of 3-Month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; TICO = Ticagrelor monotherapy vs ticagrelor with aspirin in patients with acute coronary syndrome after percutaneous coronary intervention; TWILIGHT = Ticagrelor with aspirin or alone in high-risk patients after coronary intervention; ZES = zotarolimus-eluting stent.

Individual trial name abbreviations are detailed in the list of abbreviations in the main text.

a Enrollment years.

b Average of the percentage of acute coronary syndrome in abbreviated and standard dual antiplatelet groups.

c Any antiplatelet at the discretion of the ordering physician: aspirin (64.1%), clopidogrel (33.7%), ticagrelor (1.9%), prasugrel (0.3%) in the trial.

d Median of 100 d with interquartile range 91 to 151 d.

e Second-generation drug-eluting stent: durable polymer cobalt-chromium EES, durable polymer platinum-chromium EES, durable polymer ZES, durable polymer cobalt-chromium SES, biodegradable polymer DES, polymer-free DES,

bioresorbable vascular scaffold, sirolimus-eluting self-apposing stent, tacrolimus-eluting carbostent.

The risk of bias was largely low in the included trials, apart from performance bias, which was high in 9 trials due to their open-label design (**Supplemental Table 7**). The quality of pooled outcomes was moderate owing to some biases and imprecisions (**Supplemental Table 8**). Heterogeneity observed in the frequent network models ranged from none to moderate (**Supplemental Table 9**). No statistically significant inconsistencies in the frequentist network models were observed with random effects applied (**Supplemental Table 10**). The full results of the node-splitting analysis of inconsistency can be found in the supplementary appendix (**Supplemental Table 11**, **Supplemental Figure 1**).

In men, no significant difference in the risk of NACE or MACE was observed between 1 month and 3, 6, or 12 months of DAPT; between 3 months and 6 or 12 months of DAPT; and between 6 and 12 months of DAPT (**Table 2**). DAPT for 1 month (RR: 0.56; 95% CI: 0.34-0.91; *P* = 0.018) and 3 months (RR: 0.54; 95% CI: 0.33-0.89; *P* = 0.015) were each associated with a lower risk of bleeding compared with 12 months of DAPT, but no difference was observed between 1 and 3 months of DAPT, 1 and 6 months of DAPT, 3 and 6 months of DAPT, and 6 and 12 months of DAPT. In women, similar to men, no significant difference in the risk of NACE or MACE was seen in all the combinations of 1, 3, 6, and 12 months of DAPT (**Central Illustration**). However, 1 month (RR: 0.86; 95% CI: 0.74-0.99; *P* = 0.049) and 3 months of DAPT (RR: 0.55; 95% CI: 0.35-0.86; *P* = 0.008) were each associated with lower risk of bleeding compared with 12 months of DAPT. In addition, 3 months of DAPT was associated with lower risk of bleeding compared with 6 months of DAPT (RR: 0.50; 95% CI: 0.27-0.90; *P* = 0.022) in women. No difference in the risk of bleeding was demonstrated between 1 and 3 months of DAPT and 6 and 12 months of DAPT. In men, P scores were the highest at 1 month of DAPT for the outcomes NACE and bleeding, but at 3 months of DAPT for MACE. In women, P scores were the

highest at 3 months of NACE and bleeding but at 1 month of DAPT for MACE (**Figure 3**).

Table 2Pooled Estimates of Frequentist Network Meta-Analysis for Each Outcome in Men and Women

Men	Net adverse clinical events (11 trials included)	1 mo			
		1.00 (0.82-1.23) *P* = 0.986	3 mo		
		0.97 (0.80-1.17) *P* = 0.728	0.96 (0.74-1.26) *P* = 0.793	6 mo	
		0.95 (0.87-1.03) *P* = 0.179	0.94 (0.79-1.13) *P* = 0.539	0.98 (0.80-1.19) *P* = 0.829	12 mo
	Major adverse cardiovascular events (9 trials included)	1 mo			
		1.10 (0.81-1.51) *P* = 0.537	3 mo		
		1.01 (0.78-1.31) *P* = 0.913	0.92 (0.64-1.32) *P* = 0.651	6 mo	
		1.07 (0.90-1.28) *P* = 0.455	0.97 (0.75-1.25) *P* = 0.813	1.05 (0.82-1.36) *P* = 0.686	12 mo

	Bleeding (7 trials included)	1 mo						
		3 mo	1.04 (0.51-2.08) P = 0.928					
		6 mo	0.66 (0.32-1.35) P = 0.258	0.64 (0.32-1.74) P = 0.384	0.64 (0.24-1.74) P = 0.384			
		12 mo	0.56 (0.34-0.91) P = 0.018	0.54 (0.34-0.89) P = 0.015	0.84 (0.33-1.99) P = 0.689	0.84 (0.35-1.99) P = 0.689		
Women	Net adverse clinical events (11 trials included)	1 mo						
		3 mo	1.21 (0.83-1.76) P = 0.320					
		6 mo	0.85 (0.61-1.17) P = 0.318	0.70 (0.61-1.10) P = 0.124	0.70 (0.45-1.10) P = 0.124			
		12 mo	0.95 (0.76-1.18) P = 0.625	0.78 (0.76-1.06) P = 0.114	0.78 (0.58-1.56) P = 0.519	0.78 (0.80-1.56) P = 0.519		
	Major adverse cardiovascular events (9 trials included)	1 mo						
		3 mo	1.01 (0.63-1.60) P =					

		0.977			
		0.76 (0.53-1.09) P = 0.138	0.76 (0.53-1.29) P = 0.977	0.76 (0.45-1.29) P = 0.308	6 mo
		0.88 (0.69-1.12) P = 0.305	0.88 (0.69-1.31) P = 0.515	1.16 (0.59-1.64) P = 0.421	12 mo
	Bleeding (7 trials included)	1 mo			
		1.58 (0.98-2.55) P = 0.059			3 mo
		0.78 (0.55-1.13) P = 0.191	0.50 (0.27-0.90) P = 0.022		6 mo
		0.86 (0.74-0.99) P = 0.0.49	0.55 (0.35-0.86) P = 0.008	1.10 (0.74-1.63) P = 0.635	12 mo

The duration of dual antiplatelet therapy in the rightmost column serves as the reference group for the respective column.

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Central Illustration

Meta-Analysis: Sex Differences in Safety and Efficacy of Different Durations of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention

The central illustration summarizes the main findings of this study.

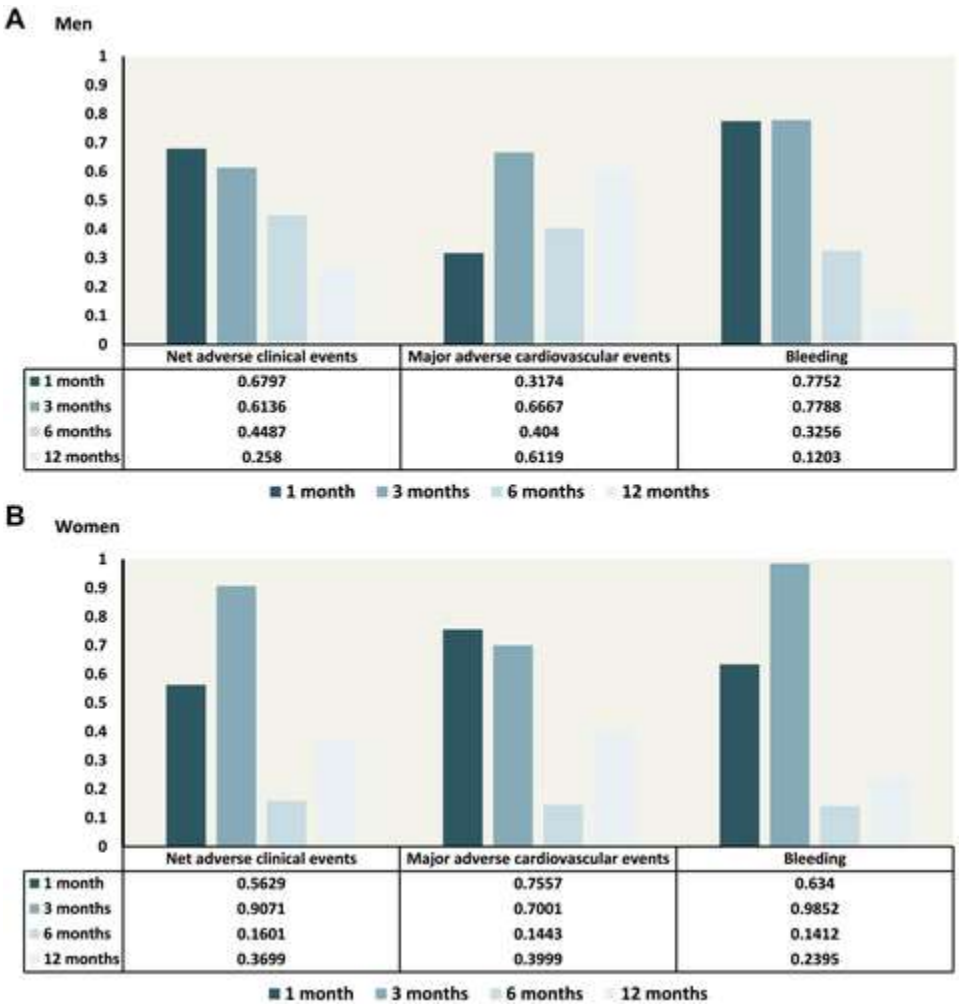

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Figure 3

P-Scores of Each Duration of Dual Antiplatelet Therapy

The bar graphs demonstrate the P-scores of 1 month, 3 months, 6 months, and 12 months of dual antiplatelet therapy after percutaneous coronary intervention in (A) men and (B) women. P-scores measure the extent of certainty that the specified duration of dual antiplatelet therapy is superior to other durations of dual antiplatelet therapy.

In a sensitivity analysis of trials that reported major bleeding, 3 months of DAPT was associated with marginally lower risk of major bleeding compared with 12 months of DAPT in both men (RR: 0.60; 95% CI: 0.33-1.08; *P* = 0.087)

and women (RR: 0.47; 95% CI: 0.21-1.09; *P* = 0.078) (**Supplemental Table 12**). A sensitivity analysis of trials that exclusively enrolled patients with ACS showed no difference in the risk of NACE and MACE among all the combinations of 1, 3, 6, and 12 months of DAPT in both men and women (**Supplemental Table 13**). In men, DAPT for 1 month was associated with significantly lower risk of bleeding compared with DAPT for 12 months (RR: 0.40; 95% CI: 0.26-0.61; *P* < 0.001), and DAPT for 3 months was associated with marginally lower risk of bleeding compared with DAPT for 12 months (RR: 0.60; 95% CI: 0.33-1.08; *P* = 0.087). In women, DAPT for 3 months was also associated with marginally lower risk of bleeding compared with DAPT for 12 months (RR: 0.47; 95% CI: 0.21-1.09; *P* = 0.078). Similar findings were observed in sensitivity analysis of trials that used ticagrelor as the single antiplatelet agent in men (**Supplemental Figure 14**). In women, however, 1 month of DAPT was associated with higher risk of NACE than 3 months of DAPT when ticagrelor was used. On the other hand, 3 months of DAPT was associated with lower risk of NACE and marginally lower risk of bleeding compared with 12 months of DAPT.

Four trials separately published post-hoc analysis based on sex differences. Three [10,22,23] of these trials shortened the duration of DAPT to 3 months, and the remaining 1 trial[21] shortened the duration to 1 month. Significant differences were observed between women and men at baseline (**Supplemental Table 15**). In the experimental groups who underwent shortened DAPT, no difference in the risk of all-cause mortality, MACE, and myocardial infarction was observed between women and men (**Supplemental Figures 2** to **4**). However, women had a higher risk of major bleeding compared with men despite undergoing a shortened duration of DAPT (**Supplemental Figure 5**). Findings were similar in the meta-analysis using RRs adjusted for differences in select covariates between women and men (**Supplemental Figures 6** to **9**).

Discussion

The results of this systematic review and meta-analysis of RCTs demonstrate that there were no significant differences in the risk of NACE or MACE between different durations of DAPT (1, 3, 6, or 12 months) compared to a SAPT or usual care among both men and women after PCI, including among patients with ACS. Additionally, the risk of major bleeding was significantly lower with 1 and 3 months of DAPT compared with longer durations of DAPT in both men (12 months) and women (6 and 12 months), though there was no significant difference between 1 and 3 months of DAPT in either group. Similarly, shorter duration of DAPT in both men and women with ACS was associated with a lower risk of bleeding, although these estimates were statistically significant only among men. Furthermore, direct comparison of men and women among patients with shortened DAPT showed no difference in all-cause mortality, MACE, or myocardial infarction between the 2 sexes; however, women had a higher risk of bleeding despite shortened duration of DAPT.

Ascertaining the optimal duration of DAPT is especially important in women for several reasons. Prior studies have demonstrated that women have a higher risk of ischemic events and worse outcomes after PCI.[4] Women undergoing PCI after ACS tend to be older and have a higher burden of comorbidities than men.[10,23] Women also have a higher risk of bleeding after PCI, as compared with men.[3] Differences in platelet reactivity and responsiveness to antiplatelet therapy have also been reported.[36] Whether the higher risk profile observed in women might lead to heterogeneity of treatment effects from varying DAPT durations remained unknown up to this point. Prior individual studies on sex differences in ischemic and bleeding outcomes with short-term vs long-term use of DAPT have been inconsistent. The PRODIGY trial, which compared 6 months vs 12 months of DAPT use after PCI, showed no significant difference in the 2-year ischemic and bleeding outcomes.[9] Similarly, a subgroup analysis of the TWILIGHT (Ticagrelor with aspirin or alone in high-risk patients after

coronary intervention) trial evaluating the effects of monotherapy with ticagrelor after 3 months vs 12 months of ticagrelor-based DAPT showed that rates of ischemic and bleeding events were similar among men and women after adjustment for comorbidities.[23] On the other hand, the TICO trial demonstrated a higher risk of NACE and major bleeding among women even after multivariable adjustment [10] and a subgroup analysis of the GLOBAL LEADERS (Global Leaders Strategy With the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus 2-Month Dual Antiplatelet Therapy in Patients Undergoing PCI) trials revealed a higher risk of major bleeding among women after PCI.[21] In this large meta-analysis synthesizing all available trials to date, we found that a shorter duration of DAPT (3 months) lowers the risk of major bleeding in both men and women, without any significant cost in terms of ischemic events. These findings should provide reassurance to clinicians, in the absence of competing prothrombotic comorbidities, that shortening DAPT duration to 3 months can be done safely in appropriately selected patients irrespective of sex and does not reduce efficacy.

Current European and U.S. guidelines recommend 6 months of DAPT after PCI with second-generation drug-eluting stent (DES) among patients with stable coronary artery disease and at least 12 months of DAPT for patients with ACS not at increased risk for bleeding.[37] This meta-analysis, one of the largest in evaluating sex-based differences in safety and efficacy of different durations of DAPT after PCI, suggests that a very short duration of DAPT (1 month) may be appropriate in both men and women after PCI for stable coronary artery disease as well as among patients with ACS. These findings may be especially relevant for individuals at higher bleeding risk. Given the higher risk of NACE with 1 month of DAPT (vs 3 months) among women who used ticagrelor as the single antiplatelet agent in our analyses, caution should be exercised before shortening to <3 months of DAPT.

Study Limitations

This meta-analysis has some limitations. First, various types of DES were used across the studies, some of which are no longer in wide use. However, there was no sex-specific bias in the selection of the DES used. As the newer generation DES is considered to be safer and have a lesser thrombogenic profile than the early generation DES, the net benefit for shorter duration of DAPT may even be greater in contemporary practice. Second, many of the trials included in this meta-analysis were open-label, potentially leading to performance bias. Third, a large proportion of the study population were of East Asian descent, which may limit the generalizability of our findings to other races and ethnicities. Fourth, there was clinical heterogeneity in baseline characteristics and definitions of clinical endpoints across trials, potentially introducing bias into our findings. In particular, the baseline bleeding risk of the participants included in the trials were variable, with 2 trials exclusively enrolling patients with high bleeding risk. Fifth, there were baseline differences between the male and female cohorts in the studies included, which likely impacted the observed clinical effectiveness and safety for different treatment approaches. Sixth, we had limited number of patients who were 65 and older, and as such, more evidence is needed regarding the older population. Seventh, different P2Y12 inhibitors were used across different trials, which could have affected the comparisons and its transitivity. 8, the use of RRs in meta-analysis require compatibility with study-level event rates, which can result in bias.[38] Finally, we had limited information on complete vs incomplete revascularization in each trial particularly in patients with ACS to determine whether MACE was due to the original culprit vessel or a nonculprit vessel.

Conclusions

This meta-analysis demonstrates that there were no significant sex-based differences in risk of NACE or MACE with different durations of DAPT after PCI, with lower risk of major bleeding with shorter durations of treatment (1-3

months) among both men and women. Taken together, these data suggest that shorter duration (1-3 months) of DAPT may be appropriate in both men and women after PCI and that sex alone should not determine DAPT duration.

10.Trends of Representation of Women in Professional Medical Societal Leadership in the United States and Europe

Background

There continue to be significant gender disparities with women being underrepresented in medical professional society leadership roles, despite more women entering medical school.

Objectives

This study aimed to elucidate the pattern of representation of women in medical society presidential positions in the United States and Europe over the past 50 years. It further examines gender-related trends in the field of cardiology and among medical trainees.

Methods

Using publicly available data from major medical societies, we calculated the number of male and female presidents in major medical societies across most specialties in the United States and Europe over the past 50 years. We also examined cardiology societies specifically. These numbers and percentages were observed alongside those of medical students, internal medicine residents, cardiology fellows, and attending cardiologists.

Results

Women constituted 4% and 0% of medical professional society presidents from 1974 to 2023 in the United States and Europe, respectively; this increased to a respective 32% and 40% in the past decade. For cardiology societies, the

United States trended from 7% to 22% female presidents in the past 50 years, and Europe trended from 0% to 10%. Doctor of medicine and doctor of osteopathic medicine students have shown steady increases in women to now >50%. Medicine residents, cardiology fellows, and cardiology attendings all have smaller percentages of women, though the number is increasing with time.

Conclusions

While women remain underrepresented in medical professional society leadership in the United States and Europe, there is a trend toward more representation of women, which mirrors growth in this realm among medical trainees.

Introduction

Across the world, male physicians in high-ranking academic medical positions and medical professional society leadership significantly outnumber female physicians in comparable roles.[1,2] Even though more women than men are now enrolling in medical school, there are a handful of subspecialties in which women account for 16% or less of the attending workforce.[3-5] For instance, women comprise approximately 15% of attending cardiologists in the United States, 16% in the United Kingdom, and 8% in the public health sector in Ireland.[6-8] Numbers are only slightly better for cardiology trainees, of whom 29% are women in both the United States and the United Kingdom.[6,9] The fields with less representation of women tend to be more procedure-oriented fields; according to a 2021 report by the American Association of Medical Colleges (AAMC), cardiology, pulmonology, orthopedic surgery, vascular surgery, neurosurgery, thoracic surgery, and urology have the fewest numbers of women.[4] Although there has been some progress toward improving representation of women at early career stages, there continue to be significant gender disparities in more advanced faculty positions and medical society leadership positions.[1,2] Many medical and surgical subspecialties, including

cardiology as illustrated above, follow the “broken pipeline” model, with the proportion of women decreasing as seniority or leadership increases.[10] This is true even in specialties that consist of predominantly women, such as dermatology.[11] Although recent studies have examined gender disparities in academic advancement in medical subspecialties, less is known about the representation of women in medical professional society leadership positions. Therefore, we sought to examine contemporary trends in gender differences in medical professional society leadership in the United States and Europe over the past 50 years. Furthermore, our study focuses on cardiology society leadership as one example, among many possibilities, of a field that has historically been male-dominated. Lastly, trends will be considered in the context of the overall representation of women in medical school, residency, cardiology fellowship, and cardiology attending or faculty positions. The goal of this study is to elucidate the pattern of representation of women in medical professional society leadership positions, with an added focus on cardiology societies, and identify opportunities for growth in this realm.

Methods

Data collection

We assessed gender differences in presidential leadership of major professional medical societies in the United States and Europe over the last 5 decades from 1974 to 2023. This data were obtained from public-facing webpages published by individual societies. Since the data were obtained from publicly available websites, institutional review board or ethics committee approval was not required for this study. Societies were selected based on larger size (>2,000 members, aside from the American Surgical Association and American Ophthalmic Society, which have <500 members) and >10 years of establishment with the aim of covering most national medical, medical subspecialty, and surgical societies. American or European societies with past presidential data not publicly accessible were excluded from the study.

The societies analyzed are outlined in **Tables 1** and **2**; they include the number of years with men and women presidents over the period of the last 5 decades or since establishment of the society, whichever is later. We also gathered data on presidents for major cardiology societies in the United States and Europe, as seen in **Tables 3** and **4**. In addition, we excluded country-specific societies in Europe that fell under the umbrella of larger, already included societies. Data on year founded and number of members were obtained from public-facing websites published by the societies. Many of the membership sizes are estimates, as many websites used phrasing such as "membership greater than" a certain total. In these cases, membership estimate was rounded down. Lists of past and current society presidents were also obtained from societies' public-facing websites except where specified with a citation in the tables below.

Table 1Leadership Data in American Medical Societies Over the Last 5 Decades With Year of Establishment and Membership Size

American Medical Societies' Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
1	American College of Cardiology (ACC)	1949	56,000	45	5
2	American Society Echocardiography (ASE)[a]	of 1975	17,000	42	7
3	American Academy Pediatrics (AAP)	of 1930	67,000	39	11
4	American Gastroenterological Association (AGA)	1897	16,000	47	3

Table 1Leadership Data in American Medical Societies Over the Last 5 Decades With Year of Establishment and Membership Size

American Medical Societies' Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
5	American College of Emergency Physicians (ACEP)	1968	38,000	43	7
6	American Medical Student Association (AMSA)	1950	30,000	27	23
7	American Academy of Allergy, Asthma, and Immunology (AAAAI)	1943	7,000	44	6
8	American College of Physicians (ACP)	1915	161,000	41	9
9	American College of Rheumatology (ACR)[a]	1934	9,100	27	9
10	American Society of Hematology	1958	18,000	39	11
11	American Medical Association (AMA)	1847	250,000	44	6
12	American Thoracic Society (ATS)	1905	15,381	41	9
13	Society of Critical Care Medicine (SCCM)	1970	16,000	40	10
14	American College of	1935	22,000	44	6

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American Medical Societies' Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
	Chest Physicians (CHEST)				
15	American Society of Clinical Oncology (ASCO)	1964	50,000	40	10
16	American Society of Anesthesiologists (ASA)	1905	53,000	45	5
17	American Academy of Ophthalmology (AAO)[a]	1979	32,000	41	5
18	American Academy of Orthopedic Surgeons (AAOS)	1933	39,000	49	1
19	American Urology Association (AUA)	1902	23,000	50	0
20	American College of Surgeons (ACS)	1913	90,000	44	6
21	American Surgical Association	1880	460	47	3
22	American Congress of Obstetricians and Gynecologists (ACOG)	1951	60,000	42	8
23	American College of	1923	41,000	44	6

Table 1Leadership Data in American Medical Societies Over the Last 5 Decades With Year of Establishment and Membership Size

American Medical Societies' Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
	Radiology (ACR)				
24	American Psychiatric Association (APA)	1844	389,000	36	14
25	American Academy of Neurology (AAN)	1948	40,000	46	4
26	American Society of Nephrology (ASN)	1966	11,000	44	6
27	American Academy of Physical Medicine and Rehabilitation	1938	10,000	44	6
28	Infectious Disease Society of America (IDSA)	1963	13,000	43	7
29	American Academy of Family Physicians (AAFP)	1947	72,349	44	6

a Leadership data <50 y.

Table 2Leadership Data in European Medical Societies Over the Last 5 Decades With Year of Establishment and Membership Size

European Medical Societies' Leadership in the Last 50 Years

Serial No.	Name of Society	Year Founded	Membership Size	Years With Male President	Years With Female President
1	European Society of Cardiology (ESC)	1950	100,000	46	4
2	Royal College of Anaesthetists	1948	24,000	41	9
3	Royal College of Emergency Medicine[a] (RCEM)	1967	10,000	15	3
4	Royal College of Obstetricians and Gynaecologists (RCOG)	1929	17,500	45	5
5	Royal College of Paediatrics and Child Health (previously British Paediatrics Association)	1996 (BPA - 1928)	22,000	35	15
6	Royal College of Pathologists	1962	10,000	41	9
7	Royal College of Physicians	1518	40,000	37	13
8	Royal College of Psychiatrists	1841	21,000	34	16
9	Royal College of Radiologists	1897	16,000	36	14
10	Cardiovascular and Interventional	1985	8,722	33	1

Table 2Leadership Data in European Medical Societies Over the Last 5 Decades With Year of Establishment and Membership Size

European Medical Societies' Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
	Radiological Society of Europe (CIRSE)[a]				
11	Royal College of Physicians of Ireland	1654	13,000	44	6
12	Royal College of Surgeons of Ireland	1784	11,000	46	4
13	Royal College of Surgeons of England	1800	30,000	47	3
14	Royal College of Surgeons of Edinburgh	1505	32,000	50	0
15	Royal College of Physicians of Edinburgh	1681	10,658	49	1

a Leadership data <50 y.

Table 3Leadership Data in American Cardiology Societies Over the Last 5 Decades With Year of Establishment and Membership Size

American Cardiology Societies Leadership in the Last 50 Years

Serial No.	Name of Society	Year Founded	Membership Size	Years With Male President	Years With Female President
1	American College of Cardiology (ACC)	1949	56,000	45	5
2	American Heart Association (AHA)	1924	43,000	38	12
3	American Society of Echocardiography (ASE)[a]	1975	17,000	42	7
4	Heart Rhythm Society (HRS)[a]	1979	8,200	38	7
5	Society for Cardiovascular Angiography & Interventions (SCAI)[a]	1978	4,500	44	3
6	Heart Failure Society of America (HFSA)[a]	1995	2,600	24	4
7	Society of Cardiovascular Computed Tomography (SCCT)[a]	2005	5,950	18	1
8	American Society of Nuclear Cardiology (ASNC)[a]	1993	5,200	27	3
9	Society for Cardiovascular Magnetic Resonance	1994	3,000	25	3

Table 3Leadership Data in American Cardiology Societies Over the Last 5 Decades With Year of Establishment and Membership Size

American Cardiology Societies Leadership in the Last 50 Years					
Serial No.	Name of Society	Year Founded	Membership Size	Years With Male President	Years With Female President
	(SCMR)[a]				

a Leadership data <50 y.

Table 4Leadership Data in European Cardiology Societies Over the Last 5 Decades With Year of Establishment and Membership Size

European Cardiology Societies Leadership in the Last 50 Years					
Serial No.	Name of Society	Year Founded	Membership Size	Years With Male President	Years With Female President
1	European Society of Cardiology (ESC)	1950	100,000	46	4
2	British Cardiovascular Society[12]	1922	3,000	47	3
3	European Association of Preventive Cardiology (EAPC)[a,13]	2004	4,000	20	0
4	European Association of Cardiovascular Imaging (EACVI)[a]	2013	10,000	21	0

Table 4Leadership Data in European Cardiology Societies Over the Last 5 Decades With Year of Establishment and Membership Size

European Cardiology Societies Leadership in the Last 50 Years					
Serial No.	**Name of Society**	**Year Founded**	**Membership Size**	**Years With Male President**	**Years With Female President**
5	European Heart Rhythm Association (EHRA)[a,14]	2003	4,000	19	2

a Leadership data <50 y.

We investigated the percentage of female medical students (both doctor of medicine [MD] and doctor of osteopathic medicine [DO]), internal medicine residents, cardiology fellows, and cardiologists over the last 50 years in the United States, as well as general trainees, cardiology trainees, and practicing cardiologists in the United Kingdom and Ireland. Data from all European countries could not be feasibly obtained due to the scope of this paper and limited data availability. We have investigated data on gender-related trends from the United Kingdom and Ireland in recent years as a representative example. This information was obtained from lists published by national medical governing bodies, including the AAMC, American Association of Colleges of Osteopathic Medicine, American Board of Internal Medicine, and Ireland's Health Service Executive. Direct inquiries were sent to the AAMC, American Board of Internal Medicine, and Accreditation Council for Graduate Medical Education, none of whom were able to provide gender-related data on internal medicine residents and cardiology fellows dating back to 1974.

Data analysis

We set out to graphically evaluate the gender-related trends in medical professional society leadership for each decade among American and European medical societies. We used Microsoft Excel for data collection, calculation of percentages, and graph creation. Due to differing terms of presidential duration among various societies, we have calculated the number of years in total with women serving as presidents instead of the total number of women presidents themselves. Our data have been represented in the form of 10-year time periods. We initially plotted trends graphically in absolute numbers with the sum of total years of male presidents to total years of female presidents over each decade. We also calculated total percentages of years with male presidents as compared to years with female presidents over each decade. In addition, we plotted data on medical students, internal medicine residents, cardiology fellows, and cardiologists in the United States and Europe to ascertain gender-related trends with percentage of women cardiologists overall and in medical professional society leadership. Our study findings are depicted as varying graphical representations in the subsequent portion.

Results

Medical professional society leadership trends

On initial analysis of gender differences in trends among American medical professional societies, there is a substantial increase in the total years with women presidents over the last 5 decades, beginning with 10 between 1974 and 1983, 13 between 1984 and 1993, 34 between 1994 and 2003, 60 between 2004 and 2013, and 92 between 2014 and 2023 (**Figure 1**). European societies had no female presidents between 1974 and 1983, had 12 between 1984 and 1993, had 5 between 1994 and 2003, had 26 between 2004 and 2013, and had 60 between 2014 and 2023 (**Figure 2**). American societies had an increase in percentages of years with women presidents from 4% in 1974 to 1983 to 32%

in 2014 to 2023, while European societies had an increase from 0% to 40% in the same decades; these trends are shown in **Figures 1** and **2**.

Gender Differences Among American Medical Professional Society Presidents by Decade

Gender-difference trends in american societies over the last 5 decades plotted as percentage of men and women (above) and as total years of presidency of men and women (below).

Gender Differences Among European Medical Professional Society Presidents by Decade

Gender-difference trends in European societies over the last 5 decades plotted as percentage of men and women (above) and as total years of presidency of men and women (below).

Cardiology professional society leadership trends

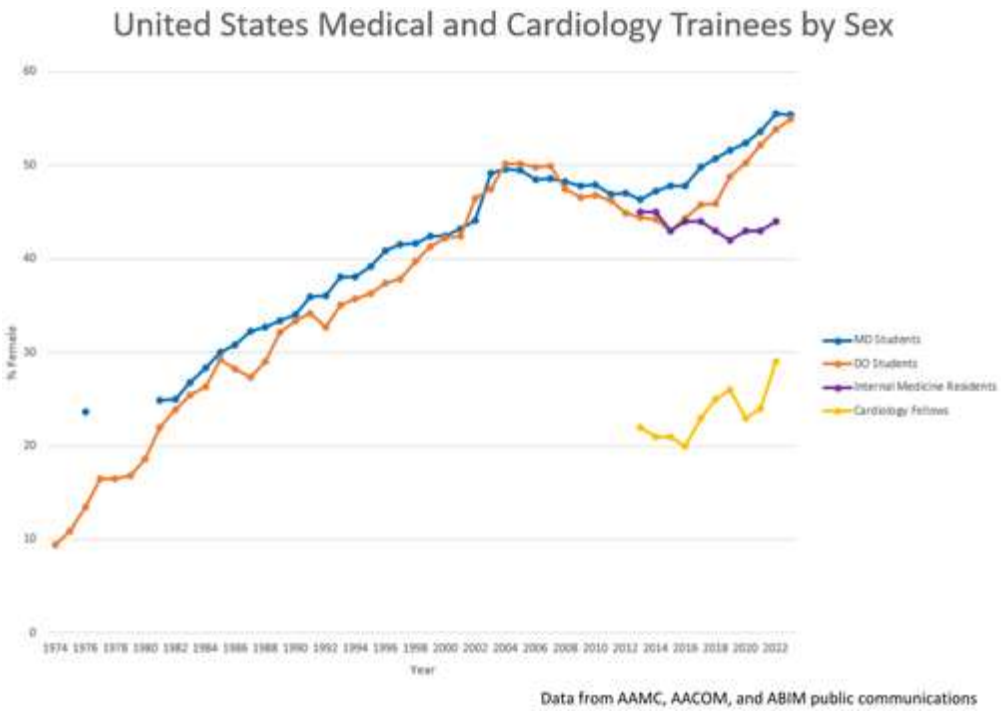
Figure 3 demonstrates the trends in women in cardiology society leadership in Europe vs the United States over the past 50 years. European cardiology societies had women as presidents over only the last 2 decades, with 8% and 10% female presidents, respectively. On the other hand, American cardiology societies showed women in presidential roles from the 1970 s, which was initially at 7% and increased to approximately 22% in the last decade. It should be noted that not all presidents of cardiology societies are cardiologists.

Gender Differences Among American and European Professional Cardiology Society Presidents by Decade

Gender-difference trends in cardiology societies in America (above) and Europe (below) over the last 5 decades plotted as percentage of men and women.

Medical student, trainee, and faculty trends

The number of female medical students over the last 50 years enrolled in both DO and MD medical schools in the United States has increased to more than 50% of the total in the last 5 years, per data published by the AAMC and American Association of Colleges of Osteopathic Medicine. In the 1970 s, <20% of DO students and <25% of MD students were female.[3,5] These numbers steadily increased until 2005, at which time percent of female medical students (both MD and DO) declined. Starting in 2014 for MD students and 2017 for DO students, the percentage of female medical students has again been consistently uptrending.[3,5] Women at MD schools surpassed 50% of total students in 2018 and DO students did in 2020.[3,5] Less data were publicly available for third-year internal medicine residents and first-year cardiology fellows; data from 2013 to 2022 was available and has been included.[9,15] The percentage of female internal medicine residents over these years remained between 42% and 45% without any significant upward or downward trends.[15] The percentage of female cardiology fellows was 22% in 2013 and 29% in 2022; the lowest percentage of female cardiology fellows over this time period was 20% in 2016.[9] In 2016, 16% of cardiology attendings were women.[4] Available data for gender-related trends among medical students, internal medicine residents, and cardiology fellows over the past 50 years are plotted in **Figure 4**.



Proportions of Female Medical Students, Internal Medicine Residents, and Cardiology Fellows

Gender-difference trends in American medical students, internal medicine residents, and cardiology fellows over the last 5 decades.

In the United Kingdom, data from the year 2020 shows that 46% of all attendings and 51% of all trainees across all medical specialties are women, while 16% of cardiology attendings and 29% of cardiology trainees are women.[6,16] A report published by the Health Service Executive in Ireland from the year 2020 shows that 55% of all medical trainees are women with internal medicine specifically being 56% women. Female cardiology attendings account for only 8% in the public sector, with 92% being male attendings.[7] Percentages of female trainees and attendings are plotted in **Figure 5**.

American and European Medical Trainees and Attendings By Gender

Gender-related demographics among medical students, internal medicine residents, cardiology fellows, and attending cardiologists in (A) the United States, (B) United Kingdom, and (C) Irish Public Sector in recent years.

Discussion

Our study demonstrates that while the number of female presidents in professional medical societies, including cardiology societies, is increasing, it lags behind the total proportion of women in medicine (**Central Illustration**). Over half of medical students have been women since the 2010 s, and almost half of internal medicine residents in the United States are women. Despite that, women are still a minority in presidential roles in medical professional societies. This is more pronounced when looking specifically at cardiology societies. This aligns with prior work by Silver et al who found that from 2008 to 2017, women were significantly underrepresented in medical professional society leadership, particularly when accounting for the overall percentage of society membership who were women.[2] This current study expands upon this existing work by collecting data through the year 2023 and focusing on multiple societies in a field that consists of primarily men (cardiology). The trend of women being underrepresented in presidential roles is consistent in both cardiology societies and medical societies as a whole. However, recent decades have shown dramatic growth in the percentages of female presidents, suggesting that with time there may be progression toward more equal representation of genders in medical society presidential roles.

Changes in Gender Demographics Among Medical Trainees and Professional Society Leadership With Time

Gender-difference trends among medical trainees and medical society leadership in United States and Europe.

The current study also expands knowledge on the subject by comparing gender-related trends in medical professional society leadership to the percentages of medical trainees who are women. Female medical students have outnumbered male students in American MD schools since 2018 and in DO schools starting in 2004. Despite this, the growth of women's representation among internal medicine residents and cardiology fellowship has been slower. There are fewer gender disparities among general internal medicine trainees in the United States and Ireland, which are roughly evenly represented between genders. Women make up significantly less than one-half of the cardiology trainees in the United States, United Kingdom, and Ireland, though numbers are improving in this realm. This trend is seen in many medical specialties, with fewer and fewer women as medical training advances, suggesting that as seniority increases, the number of women in the field decreases. However, numbers of women in attending positions are also increasing, suggesting a potential change in this pattern in the coming decades.

The trends observed here for medical professional society leadership are consistent even when looking only at a field that is made up of predominantly women; a study of dermatologic society presidents reveals a discrepancy between numbers of practicing female dermatologists and society presidents on a global scale.[11] Prior work by Silver et al evaluating all 43 specialties in the *Physician Specialty Data Report* also found women were globally underrepresented in professional medical society presidential roles.[2] One proposed contributor to the lack of female society presidents is a lack of role models.[10] Lack of female role models in medical professional societies may hinder other women from seeing themselves in similar positions. Additionally, if

there are few women in presidential roles, it may reinforce the gender or gender bias—implicit or not—that women are followers and not destined for leadership roles.[10]

Another contributor to the greater representation of men in society leadership relates to the longstanding prevalence of men in medicine.[11] Since there have been more men in medicine for decades, and it takes time to build the seniority required for leadership roles, it follows that men have had more time to fill professional society presidential roles. Hopefully, this trend will improve as women have more time with increased representation in medicine, as evidenced by the increasing numbers of women medical students, internal medicine residents, cardiology fellows, and attendings in the past decades. Our data suggest that there is more female representation in medical professional society leadership in Europe over the last decade than in the United States. Unfortunately, the fact that there are almost no female presidents in European cardiology societies and that there were no women in these presidential roles until 2004 suggests that even in Europe, where representation in medical professional societies has been more equal, there is still significant work to be done to achieve gender-related equality in professional societies.

There has been some evidence that structured interventions can empower women to take on more leadership roles.[17,18] The Sandra J. Lewis Mid-Career Leadership Institute developed a leadership program for a cohort of 22 mid-career female cardiologists, offering networking opportunities, mentorship, and formal education on topics including communication, negotiation, and financial independence. After the 2-year intervention, members of the cohort achieved several types of leadership roles, including chiefs of cardiology, hospital leader of operations, and numerous invitations to speak at grand rounds.[17] This suggests that structured programs focusing on skill-building and mentorship can help female physicians achieve leadership roles. Interventions have been shown to be beneficial much earlier in women's medical careers, too. Wayne et

al[18] found that in a control group of first-year medical students completing a small group activity, men were more likely to take on leadership roles than women, even when the class was 50% women. However, when the activity was preceded by a “pep talk” about the importance of gaining leadership experience in a safe environment, both genders were equally likely to assume leadership of the group.[18] Encouraging women to pursue leadership positions from the time they are medical students may help the growing numbers of women in medicine to even the gender-related divide in medical professional society leadership.

Study limitations

Limitations of this study include the relatively early age of many cardiology societies, meaning that there are significantly fewer years of data available on gender distribution. This is particularly true for subspecialty societies. Given the smaller number of cardiology societies compared with the total number of professional societies studied, even one added presidential position significantly skews the denominator. Percentages of female presidents should be considered alongside the total number of presidential positions available. Additionally, because there were markedly fewer cardiology societies than medical societies in total, it was not feasible to perform statistical analysis upon subgroups of medical societies. Future research could explore this comparison by evaluating total membership numbers in cardiology vs general medical or surgical societies.

Another limitation is that different societies have different presidential term limits. The data presented represent the total number of years that a woman has been a society president, not the total number of female presidents.

Conclusions

Our study shows a positive trend of increasing women in medical professional society leadership positions in both American and European medical societies, with European societies demonstrating more gender equity in the last decade. This trend is also noted in cardiology with increasing women in leadership over the last few decades. There has already been significant improvement in representation of women in medical leadership roles, and as barriers to representation are addressed, possibly with structured leadership interventions, we should continue to see increasing numbers of women in positions of seniority.

11.Pregnancy in Adult Congenital Heart Disease

The prevalence of congenital heart disease (CHD) in pregnancy increased by >30% during the 2010s. CHD is now present in approximately 8:10,000 pregnant persons.[1] Cardiovascular (CV) diseases such as CHD are major causes of maternal morbidity and mortality, and their increasing presence represents a public health challenge.

Maternal history of CHD increases the risk of stroke, heart failure (HF), and arrhythmia during pregnancy and the peripartum period.[2,3] Although these risks may provoke alarm among providers, the absolute rate of severe cardiac complications in pregnancy complicated by CHD is low, approximately 2% overall. Of note, when care is delivered in an advanced health care system, there is no noted increase in maternal mortality, which remains at approximately 0.15% in the United States.[2,3]

Neonatal complication rates reflect maternal health status. The incidence of neonatal complications is higher among pregnant persons with CHD than among those without, including increased rates of infant deaths and stillbirths, as well as prematurity and low birth weight.[3,4] An analysis of pregnancies with

CHD from a German administrative database revealed a 2% combined rate of stillbirths and neonatal deaths, as well as a nearly 12% preterm birth rate.[3]

Several factors predict complication rates among pregnant persons with CHD and their offspring. Maternal CHD complexity is one such factor; those with more complex lesions experience higher complication rates.[3] Unrepaired CHD, compared with surgically palliated CHD, is also associated with worse maternal CV outcomes, particularly if there is history of pulmonary hypertension or HF.[4] Data from a multinational registry showed a 0.7% maternal mortality rate and 8.7% incidence of HF in pregnant persons with unrepaired CHD.

Some contributors to poor maternal and fetal outcomes in CHD are modifiable. In a multicenter cohort of patients with heart disease in pregnancy recruited as part of the CARPREG (Cardiac Disease in Pregnancy Study), Pfaller et al. found that approximately one-half of severe cardiac events were preventable. Provider factors accounted for almost three-quarters of the preventable events. These factors included identification and appropriate risk stratification of cardiac conditions, as well as identification and prompt action in response to deteriorating clinical status.[5] This result suggests that better education about cardiac risk stratification in pregnancy can reduce adverse events.

Cesarean delivery rates represent another area for practice improvement. Pregnant persons with CHD are more likely to undergo cesarean delivery than are those without CHD.[3,6] This delivery method subjects them to higher rates of infection and hemorrhage, among other complications. A group in Boston reported results from a practice in which vaginal birth is planned in all cases of maternal cardiac disease without an obstetric indication for cesarean delivery. Operative vaginal delivery was offered for those experiencing adverse CV symptoms during labor. In that cohort, which included a 66% prevalence of maternal CHD, adverse cardiac outcomes were similar between the two modes of delivery, with lower rates of postpartum hemorrhage in the vaginal delivery group. In this report, vaginal delivery with assisted second stage was

undertaken successfully for patients with the well-described higher-risk conditions of severe aortic stenosis and high-risk aortopathy.[7] These results provide encouragement for obstetricians and their collaborators to reduce cesarean delivery rates for patients with CHD.

Finally, socioeconomic factors contribute to poor maternal outcomes. In the United States, Black and Hispanic pregnant persons fare worse than others.[2] Coming from an emerging country or having public health insurance also correlate with worse maternal outcomes.[2,4] These health care disparities warrant corrective action. The health care system in the United States and its providers would benefit from both awareness and specific policies to improve health in these vulnerable groups.

Although maternal CHD increases the risks of maternal and fetal adverse events (**Figure 1**), appropriate risk stratification, clinical monitoring, and delivery planning—as well as thoughtful public health initiatives—have the potential to improve outcomes for this population.

12.Pickering Syndrome Manifesting as Recurrent Pulmonary Edema in an Older Woman With Renal Artery Stenosis

Abstract

Pickering syndrome, characterized by recurrent episodes of flash pulmonary edema (FPE) and renal impairment, is associated with renal artery stenosis (RAS). This case highlights its manifestation and management in an older adult patient. An 86-year-old woman with hypertension, chronic kidney disease, and a single functioning kidney presented with recurrent FPE episodes. Imaging revealed severe left RAS and an atrophic right kidney. Despite initial medical management, recurrent episodes of pulmonary edema led to renal angioplasty with stent placement. Follow-up imaging revealed restenosis in the left renal

artery, necessitating a second angioplasty. The patient's condition stabilized after intervention, with improvement in both cardiac and renal function. This case illustrates the critical importance of considering RAS in patients with recurrent FPE and resistant hypertension and emphasizes timely diagnosis and intervention. Early detection and intervention in Pickering syndrome can prevent recurrent pulmonary edema and renal failure.

History of Presentation

An 86-year-old woman presented with sudden onset dyspnea and flash pulmonary edema (FPE). Her physical examination revealed pulmonary crackles, jugular venous distention, and blood pressure of 170/95 mm Hg. Initial laboratory results showed elevated creatinine (1.5 mg/dL) and natriuretic peptides, suggesting acute heart failure with renal involvement. A chest radiograph confirmed pulmonary edema, and echocardiography revealed preserved left ventricular ejection fraction (left ventricular ejection fraction [LVEF], 48%), consistent with heart failure with preserved ejection fraction (HFpEF).

Take-Home Messages

- RAS should be suspected in patients with recurrent pulmonary edema and resistant hypertension, particularly when renal dysfunction is present. ACEIs, although effective for blood pressure control, should be used with caution in patients with significant RAS because they may exacerbate renal dysfunction.

- Timely intervention with renal angioplasty can prevent further episodes of edema and improve both cardiovascular and renal outcomes in Pickering syndrome. Regular follow-up and imaging are essential in monitoring for restenosis and ensuring long-term stability in patients treated with renal artery stenting.

Past Medical History

The patient's medical history included hypertension, chronic kidney disease stage 3A (caused by nephroangiosclerosis), dyslipidemia, and a functional single kidney (right kidney atrophy). Ten years earlier, she had her first episode of FPE, requiring hospitalization, which marked the onset of her heart failure symptoms. She had experienced several similar episodes over the years, with the most recent event occurring last year, after a COVID-19 infection exacerbated her heart failure. Additionally, she had a history of colorectal cancer (stage I) and hypothyroidism.

Differential Diagnosis

Given her presentation with recurrent pulmonary edema and worsening renal function, the differential diagnosis included FPE secondary to renal artery stenosis (RAS; Pickering syndrome), congestive heart failure exacerbation, acute coronary syndrome, pulmonary embolism, and aortic stenosis.

After ruling out acute coronary syndrome and pulmonary embolism through coronary angiography and thoracic computed tomography (CT) angiography, the suspicion of Pickering syndrome grew stronger because of the patient's concurrent renal impairment and uncontrolled hypertension.

Investigations

Initial investigations revealed the following:

- Elevated troponin and B-type natriuretic peptide levels suggested myocardial strain.
- A chest radiograph confirmed pulmonary edema (**Figure 1**).
- Echocardiography revealed preserved LVEF (48%), consistent with

HFpEF.

- Renal ultrasound demonstrated an atrophic right kidney and a normal-sized left kidney.
- Doppler ultrasound of the renal arteries was inconclusive because of poor visualization.
- Abdominal CT angiography showed significant atherosclerotic disease, with a critical stenosis at the ostium of the left renal artery and a nonfunctioning right kidney (**Figure 2**). This finding supported the diagnosis of RAS as the cause of recurrent FPE.

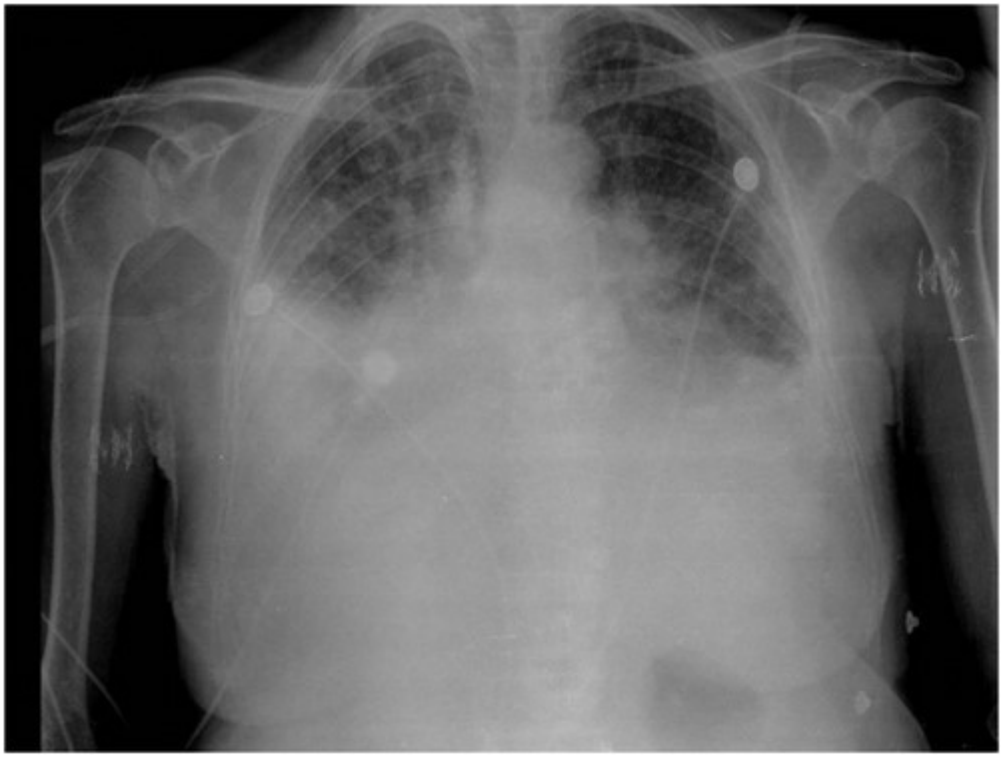


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Figure 1

Posteroanterior Chest Radiograph Showing Findings Consistent With Acute Pulmonary Edema

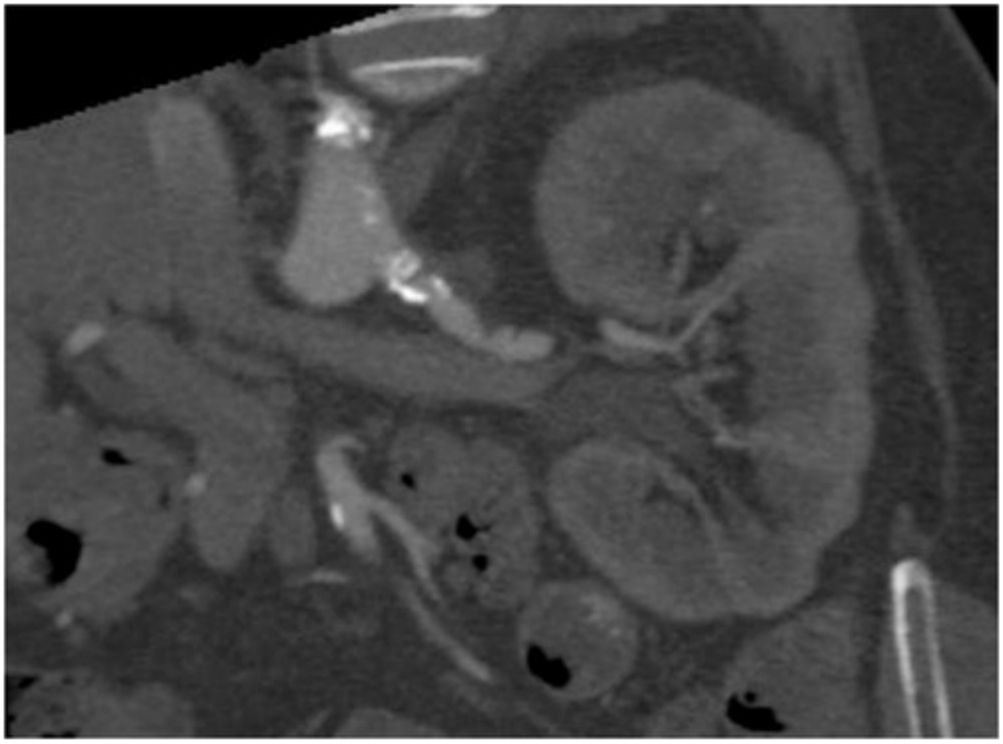

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Figure 2

Atherosclerotic Plaque Causing Significant Stenosis at the Proximal Segment of the Left Renal Artery

Management

For medical management, the patient initially received intravenous diuretic agents for acute decongestion, along with antihypertensive agents. Despite optimization of heart failure therapy, including angiotensin-converting enzyme inhibitors (ACEIs), she developed angioedema, necessitating their discontinuation. Given her deteriorating renal function and recurrent pulmonary edema, medical management alone was insufficient.

The next step was interventional management. Six years ago, the patient underwent renal angioplasty with stent placement in the left renal artery. This initially resulted in improved blood pressure control and stabilization of renal function (creatinine levels of 0.9-1.0 mg/dL). However, last year, a follow-up CT

angiogram revealed critical restenosis of the stent in the left renal artery, along with a new stenosis in the right renal artery (**Figure 3**). A second renal angioplasty was performed, with successful placement of a second stent in the left renal artery (**Figure 4**).

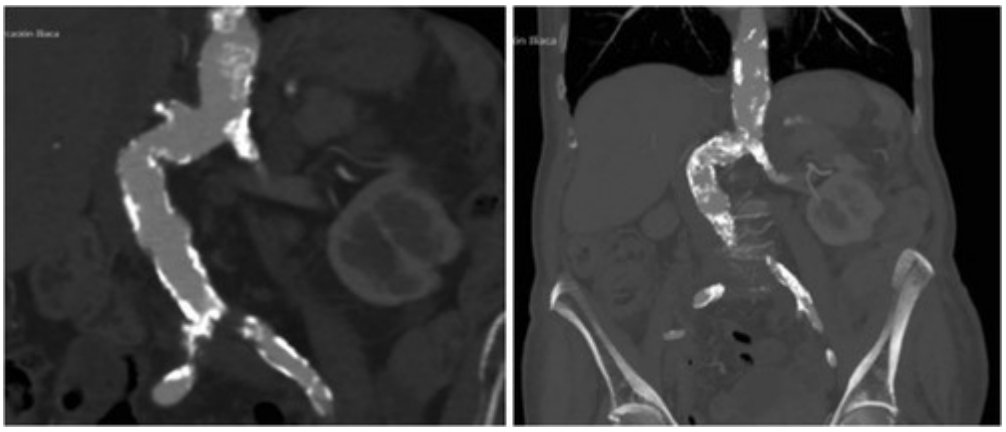

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Figure 3

Critical Renal Artery Stenosis

The images show the re-stenosis of the stent implanted in the left renal artery, as well as a stenosis at the origin of the right renal artery.

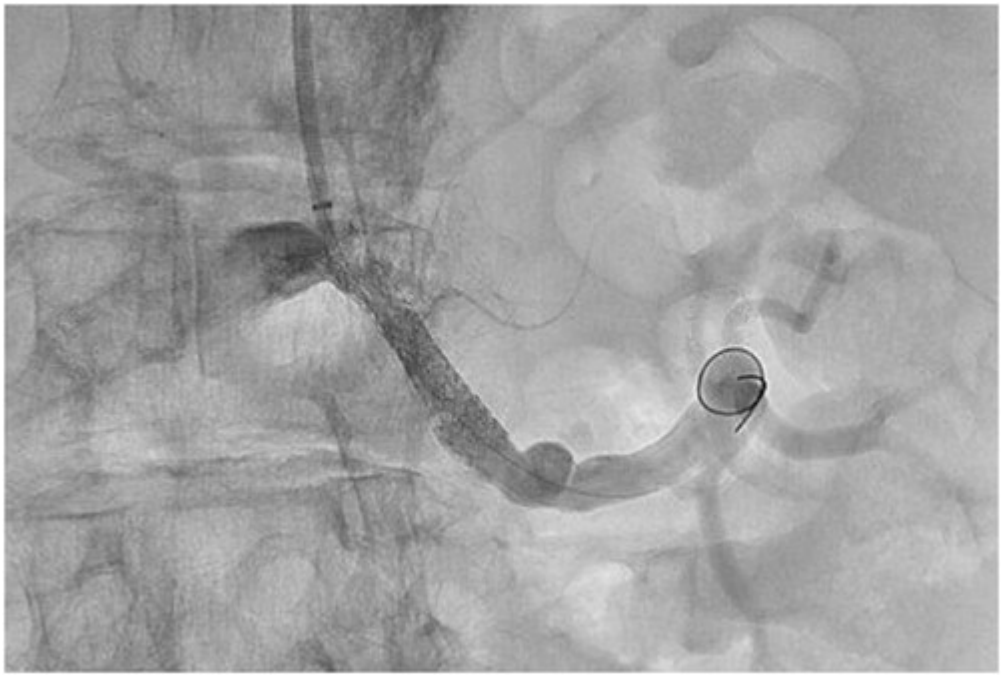

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Figure 4

Final Result After Implantation of a Second Stent in the Left Renal Artery

Outcome and Follow-Up

Following the second angioplasty, the patient showed significant clinical improvement. Her pulmonary edema resolved, and her renal function stabilized, with an estimated glomerular filtration rate of 45 mL/min. Echocardiography also demonstrated improved left ventricular function (LVEF, 48%). During follow-up, she remained stable, with no recurrent episodes of pulmonary edema or hospitalizations. Regular monitoring and imaging continue to be critical in managing her long-term prognosis.

Discussion

Pickering syndrome, a condition characterized by recurrent FPE and renal impairment, often arises from bilateral or severe unilateral RAS. The syndrome exemplifies the complex interplay between the cardiovascular and renal systems, commonly referred to as cardiorenal syndrome. This case highlights the importance of considering RAS in patients with resistant hypertension and recurrent pulmonary edema, particularly when standard medical therapy fails.[1]

In this case, the patient's multiple episodes of FPE, combined with resistant hypertension and progressive renal dysfunction, pointed toward a renovascular cause. Initial management with diuretic agents and antihypertensive therapy provided temporary relief but was insufficient in preventing further episodes of edema. The definitive diagnosis of RAS was confirmed through abdominal CT angiography, thus underscoring the role of imaging in detecting this condition when other diagnostic tools, such as Doppler ultrasound, are inconclusive.

Renal artery stenting has been shown to improve blood pressure control and reduce recurrent pulmonary edema episodes in patients with significant

RAS.[1,2] Although randomized controlled trials, such as the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions)[3] and CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions)[4] trials, did not demonstrate a significant benefit of revascularization in patients with mild RAS, this case illustrates the importance of selecting patients with hemodynamically significant stenosis, such as in Pickering syndrome. Our patient benefited from renal angioplasty and stenting, leading to an improvement in both her cardiovascular and renal outcomes. Regular monitoring and imaging continue to be critical in managing her long-term prognosis.[5]

This case underscores the need for vigilance in identifying renovascular causes in patients with unexplained pulmonary edema, especially in older adults with multiple comorbidities. Early detection and intervention can significantly reduce morbidity and improve quality of life in affected individuals.

Conclusions

Pickering syndrome should be considered in patients with recurrent FPE and renal dysfunction, especially in the presence of resistant hypertension. RAS can often be underdiagnosed, but timely recognition and interventional treatment can lead to significant improvements in clinical outcomes. In this case, renal angioplasty with stenting resolved the patient's recurrent pulmonary edema and stabilized her renal function.

13.Pregnancy-Associated Spontaneous Coronary Dissection in a 32-Year-Old During the Third Trimeste

Abstract

We report a case of spontaneous coronary dissection (SCAD) in a 32-year-old pregnant patient during the seventh month of her second pregnancy. A 32-year-old pregnant woman in the 28th week of gestation was referred to our intensive care unit because of angina as well as elevated troponin levels. The

initial electrocardiogram and transthoracic echocardiogram (TTE) were normal. Four hours after admission, the patient experienced angina with ST-segment elevation, and the TTE showed de novo apical hypokinesia. The episode lasted approximately 10 minutes, with subsequent resolution of the ST-segment elevation. An emergency coronary angiogram revealed dissection of the left anterior descending artery. A conservative approach with aspirin monotherapy was chosen. Follow-up TTE at 3 months revealed full recovery of left ventricular function. A multidisciplinary approach is crucial in pregnancy-associated SCAD. Conservative management is generally recommended because of the potential for angiographic healing, with percutaneous coronary intervention reserved for severe cases.

Introduction

Spontaneous coronary artery dissection (SCAD) and pregnancy-associated SCAD (P-SCAD) have been increasingly identified over the past decades as a significant cause of acute myocardial infarction, heart failure, and sudden cardiac death. In this case report, we highlight a particularly rare case of P-SCAD in an otherwise healthy woman during her seventh month of pregnancy that manifested as an ST-segment elevation myocardial infarction (STEMI).

Take-Home Messages

- P-SCAD should be suspected in any patient with peripartum or postpartum angina and should preferably be treated in a hospital with maximal capacities by a multidisciplinary team.
- Individualized decision making regarding PCI should be prioritized.

History of Presentation

A 32-year-old pregnant woman, in the 28th week of her second pregnancy, was referred to our cardiology intensive care unit (ICU; University Hospital Giessen,

Hesse, Germany) from a peripheral hospital for suspected myocarditis requiring further monitoring, diagnostic evaluation, and treatment. She had presented to the external emergency department with sudden onset chest pain, lasting up to 15 minutes, which subsequently resolved. The symptoms were isolated, without pain radiation.

Past Medical History

The patient had no previous history of coronary artery disease, SCAD, aortic dissection, pulmonary embolism, or myocarditis. She denied experiencing palpitations or syncope and had no family history of coronary artery disease, SCAD, or P-SCAD. Previous medication consisted of L-thyroxine, 112 µg.

Physical Examination

The results of a physical examination were unremarkable, with a blood pressure of 137/93 mm Hg and a heart rate of 76 beats/min; her oxygen saturation was normal at 96%. No cardiac murmurs, dilated jugular veins, or leg edema were noted. Lung auscultation was normal. A gynecologic examination, a cardiotocogram, and an ultrasound scan ruled out any pregnancy complications.

Investigations

Laboratory test results revealed that cardiac biomarker levels were elevated: high-sensitivity-troponin I, 2,194 ng/L, peaking at 17,410 ng/L; creatine kinase, 762 U/L; and creatine kinase-myocardial band, 88 U/L. The initial electrocardiogram (ECG) was normal, without signs of ischemia or accelerated heart rhythm (**Figure 1**). A transthoracic echocardiogram (TTE) showed normal left ventricular function without abnormalities. Four hours after admission, the patient experienced another episode of sudden onset chest pain. The ECG showed hyperacute ST-segment elevation in leads I, II, aVL, and V_4 to V_6, as well as concordant ST-segment depression in leads aVR and V_1 (**Figure 2**). A

TTE indicated good left ventricular function overall, with apical hypokinesia. The episode lasted approximately 10 minutes, and a subsequent ECG showed resolution of the ST-segment elevation, albeit with residual discrete elevation in lead V_6 as well as negative T waves in leads V_5 and V_6 (**Figure 3**).

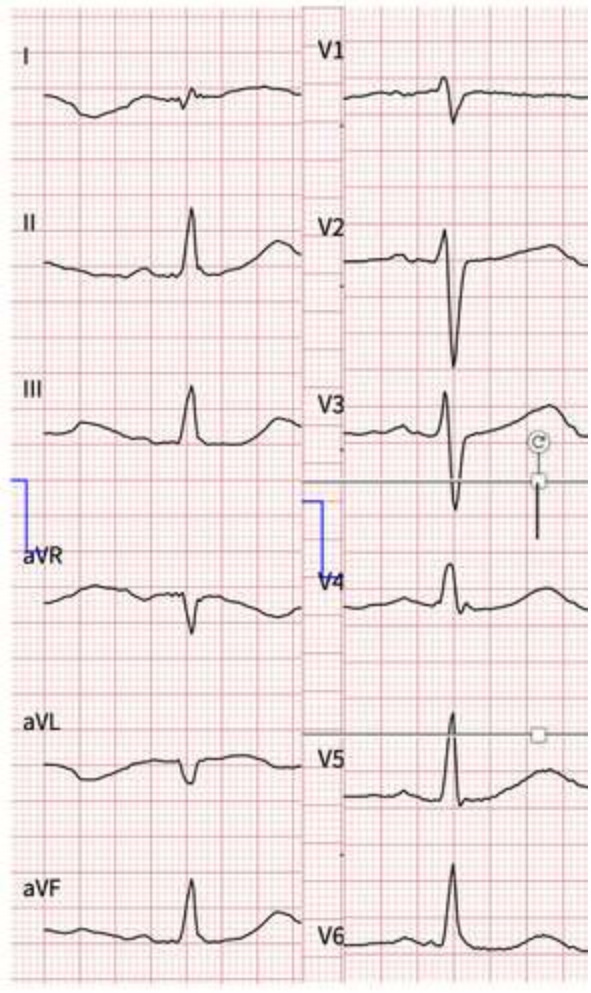

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Figure 1

Baseline Electrocardiogram

Initial electrocardiogram without any signs of acute coronary ischemia.

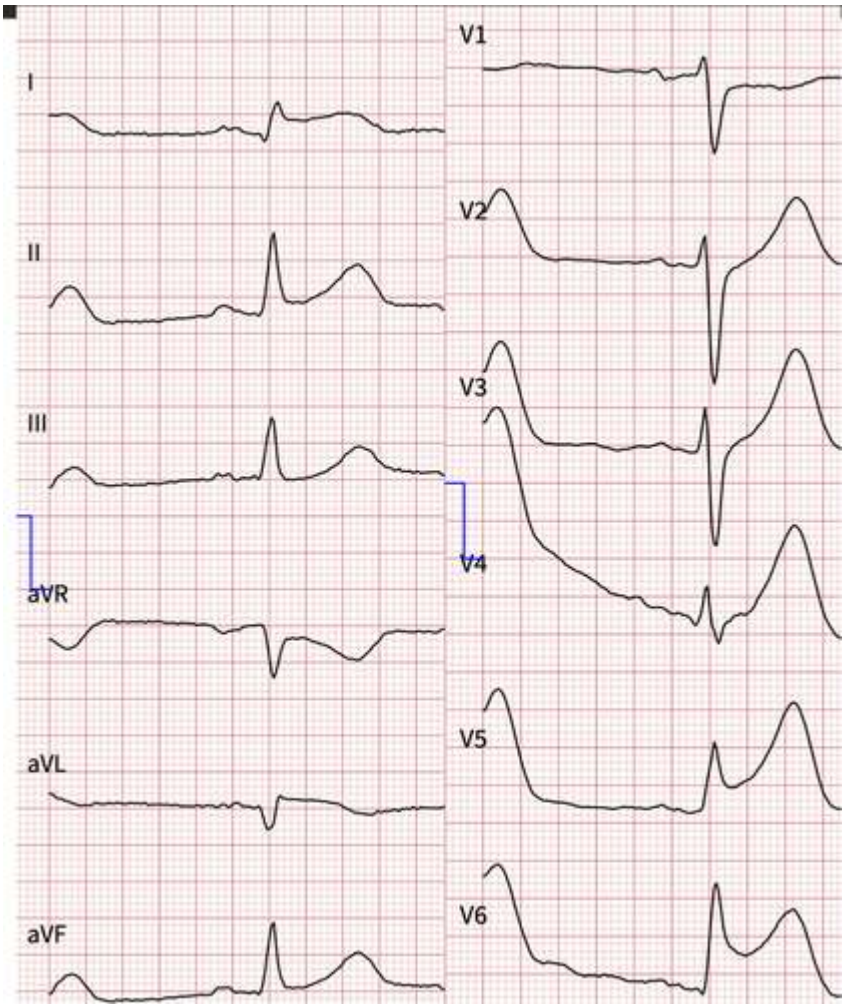

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Figure 2

ST-Segment Elevation Myocardial Infarction Electrocardiogram

Hyperacute ST-segment elevation in leads I, II, aVL, and V_4 to V_6 during a sudden onset angina episode.

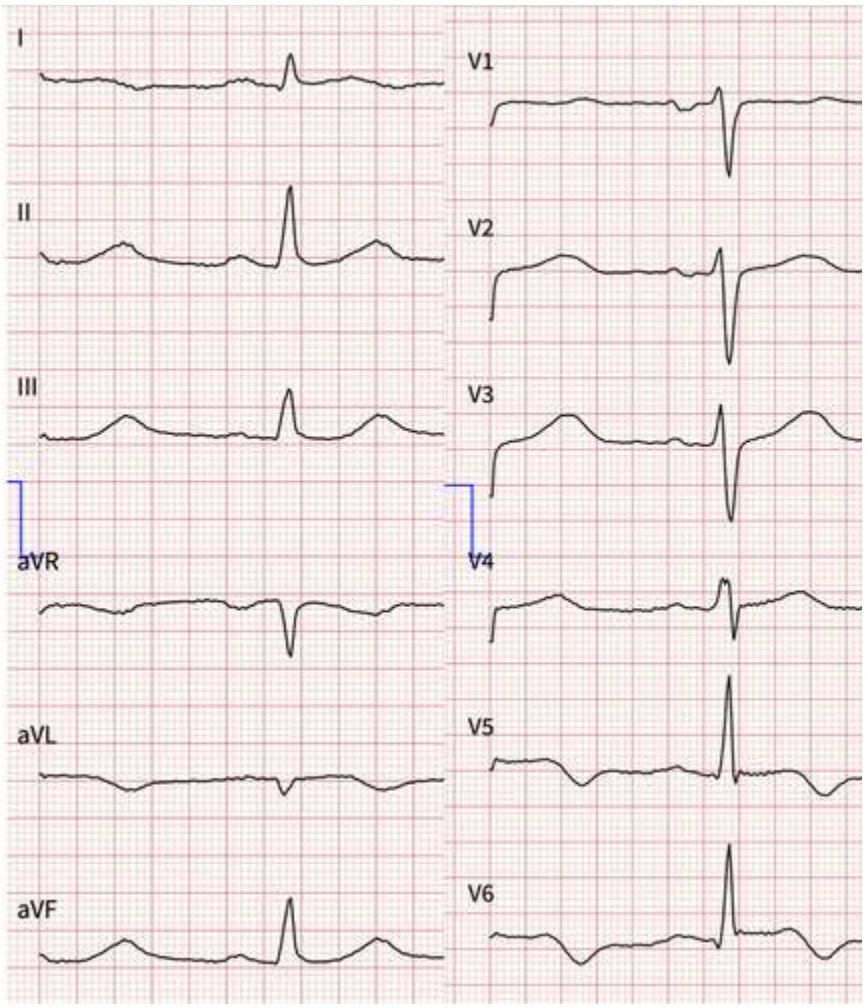

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Figure 3

Electrocardiogram After Angina Episode

Resolution of ST-segment elevation, residual elevation in lead V_6, negative T waves in leads V_5 and V_6.

Management

A multidisciplinary team consisting of cardiologists, anesthesiologists, obstetrician/gynecologists, and neonatologists was convened for further diagnostic and therapeutic planning. The consensus was to perform a diagnostic coronary angiogram, with readiness to perform an emergency cesarean delivery contingent on the findings. The patient was hemodynamically

stable at the point of the coronary angiogram. The angiogram revealed a slight illumination with delayed coronary flow in the left anterior descending (LAD) artery; the remainder of the vessels appeared intact (**Figures 4** and **5**, **Videos 1 and 2**). The finding in the LAD artery was suggestive of a spontaneous dissection (Yip-Saw classification type 2), with coronary flow in the distal part of the artery still present. Intracoronary imaging was not performed because of the obvious angiographic features of the lesion and to avoid further radiation exposure and reduce procedural risk during the preterm pregnancy. Additionally, we decided against percutaneous coronary intervention (PCI) on the basis of the position of the lesion (mediodistal) and to avoid complications such as vessel occlusion and hematoma propagation. Because of the high bleeding risk during the planned repeat cesarean operation, a conservative approach with permanent aspirin therapy was initiated. The procedure ended without any complications. Subsequently, aspirin monotherapy was initiated.

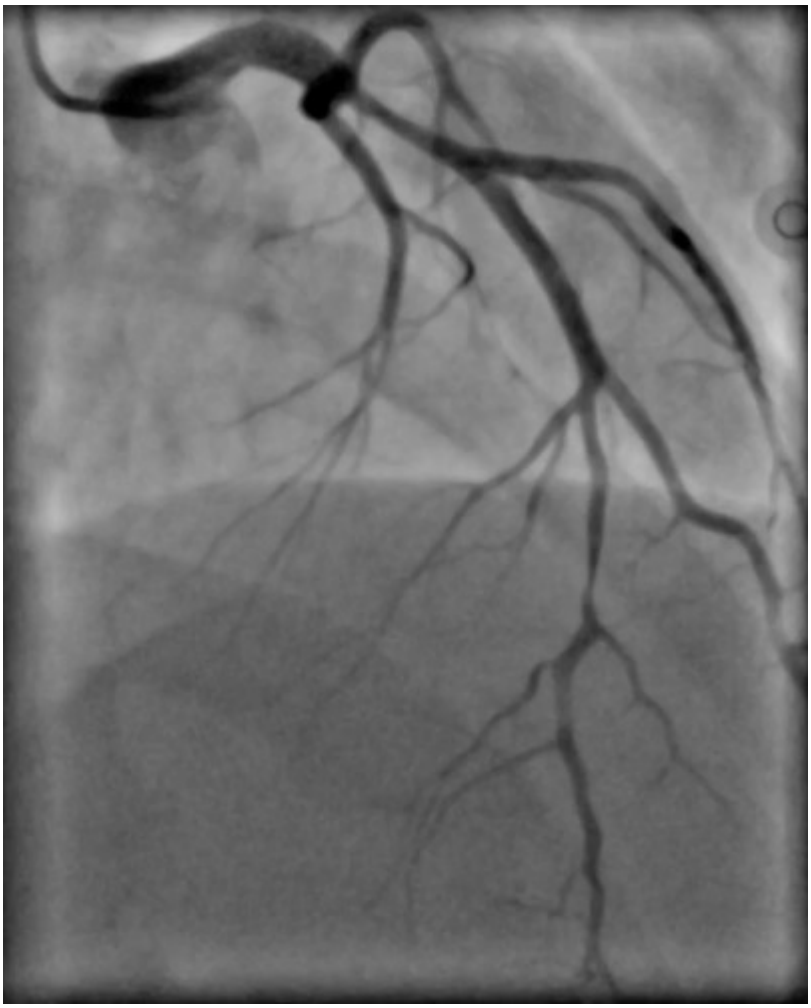

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Figure 4

Emergency Coronary Angiogram (Left Anterior Oblique Projection)

Spontaneous dissection in the mediodistal part of the left anterior descending artery.

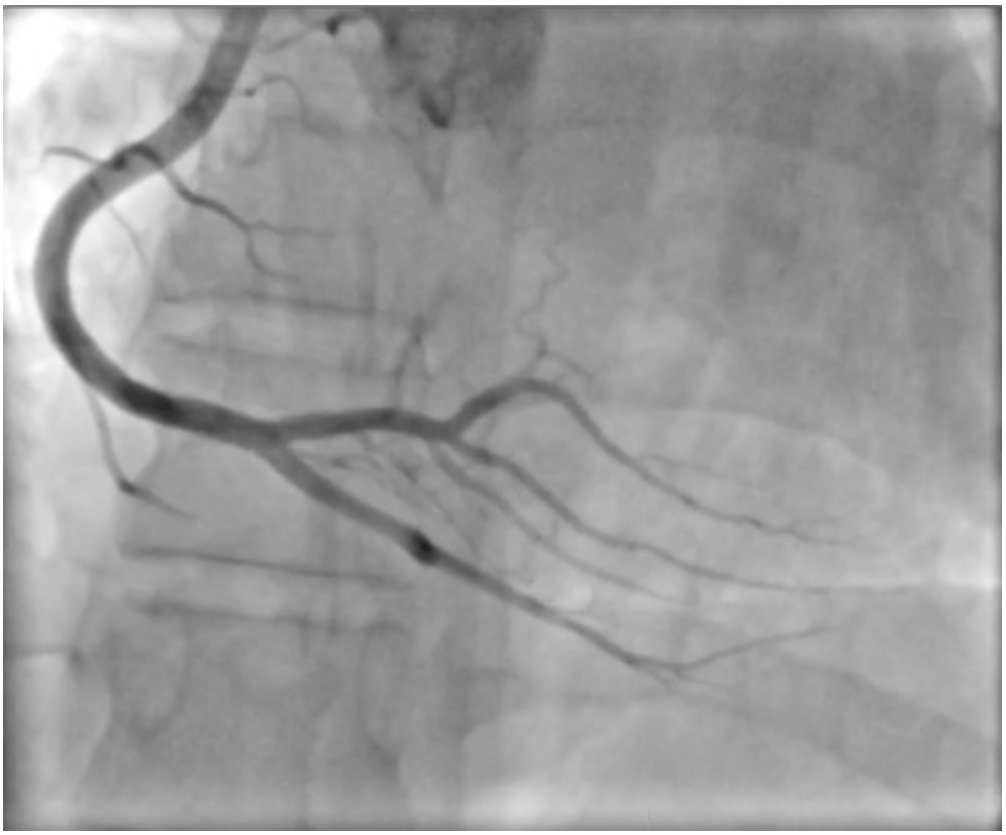


Figure 5

Emergency Coronary Angiogram (Right Anterior Oblique Projection)

Normal right coronary artery.

Outcome and Follow-Up

The patient was monitored in the ICU for an additional 10 days without further incidents. An early follow-up TTE 2 weeks later showed complete recovery of the apical wall contraction. The delivery was uncomplicated and occurred 8 weeks later. No peripartum or postpartum cardiac events were noted. Follow-up TTE and ECG at 3 months revealed full recovery of left ventricular function without signs of apical hypokinesia.

Discussion

P-SCAD is an extremely rare cause of acute myocardial infarction of unknown origin that can occur at any time during pregnancy, although it most commonly occurs post partum, primarily within the first week.[1] Current data suggest a prevalence of 1.81 per 100.000 pregnancies,[2] and P-SCAD comprises 5% to 17%[3-5] of all SCAD cases. Approximately 14.5% to 43%[6,7] of P-SCAD cases manifest as acute myocardial infarction. Multiparity, fertility hormones, and preeclampsia have been reported as the main risk factors.[8,9] Previous data have linked P-SCAD to conditions that are more severe than SCAD, in particular STEMI and occlusion of the proximal coronary arteries, as well as reduced ejection fraction in P-SCAD survivors.[2,10] Other identified risk factors for SCAD, such as fibromuscular dysplasia, inflammatory and/or connective tissue disorders, atherosclerosis, genetic predisposition, and mechanical and emotional stressors, may play a role in the pathogenesis of P-SCAD, albeit data on this remain scarce.[11] Moreover, P-SCAD is frequently associated with left main (LM) coronary artery and multivessel dissections, cardiogenic shock, and impaired left ventricular ejection fraction during the acute phase of the dissection.[10]

SCAD or P-SCAD typically manifests with symptoms similar to those of acute coronary syndrome. The main difference is the phenotype because the typical patient with SCAD or P-SCAD is a young or middle-aged woman during or after pregnancy with few or no cardiovascular risk factors. The primary diagnostic tool is coronary angiography. The Yip-Saw classification[12] and morphologic characteristics such as the absence of intraluminal thrombus and vessel tortuosity are key factors in correctly diagnosing SCAD and differentiating it from “typical,” plaque rupture–mediated coronary dissection. PCI is associated with an elevated risk of complications and adverse outcomes. Data suggest that especially distal lesions with preserved flow should be managed conservatively because angiographic healing has been demonstrated in repeat

angiograms.[4,13] However, the treatment of SCAD or P-SCAD affecting the LM coronary artery, the proximal LAD artery, or more than 1 major vessel, or in patients with hemodynamic deterioration or malignant arrhythmias, remains even more challenging and more complex, with the potential negative impact of the hemodynamic status. In these cases, PCI should be performed in patients with SCAD or P-SCAD, even when taking into account slow or low flow in the target lesion.

In a retrospective study comparing patients with SCAD who underwent PCI with patients who were treated conservatively, there were more in-hospital complications and recurrent myocardial infarctions in the PCI cohort.[14]Additionally, in a case report of a patient with P-SCAD of the LM artery with subsequent cardiogenic shock, a conservative approach was chosen and the patient recovered completely, without requiring further angiographies or PCI.[15] Nevertheless, the present case was more difficult in terms of decision making because the patient was pregnant and a cesarean delivery was scheduled in the near future.

Given the paucity of data on the appropriate medical management of SCAD/P-SCAD, recommendations are generally varied. There is consensus around the necessity of dual antiplatelet therapy (DAPT) in patients undergoing PCI.[16] However, there is still debate on the use of DAPT in conservatively treated patients, the dose and duration of DAPT, or the use of single antiplatelet therapy (SAPT).[17] Data from the DISCO (DIssezioni Spontanee COronariche [Spontaneous Coronary Dissection]) registry reported a more than 2-fold increased risk of major adverse cardiovascular events in conservatively treated patients with SCAD who were discharged on DAPT compared with patients receiving SAPT.[18] Most current data on medical therapy is based on the general group of patients with SCAD because data on the optimal treatment in patients with P-SCAD is scarce.

The present case highlights several key factors in patient management and decision making. First, patients with suspected P-SCAD should be referred to a hospital with facilities to allow for a multidisciplinary diagnostic and therapeutic strategy that will safeguard against complications for both the patient and the infant. Second, intracoronary imaging should be used only in cases where the diagnosis cannot be established by standard coronary angiography, to avoid unnecessary complications. Additionally, individual decision making regarding the use of PCI, apart from the region of the culprit lesion, should also take into account immediate and future adverse effects. Iatrogenic injury of the vessel, as well as long-term bleeding complications, should be considered before PCI in undertaken. Moreover, especially in patients with P-SCAD while still pregnant, complications from perioperative bleeding during childbirth should be carefully considered. Finally, this case highlights the paroxysmal nature of the ST-segment elevation with which patients with P-SCAD can present.

Conclusions

This case highlights the complex nature of P-SCAD and the demanding management required for pregnant patients with this condition, and it adds to the relatively small data pool of these cases. A multidisciplinary approach is necessary to achieve the best possible outcome.

13.Takotsubo Syndrome in a 47-Year-Old Woman With Repaired Tetralogy of Fallot

Abstract

Takotsubo syndrome or broken-heart syndrome is a rare form of nonischemic cardiomyopathy characterized by regional systolic dysfunction of the left ventricle without evidence of coronary artery disease or acute plaque rupture. This transient impairment in myocardial contractility leads to symptoms and

signs that can mimic a myocardial infarction. We present a case of Takotsubo syndrome in a 47-year-old premenopausal woman with complex congenital heart disease who initially presented with acute onset of shortness of breath and chest tightness after a verbal altercation. Extremely rare cases of Takotsubo syndrome have been described in the congenital heart disease population in premenopausal women. This case emphasizes the need to highlight acquired cardiac disease in patients with adult congenital heart disease as this cohort continues to age.

History of Presentation

A 47-year-old premenopausal woman with history of tetralogy of Fallot and pulmonary atresia with multiple prior surgical procedures and ultimately complete repair, presented to an emergency department with acute shortness of breath, chest tightness, and 1 episode of nonbloody emesis. Her symptoms started shortly after a verbal altercation with a family member. She was found to have oxygen saturation of 89% on room air, initially requiring bilevel positive airway pressure before being transitioned to 5-L nasal cannula. The rest of her vital signs were stable. She had a loud systolic murmur, clear lungs, and no peripheral edema.

Take-Home Messages

- When an adult patient with congenital heart disease presents with cardiac symptoms, it is imperative to consider common acquired cardiac pathologies as part of the differential diagnosis.
- A thorough work-up must be completed and the Revised Mayo Clinical Criteria should be met to make to an accurate diagnosis of Takotsubo syndrome in a patient.

Past Medical History

The patient had a history of tetralogy of Fallot with pulmonary atresia status post initial Blalock-Taussig-Thomas shunt at 16 months of age, a right ventricle to pulmonary artery (RV-PA) conduit at 3 years of age, and surgical ventricular septal defect closure at 4 years of age. She subsequently underwent a RV-PA conduit replacement at 8 years of age. She did well for several years and underwent a transcatheter Melody valve implantation in the RV-PA conduit at 42 years of age. She also developed atrial flutter for which she underwent radiofrequency ablation. She had inducible monomorphic ventricular tachycardia on an electrophysiology study leading to an implantable cardioverter-defibrillator.

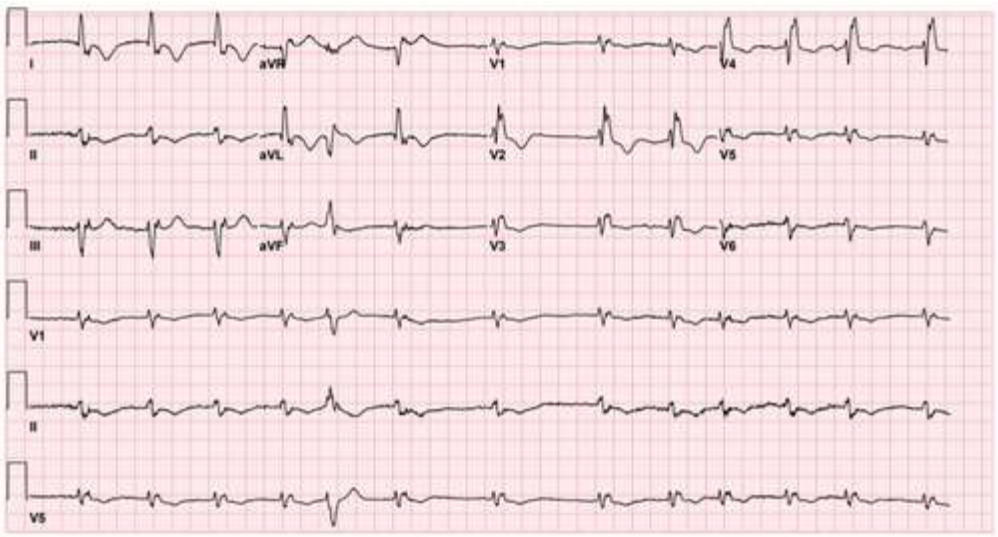
Differential Diagnosis

Differential diagnosis included the following: acute decompensated heart failure, acute coronary syndrome, acute myocarditis, or an acute pulmonary embolism.

Investigations

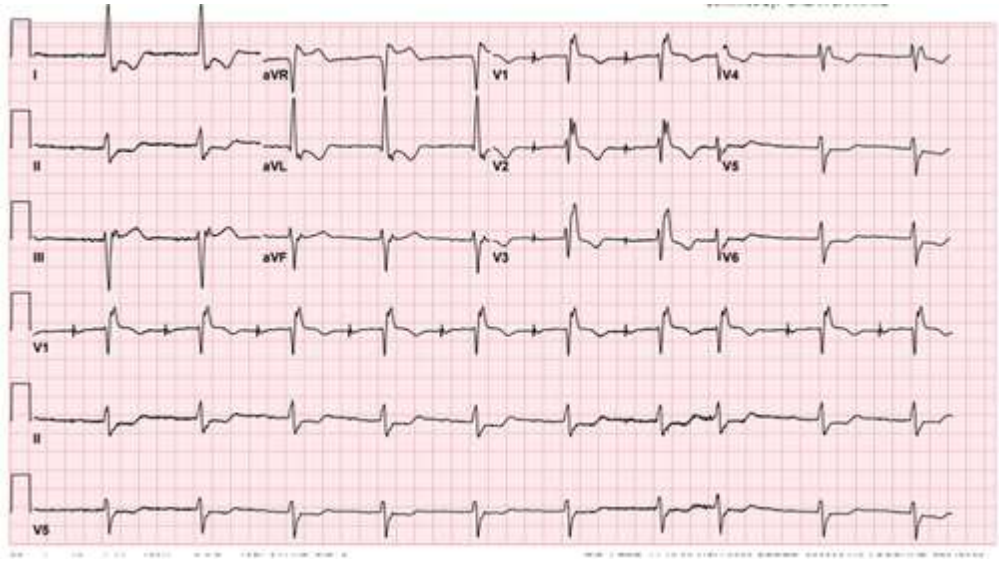
An initial 12-lead electrocardiogram (ECG) was notable for an atrial paced rhythm and right bundle branch block with a QRS duration of 144 milliseconds and QTc duration of 471 milliseconds, similar to her prior ECGs. Computed tomography angiography of the chest was negative for pulmonary embolism. Initial laboratory work was notable for high-sensitivity troponin of 211 ng/L that up-trended to 289 ng/L, and N-terminal pro–B-type natriuretic peptide of 2,194 pg/mL. Additional work-up included a transthoracic echocardiogram (TTE) that showed a left ventricular (LV) ejection fraction (EF) of 15% and new wall motion abnormalities of the inferior and anterior lateral walls with severe apical hypokinesis and sparing of the LV base (**Video 1**). On prior echocardiograms, she had preserved LV EF of 50% to 55%. She was initially given aspirin (81 mg daily) and anticoagulation (dosage included home

regimen which was continued of eliquis 5 mg twice daily, diuresed with IV furosemide 40 mg twice daily), and then was managed for acute decompensated heart failure with intravenous furosemide with improvement in her symptoms. Her laboratory work-up the following day showed a down-trending troponin to 190 ng/L, but elevated erythrocyte sedimentation rate to 120 mm/h and C-reactive protein of 57.4 mg/L. Her infectious panel was negative. While on telemetry, the patient experienced paroxysmal atrial fibrillation as shown by 12-lead ECG in **Figure 1**. A follow-up TTE after 24 hours showed improvement in the LV EF to 45% with resolution of apical akinesis (**Video 2**). A coronary computed tomography examination showed no evidence of coronary artery stenosis and normal LV EF of 60% on the third day after presentation (**Video 3**). A repeat ECG prior to discharge showed an atrial paced rhythm with similar QRS and QTc values compared with baseline (**Figure 2**).



12-Lead Electrocardiogram

Twelve-lead electrocardiogram showing atrial fibrillation with a premature ventricular contraction, right bundle branch block, and diffuse T-wave abnormalities. The QRS duration is 154 milliseconds and QTc duration is 500 milliseconds.



Repeat 12-Lead Electrocardiogram

Repeat 12-lead electrocardiogram before discharge showing an atrial paced rhythm with premature atrial contraction, right bundle branch block, and diffuse T-wave abnormalities. The QRS duration is 156 milliseconds and QTc duration is 501 milliseconds.

Management

The patient was found to have transient severe dyskinesis of the left ventricle, regional wall motion abnormalities beyond a single coronary vascular distribution, with moderately elevated troponin. She had no evidence of obstructive coronary artery disease, acute plaque rupture, pheochromocytoma, or myocarditis, thus meeting the Revised Mayo Clinic Criteria for Takotsubo syndrome.[1] After intravenous diuresis, she had rapid improvement in her symptoms with normalization of the LV EF. She was weaned off supplemental oxygen and discharged in stable condition after 3 days on her prehospital medication.

Follow-Up

The patient was seen at an outpatient follow-up appointment approximately 2 weeks after discharge. She was found to be feeling overall well and much improved since the hospitalization. Follow-up echocardiogram after 7 months showed markedly improved function with global LV EF of 65% (**Video 4**).

Discussion

Although the precise etiology of Takotsubo syndrome has yet to be elucidated, it is thought to be at least partially explained by increased sympathetic activity and a catecholamine surge that impairs myocardial function.[2,3] Patients with Takotsubo syndrome commonly present after episodes of significant physical and/or emotional stress. It has been estimated that approximately 2% of patients who present with concern for acute coronary syndrome have Takotsubo syndrome, most commonly seen in postmenopausal women.[4,5]

Advancements in pediatric cardiology and cardiothoracic surgery have extended the average lifespan of patients with congenital heart disease (CHD). However, as this cohort enters middle age, there is limited information on the presentation and management of cardiomyopathies, including nonischemic cardiomyopathies (eg, Takotsubo syndrome). Takotsubo syndrome has not been well described in the CHD population with only rare cases occurring in premenopausal women.[6] Additional research is needed to further elucidate an association, if any, between CHD and Takotsubo syndrome. Although thus far there is little evidence to suggest that pathophysiology may predispose individuals with CHD to an increased risk of having Takotsubo syndrome, it is plausible that patients with CHD have many prominent risk factors that place them at risk for developing the syndrome. For example, evidence suggests that Takotsubo syndrome is associated with a chronic inflammatory state and recent work has shown that CHD demonstrates multiple features of chronic inflammatory disease.[7-9] Furthermore, prior work has identified psychiatric

disorders, including anxiety and depression, as common predisposing factors to Takotsubo syndrome and are known be more prevalent in CHD compared with the general population.[7,10]

We report a rare case of Takotsubo syndrome in a patient with complex CHD and acute decompensated heart failure with dramatic improvement of the LV EF within 36 hours. Further investigation is needed to determine if patients with CHD are predisposed to nonischemic cardiomyopathies like Takotsubo syndrome particularly at younger ages compared with the general population.

Conclusions

This rare case highlights that as patients with CHD enter middle age, they will present with acquired cardiac pathologies that are routinely seen in patients without CHD. These patients have to be managed in the context of both acquired cardiac disease and their underlying CHD to improve long-term patient outcomes.

14.Heart Failure in Atrial Fibrillation Subtypes in Women and Men in the Tromsø Study

Abstract

Background

Atrial fibrillation (AF) and heart failure (HF) often coexist and impact morbidity and mortality. There is limited knowledge on the association of AF subtypes with HF according to sex.

Objectives

The purpose of this study was to explore sex-specific associations between AF subtypes and subsequent HF, identifying HF risk factors in participants with AF, and exploring the combined impact on mortality.

Methods

14,790 women and 13,181 men from the Tromsø Study were enrolled between 1994 and 2008 and followed for incident AF and HF through 2016. Cox regression was conducted to provide HRs and 95% CIs.

Results

Those with AF had higher risk of subsequent HF in both sexes compared to those without AF. Women with permanent AF had higher relative risk of HF than men (HR: 10.52; 95% CI: 8.72-12.70, and HR: 7.65; 95% CI: 6.40-9.15, respectively). Risk factors for HF in participants with AF included smoking in all, higher diastolic blood pressure and hypertension in women, underweight, obesity, and low alcohol consumption in men. All-cause mortality was higher in women with both subtypes (paroxysmal/persistent: HR: 2.10; 95% CI: 1.78-2.48, permanent: HR: 1.40, 95% CI: 1.14-1.72) and in men with paroxysmal/persistent AF (HR: 1.66; 95% CI: 1.40-1.96). Subsequent HF increased risk of mortality in both sexes.

Conclusions

All AF subtypes were associated with increased risk of HF. Smoking was a shared risk factor, while diastolic blood pressure and hypertension were specific to women, and underweight, obesity, and low alcohol intake were specific to men. Subsequent HF increased mortality risk in all.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are common diseases that impact morbidity, mortality, and quality of life.[1,2] Both conditions primarily affect the elderly, and their prevalence is on the rise due to aging of the population and an increase in metabolic risk factors like hypertension, obesity, and diabetes.[3,4]

There is a bidirectional relationship between AF and HF, with over one-third of individuals with AF developing HF, and about half of those with HF developing AF.[5] AF and HF share common risk factors and underlying conditions, exacerbating each other, and worsening patient prognosis.[6,7] HF accounts for almost a third of all deaths in the first year after AF onset,[8] which emphasizes the importance of preventing HF in patients with AF.

Sex differences in the development and prognosis of both AF and HF have been reported.[1,9-12] Women with AF face a higher risk of HF and have a poorer prognosis when both conditions coexist.[13] Additionally, nonparoxysmal AF has been associated with an increased risk of adverse outcomes compared to paroxysmal AF when AF precedes HF.[14,15] However, there is a need for better understanding of how modifiable risk factors contribute to the risk of HF in women and men with AF and whether the subsequent risk of mortality varies across subtypes of AF. Our study aims to address these knowledge gaps by exploring sex-specific associations between AF subtypes and subsequent HF, identifying underlying risk factors for HF in participants with AF, and exploring the combined impact on mortality in both sexes.

Materials and methods

Study design and participants

Participants were recruited from the fourth (Tromsø4, 1994-1995), fifth (Tromsø5, 2001), and sixth (Tromsø6, 2007-2008) surveys of the Tromsø Study, a longitudinal cohort study in the municipality of Tromsø, Northern Norway.[16] In these surveys, the whole population (Tromsø4) or parts of the population (Tromsø5 and Tromsø6) aged ≥25 years were invited to participate. The number of attendees was 27,158 (72%) in Tromsø4, 8,130 (79%) in Tromsø5, and 12,984 (66%) in Tromsø6. A total of 30,288 inhabitants aged 25 to 97 years attended ≥1 survey. We excluded individuals who emigrated before the examination date (n = 21), had a previous history of HF (n = 134) or AF (n =

219), had insufficient information for AF validation (n = 1,919), or were diagnosed with AF and HF on the same day (n = 24) (**Supplemental Figure 1**). The total study population consisted of 14,790 women and 13,181 men.

Data collection

Information was collected through questionnaires, physical examinations, and blood samples.[17] Resting heart rate (beats/min), systolic blood pressure (BP) (mm Hg), and diastolic BP (mm Hg) were measured by trained personnel using an automated Dinamap device.[17] The mean of the last 2 of 3 measurements was used in the current analyses. Hypertension was defined as systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg, or current use of antihypertensive medication. Weight and height were measured and used to calculate body mass index (BMI) (kg/m^2). Nonfasting serum total cholesterol (mmol/L), high-density lipoprotein cholesterol (mmol/L), and triglycerides (mmol/L) were analyzed by the Department of Laboratory Medicine, University Hospital of North Norway.

Information on current use of antihypertensive medications (yes/no), current daily smoking (yes/no), alcohol consumption, physical activity, and history of myocardial infarction (yes/no), angina pectoris (yes/no), stroke (yes/no), and diabetes mellitus (yes/no) was obtained from questionnaires. Alcohol consumption in Tromsø4 and Tromsø5 was assessed using questions regarding how many glasses of beer/wine/spirits participants drank in a fortnight. In Tromsø6, participants reported the frequency of drinking and number of units (a beer, a glass of wine, or a drink) consumed per occasion. Consumption was categorized into 0 units per week, <1 unit per week, 1 to 2 units per week, 3 to 4 units per week, and ≥5 units per week.

Physical activity was categorized into sedentary, moderate, and highly active, using participant-reported levels of exercise and physical exertion in leisure time over the last 12 months. For participants in Tromsø4 and those aged ≥70 years in Tromsø5, 2 questions on the number of hours per week of light (not

sweating or out of breath) and hard (sweating/out of breath) activity were recoded to correspond to the 3 levels.[18]

Follow-up and detection of incident AF and HF

Follow-up of participants began on the date of the first examination and ended on the date of first documented HF, emigration, death (identified through the Population Register of Norway), or the end of the follow-up period (December 31, 2016), whichever came first. Start of follow-up was changed to the date of AF in analyses restricted to the subgroup of participants with this diagnosis. In mortality analyses, those who developed HF without a prior AF diagnosis were censored at the date of HF, while for the other participants, the end of follow-up was set to the first documentation of either emigration, death, or the end of the follow-up period.

Using the unique Norwegian national identification number, incident AF and HF were detected through linkage to the diagnosis registry at the University Hospital of North Norway. This registry includes diagnoses from both outpatient and inpatient clinics. By using the International Classification of Diseases-9th Revision (ICD-9) codes 427.0 to 427.99 and -10th Revision (ICD-10) codes I47 and I48, participants with a diagnosis of AF were identified. Incident HF was identified using the ICD-9 code 428 and ICD-10 code I50. In addition, for participants with a diagnosis of a cardiovascular event but no recorded diagnosis of arrhythmia, hospital records were searched for AF. Diagnosis of AF was confirmed if documented on an electrocardiogram and validated by an independent endpoint committee following a detailed protocol.[19] The latest AF subtype recorded was used and classified according to the 2016 European Society of Cardiology guidelines for the management of AF[20]: paroxysmal (self-terminating and lasting ≤7 days); persistent (lasting >7 days, including episodes requiring intervention to terminate); and permanent (sustained AF). Data on long-term monitoring of cardiac rhythm were not available and, therefore, paroxysmal and persistent AF were combined.

Transient AF occurring within 28 days after myocardial infarction/acute cardiac event or cardiac surgery, and AF occurring during the last 7 days of life, were not classified as AF cases.

Statistical analyses

Sex-specific characteristics of the study population at first attendance are presented as mean ± SD for continuous variables and as numbers (percentages) for categorical variables. Means and proportions in AF subgroups (no AF, paroxysmal/persistent AF, and permanent AF) were adjusted for age using linear regression for continuous variables and logistic regression for categorical variables and estimated for the overall average age of 45 years. Cox proportional hazards regression models were used to estimate sex-specific HRs and 95% CIs for the association between AF subtypes and the risk of incident HF, to explore modifiable risk factors for HF in participants with and without AF, as well as the risk of mortality when AF preceded HF. All models were adjusted for systolic BP, BMI, total cholesterol, smoking status, physical activity level, alcohol consumption, history of myocardial infarction, stroke, and diabetes mellitus, and for age using age as the time scale. When we investigated systolic BP, diastolic BP, and hypertension as risk factors for HF, only one of these measurements was included in the models at a time. In the analyses investigating risk factors for HF in participants with AF, values of the covariates at the closest survey conducted prior to the AF diagnosis were used. To account for competing risk of death, the Fine-Gray subdistribution hazard model was conducted for both the association between AF subtypes and HF, and for exploring risk factors of HF in AF participants. To assess the possibility of the multiple comparisons problem in the risk factors analyses, False Discovery Rate adjusted *P* values (q-values) were calculated using the Benjamini-Hochberg procedure.

Incidence rates and mortality rates with 95% CIs were estimated per 1,000 person-years and adjusted for the overall average age of 45 years using Poisson

regression. To prevent immortal time bias, we modeled AF or HF as time dependent covariates. The data set was structured with one extra record for participants who developed AF (or HF in the mortality analyses) during follow-up, ie, if a participant developed AF, they contributed one record before AF onset and another after AF onset. The same individual contributed with only one main outcome in each analysis. To explore the risk of all-cause and cardiovascular mortality, participants were divided into 5 groups based on which AF subtype they developed and if HF succeeded AF. Participants without AF and HF were used as the reference. Tests for interaction with sex were performed by including cross-product terms in all models. To further assess the temporal relationship between AF subtypes and incident HF and all-cause mortality in AF participants with and without subsequent HF, we included graphical presentations of cumulative incidence of HF and cumulative probability of mortality estimated from Cox regression with time under study as the time scale. Models were adjusted for age at start of follow-up and the covariates above.

The proportional hazard assumption was assessed with graphical inspection of log minus log survival curves between quartiles of continuous variables or between categories of nominal variables. All analyses were performed using SAS, 9.4 (SAS Institute) and a 2-sided *P* value <0.05 was considered statistically significant.

Results

Baseline characteristics

Over a median follow-up of 21.6 years (25th, 75th percentile: 10.2, 22.0 years), 848 women (467 paroxysmal/persistent AF and 381 permanent AF) and 1,020 men (582 paroxysmal/persistent AF and 438 permanent AF) developed AF (**Table 1**). Women who developed permanent AF were older and had higher age-adjusted mean systolic BP and BMI, compared to women who developed

paroxysmal/persistent AF. Prevalence of hypertension and usage of antihypertensive medications were higher among women who developed permanent AF. Men who developed permanent AF were older compared to those who developed paroxysmal/persistent AF. Unlike women, men who developed permanent AF had lower mean systolic BP and diastolic BP than men who developed paroxysmal/persistent AF, and the proportions with hypertension and use of antihypertensive medications were nearly identical between the AF subtypes.

Table 1Baseline Characteristics of Study Participants According to Sex and Atrial Fibrillation Subtype: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)				Men (n = 13,181)			
	No AF (n = 13,942, 94.3)	Parox/Pers (n = 467, 3.1)	Perm (n = 381, 2.6)	*P* Value	No AF (n = 12,161, 92.3)	Parox/Pers (n = 582, 4.4)	Perm (n = 438, 3.3)	*P* Value
Age, y	44.5 (13.8)	61.9 (12.1)	67.1 (9.2)	<0.001	44.0 (12.8)	56.0 (12.5)	60.1 (10.9)	<0.001
Systolic blood pressure, mm Hg	129.2 (20.3)	136.1 (24.9)	138.2 (24.4)	<0.001	135.7 (16.1)	140.2 (20.8)	139.1 (21.1)	<0.001
Diastolic blood pressure, mm Hg	75.2 (11.7)	78.3 (14.0)	78.4 (13.4)	<0.001	79.3 (11.1)	81.2 (12.2)	80.9 (13.0)	<0.001
Hypertension[a]	3,433 (19.3)	307 (28.6)	299 (31.5	<0.001	4,409 (36.5)	340 (44.7)	277 (44.8	<0.001

Table 1Baseline Characteristics of Study Participants According to Sex and Atrial Fibrillation Subtype: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)				Men (n = 13,181)			
	No AF (n = 13,942, 94.3)	Paroxs/Perm (n = 467, 3.1)	Perm (n = 381, 2.6)	*P* Value	No AF (n = 12,161, 92.3)	Paroxs/Perm (n = 582, 4.4)	Perm (n = 438, 3.3)	*P* Value
Antihypertensive medication use	649 (2.8)	79 (4.1)	102 (5.7)	<0.001	585 (3.3)	82 (5.0)	72 (4.8)	<0.001
Body mass index, kg/m^2	24.8 (4.2)	25.4 (4.5)	26.6 (5.2)	<0.001	25.7 (3.4)	26.2 (3.7)	26.9 (3.6)	<0.001
Resting heart rate, beats/min	74.1 (11.9)	74.6 (13.4)	73.3 (13.1)	0.263	70.3 (12.0)	70.4 (12.9)	69.3 (12.9)	0.477
Total cholesterol, mmol/L	5.91 (1.34)	6.03 (1.33)	5.86 (1.22)	0.060	5.96 (1.21)	5.97 (1.13)	5.94 (1.13)	0.912
HDL cholesterol, mmol/L	1.64 (0.40)	1.62 (0.41)	1.60 (0.48)	0.265	1.34 (0.35)	1.32 (0.35)	1.33 (0.37)	0.358
Triglycerides, mmol/L	1.31 (0.81)	1.40 (1.00)	1.44 (1.09)	0.001	1.77 (1.17)	1.77 (1.00)	1.83 (1.18)	0.603
Current daily smoking	5,066 (36.0)	150 (38.7)	72 (25.3	<0.001	4,493 (36.8)	166 (30.0)	127 (31.0	<0.001

Table 1Baseline Characteristics of Study Participants According to Sex and Atrial Fibrillation Subtype: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)				Men (n = 13,181)			
	No AF (n = 13,942, 94.3)	Parox/Pers (n = 467, 3.1)	Perm (n = 381, 2.6)	*P* Value	No AF (n = 12,161, 92.3)	Parox/Pers (n = 582, 4.4)	Perm (n = 438, 3.3)	*P* Value
Alcohol consumption, U/week								
0 U/week	5,043 (36.6)	263 (41.0)	244 (44.1)	0.006	2,452 (20.2)	171 (22.4)	133 (21.4)	0.365
<1 U/week	1,407 (10.2)	33 (8.1)	26 (8.2)	0.787	803 (6.7)	40 (6.0)	33 (6.3)	0.834
1-2 U/week	4,551 (32.3)	97 (28.6)	76 (30.6)	0.195	3,477 (29.0)	150 (26.3)	118 (27.9)	0.601
3-4 U/week	1,780 (12.5)	42 (12.4)	18 (7.4)	0.260	2,526 (20.6)	82 (16.2)	76 (21.2)	0.096
5 or more U/week	948 (6.8)	26 (6.7)	13 (4.3)	0.258	2,728 (22.2)	139 (27.5)	74 (21.1)	0.016
Leisure time physical								

Table 1Baseline Characteristics of Study Participants According to Sex and Atrial Fibrillation Subtype: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)				Men (n = 13,181)			
	No AF (n = 13,942, 94.3)	Parox/Pers (n = 467, 3.1)	Perm (n = 381, 2.6)	*P* Value	No AF (n = 12,161, 92.3)	Parox/Pers (n = 582, 4.4)	Perm (n = 438, 3.3)	*P* Value
activity								
Sedentary	4,879 (35.5)	233 (38.2)	207 (39.0)	0.212	3,379 (28.2)	173 (24.9)	137 (24.9)	0.071
Moderate active	7,793 (56.5)	208 (53.2)	157 (52.3)	0.144	6,561 (54.4)	329 (57.9)	247 (58.6)	0.080
Highly active	1,073 (7.1)	21 (7.2)	13 (6.6)	0.957	2,096 (16.5)	77 (16.5)	49 (15.6)	0.907
History of myocardial infarction	118 (0.3)	16 (0.4)	12 (0.3)	0.554	304 (1.3)	33 (1.2)	35 (1.4)	0.798
History of angina pectoris	284 (0.6)	46 (1.0)	41 (0.8)	0.047	331 (1.3)	63 (2.4)	52 (2.2)	<0.001
History of stroke	119 (0.5)	14 (0.7)	9 (0.5)	0.466	137 (0.7)	8 (0.4)	22 (1.3)	0.011
History of diabetes mellitus	174 (0.9)	27 (1.9)	14 (1.0)	0.004	164 (1.0)	19 (1.1)	11 (0.7)	0.493

AF = atrial fibrillation; HDL = high-density lipoprotein; parox = paroxysmal AF; pers = persistent AF; perm = permanent AF.

Values are mean ± SD or n (%); the means (except age means) and percentages are adjusted for age using linear or logistic regression models, respectively, and estimated for a mean age of 45 years. Due to missing, the number of observations may be marginally different for each variable.

a Hypertension was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications.

AF subtypes and incident HF

Incident HF occurred in 753 women and 914 men, and the incidence rate per 1,000 person-years ranged from 0.9 (95% CI: 0.8-1.0) and 1.9 (95% CI: 1.7-2.2) in those without AF to 9.4 (95% CI: 7.6-11.6) and 16.7 (95% CI: 14.0-20.0) in those with permanent AF for women and men, respectively (**Table 2**). Compared to participants without AF, those with paroxysmal/persistent AF had a higher subsequent HF risk in both sexes. The risk was even higher in those with permanent AF, where women had a significantly higher HR than men. Cumulative incidence of HF by AF subtype over the observational period reflects the same findings (**Supplemental Figure 2**). These results also remained consistent when accounting for the competing risk of death (**Supplemental Table 1**).

Table 2HRs of Incident Heart Failure According to Atrial Fibrillation Subtype by Sex: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)	*P* Value	Men (n = 13,181)	*P* Value[b]

	IR (95% CI)[a]	HR (95% CI)		IR (95% CI)[a]	HR (95% CI)	*P* Value	
Participants without AF	0.9 (0.8-1.0)	1.00 (Reference)		1.9 (1.7-2.2)	1.00 (Reference)		
Paroxysmal/persistent AF	6.4 (5.0-8.0)	5.48 (4.39-6.84)	<0.001	12.8 (10.5-15.6)	5.82 (4.78-7.09)	<0.001	0.829
Permanent AF	9.4 (7.6-11.6)	10.52 (8.72-12.70)	0.001	16.7 (14.0-20.0)	7.65 (6.40-9.15)	<0.001	<0.001

IR = incidence rate; other abbreviation as in **Table 1**.

HRs are adjusted for systolic blood pressure, body mass index, serum total cholesterol, current smoking, alcohol consumption, physical activity, and history of myocardial infarction, stroke, and diabetes mellitus, as well as age by using age as the time scale in the Cox regression models.

a IR per 1,000 person-years, adjusted for a mean age of 45 years and calculating 95% CIs by using Poisson regression.

b *P* value for the difference between sexes calculated by including cross-product terms in the models.

Modifiable risk factors for incident HF

In analyses exploring risk factors collected prior to AF diagnosis, current smoking was the only risk factor associated with subsequent HF in AF participants in both sexes (**Figure 1**). In women with AF, higher diastolic BP and hypertension increased HF risk, while among men with AF, a BMI below 18.5 kg/m^2 or above 30.0 kg/m^2 was associated with an increased risk of HF. Alcohol consumption of ≥5 per week was associated with a reduced risk of HF in women with AF, while men with AF who consumed <1 u of alcohol per week had an increased risk of incident HF compared to those who were abstinent. Higher physical activity levels were associated with reduced risk of HF. In women, the risk was only decreased for the highest level, while it was decreased for both moderately and highly active men. Among potential predictors, only alcohol intake of ≥5 u per week showed a significant interaction with sex.

15.HRs of Heart Failure in Women and Men With Atrial Fibrillation: The Tromsø Study, 1994 to 2016

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medications. HRs are adjusted for systolic blood pressure, body mass index, serum total cholesterol, current smoking, physical activity, history of myocardial infarction, stroke, and diabetes mellitus, and alcohol consumption, as well as age by using age as the time scale in the Cox regression models. ∗ $P < 0.05$ for the difference between sexes calculated by including cross-product terms in the models.

Combined impact of AF and HF on mortality

Mortality rates were lowest for participants without AF and HF, and highest for participants with paroxysmal/persistent AF and subsequent HF (**Table 3**).

Compared to participants without AF and HF, women with AF (without subsequent HF) had a higher all-cause mortality risk regardless of AF subtype, whereas only men with paroxysmal/persistent AF had an increased risk. However, for cardiovascular mortality, permanent AF was associated with the highest risk in both sexes (**Supplemental Table 2**).

Table 3HRs for Mortality According to Atrial Fibrillation and Heart Failure Status by Sex: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)		*P* Value	Men (n = 13,181)		*P* Value	*P* Value[b]
	MR (95% CI)[a]	HR (95% CI)		MR (95% CI)[a]	HR (95% CI)	*P* Value	
Participants without AF/HF	3.2 (3.0-3.5)	1.00 (Reference)		4.7 (4.4-5.0)	1.00 (Reference)		
Paroxysmal/persistent AF	10.3 (8.7-12.2)	2.10 (1.78-2.48)	<0.001	12.2 (10.2-14.5)	1.66 (1.40-1.96)	<0.001	0.078
Permanent AF	6.3 (5.1-7.8)	1.40 (1.14-1.72)	0.001	8.5 (7.0-10.5)	1.16 (0.94-1.42)	0.161	0.259
Paroxysmal/persistent AF + HF	24.6 (19.2-31.4)	2.95 (2.30-3.77)	<0.001	30.8 (24.6-38.6)	3.42 (2.73-4.28)	<0.001	0.158
Permanent AF + HF	21.3 (17.6	3.99 (3.32-	<0.001	26.6 (21.7	2.88 (2.33-	<0.001	0.108

Table 3HRs for Mortality According to Atrial Fibrillation and Heart Failure Status by Sex: The Tromsø Study, 1994 to 2016

	Women (n = 14,790)		*P* Value	Men (n = 13,181)		*P* Value[b]
	MR (95% CI)[a]	HR (95% CI)		MR (95% CI)[a]	HR (95% CI)	*P* Value
	-	4.80)		-	3.56)	
	25.8)			32.7)		

MR = mortality rate; other abbreviations as in **Tables 1** and **2**.

HRs are adjusted for systolic blood pressure, body mass index, serum total cholesterol, current smoking, alcohol consumption, physical activity, and history of myocardial infarction, stroke, and diabetes mellitus, as well as age by using age as the time scale in the Cox regression models.

a MR per 1,000 person-years, adjusted for a mean age of 45 y and calculating 95% CIs by using Poisson regression.

b *P* value for the difference between sexes calculated by including cross-product terms in the models.

For both AF subtypes and sexes, the risk of all-cause mortality increased further when HF developed ($P < 0.001$) (**Table 3**). In women, permanent AF before HF was associated with a higher risk of mortality than paroxysmal/persistent AF before HF. In men, however, paroxysmal/persistent AF prior to HF diagnosis was associated with the highest risk of all-cause mortality. The association between AF subtype with or without subsequent HF and all-cause mortality over the observational period is presented

in **Supplemental Figure 3**. The trend observed for all-cause mortality was also evident for cardiovascular mortality (**Supplemental Table 2**).

Discussion

In this large population-based cohort study, all AF subtypes were associated with an increased risk of developing HF, and the risk was highest for women with permanent AF. We found that current smoking was a common risk factor for incident HF in both sexes with AF. Increasing diastolic BP and hypertension were predictors for HF exclusively in women while being underweight or obese was associated with an increased risk of HF in men only. Participants who developed paroxysmal/persistent AF had the highest risk of death in both sexes when AF was the sole condition. Development of subsequent HF further enhanced the mortality risk (**Central Illustration**).

Risk Factors and Prognosis for Heart Failure in Atrial Fibrillation Subtypes in Women and Men

HRs are adjusted for systolic blood pressure, body mass index, serum total cholesterol, smoking status, physical activity level, alcohol consumption, history of myocardial infarction, stroke, and diabetes mellitus, as well as age by using age as the time scale in the Cox regression models. Participants without atrial fibrillation and heart failure are used as the reference category. ∗ Alcohol consumption of <1 U/week was associated with increased risk compared to abstinence.

Incident HF in participants with AF

AF is an established independent predictor of HF,[21] and several studies indicate that permanent AF is associated with the highest risk of HF.[14,15,22] In ORBIT-AF (Outcomes Registry for Informed Treatment of Atrial Fibrillation),

permanent AF was associated with a 1.60 times higher risk for incident HF compared to paroxysmal AF.[14] Additionally, permanent AF was associated with incident HF during 1-year follow-up in a study by Schnabel et al.[22] Mogensen et al[23] found that patients with paroxysmal AF had greater HF hospitalization risk compared to persistent/permanent AF. Importantly, outcomes were related to AF subtype in patients with established HF, so the results likely reflect the impact of AF on the course of HF. Our findings add to previous literature by showing that the risk of incident HF was substantially higher in those with permanent AF compared to persistent/paroxysmal AF. Furthermore, women with permanent AF had a higher relative risk of developing incident HF than men with permanent AF.

AF and HF are closely interrelated and impact each other in a vicious pathophysiological cycle.[24] Irregular heart rate, loss of atrial systolic function, and neurohormonal activation due to AF can result in unfavorable hemodynamic effects, leading to left ventricular dysfunction and reduced cardiac output.[25] These mechanisms facilitating HF in patients with AF are often more prominent in those with a higher AF burden and could explain why permanent AF was associated with a higher risk of HF in both sexes. In addition, sex differences in epidemiology and pathophysiology of both AF and HF have been previously described.[26,27] Generally, women are diagnosed with these conditions later in life and are more likely to develop HF with preserved ejection fraction,[28] while men are more prone to develop a combination of AF and HF at an earlier age, often accompanied by impaired left ventricular function secondary to previous myocardial infarction.[12] There have also been noted differences in treatment approaches between sexes following an AF diagnosis. Previous literature has demonstrated that women are treated more conservatively regarding rhythm control and are less likely to receive electrical cardioversion and catheter ablation.[29-31] Additionally, Gruber et al demonstrated that patients with AF undergoing catheter ablation have a lower risk of developing HF compared to those treated with anti-arrhythmic

drugs.[32] These disparities may influence the prognosis of AF subtypes and could explain some of the observed sex differences in HF risk.

Modifiable risk factors for HF in participants with AF

Previous studies have demonstrated that well-established risk factors for HF development are also predictors of incident HF in patients with AF.[15,33] Both hypertension and increased systolic and diastolic BP were risk factors for HF in participants without AF in our study (**Supplemental Table 3**). However, in participants with AF, hypertension and higher diastolic BP were associated with HF risk in women only. Pandey et al found an increased risk of HF in patients with AF with diastolic BP above 80 mm Hg.[14] However, the association between systolic BP and increased risk of HF described previously[33,34] was not found in our study. The relationship between BP and the subsequent risk of HF could have been affected by the initiation or intensification of antihypertensive treatment following the AF diagnosis. Women have been found to have a higher prevalence of hypertensive left ventricular hypertrophy which is less modifiable with BP-lowering medications than in males.[35,36] These factors may contribute to the observed sex differences in the association between BP and risk of HF in our study.

Like others,[15,33] we found that BMI was an independent predictor of HF in participants with AF. We also showed that BMI had a U-shaped relationship with the risk of HF in men, while only obesity was associated with increased risk of incident HF in women. Physical activity has been shown to reduce the risk of HF development.[37] Contrary to the Women's Health Study where no association between physical activity and risk of HF was identified,[34] we found that highly active women with AF had reduced risk of subsequent HF. Additionally, both moderate and high activity were associated with decreased risk of HF in men.[38,39]

Previous studies suggest potential cardiovascular benefits from moderate alcohol consumption, including a reduced risk of incident HF.[38,39] In our study, men consuming <1 u of alcohol per week had higher risk of HF than abstainers, while women consuming ≥5 u per week prior to AF diagnosis had a decreased risk of developing HF. The relationship between alcohol consumption and HF is complex. Our questionnaire on alcohol consumption may not capture specific details such as drinking patterns, types of beverages consumed, and exposure to alcohol over time. Additionally, our analysis may be limited by the modest drinking levels in Tromsø, reducing the statistical power to assess the impact of high alcohol consumption on HF risk.

Risk of all-cause mortality amongst AF participants with and without HF

Although there have been conflicting results in the literature on the combined influence of AF and HF on adverse outcomes, recent research shows that the risk of mortality is increased when the 2 conditions coexist.[7,40] In the Framingham Heart Study, the risk of mortality after AF increased by 2.7 in men and 3.1 in women when incident HF occurred.[7] Ambriosio et al[41] also found that the incidence of all-cause mortality was elevated in patients with AF and HF compared to those without HF. Supporting this, we demonstrated that patients with either AF subtype had a higher risk of mortality if they developed subsequent HF. Despite previous studies indicating worse outcomes for women with AF and HF,[7,12] we found no sex differences in relative risk of mortality, regardless of AF subtype.

Previous research has shown that the risk of all-cause mortality was higher in nonparoxysmal AF than in paroxysmal AF.[42,43] In contrast, except for in women with AF and subsequent HF, we found that participants with paroxysmal/persistent AF had a higher mortality risk than those with permanent AF. This could be related to the sudden changes in ventricular rate. Transient forms of AF might act as an indicator of HF instability, especially in

patients with HF that can rapidly decompensate in response to sudden hemodynamic changes.[44]

Strengths and limitations

Strengths of this study are its population-based design, access to repeated data on an individual level, standardized diagnostic criteria and validation of AF cases, high attendance over the surveys, and comprehensive collection of variables, allowing adjustment for multiple potential confounders. Additionally, the information on risk factors and confounders is gathered before the AF diagnosis, allowing to assess the risk factors before the potential influence of AF treatment.

Some limitations require acknowledgment. Several variables are self-reported which could lead to nondifferential misclassification. Although the AF diagnosis was validated, the AF pattern may have changed during follow-up. This would however only dilute the results. Contrary to AF diagnosis, an independent validation of all incident HF cases was not performed. However, 77 randomly selected participants with HF had their diagnosis validated, showing a positive predictive value of 88%,[45] which is comparable to validation findings from other administrative databases.[46] False positive HF cases could potentially lead to underestimation of the associations.

While acknowledging the potential issue of the multiple comparison problem in our results, we have presented the results as initially conducted. Many *P* values were <0.001, suggesting robust findings likely remain significant even with stricter significance thresholds. To address the risk of false positives in the risk factor analyses, we provided q-values (False Discovery Rate adjusted *P* values) for each risk factor (**Supplemental Table 4**). Despite some results exceeding a 5% false positive rate, there is also a risk of underestimating effects due to the reduced statistical power when conducting sex-specific analyses and categorizing variables. The same applies for the

supplementary analyses accounting for competing risk of death. While the HF risk according to AF subtype (**Supplemental Table 1**) showed little change, several risk factors became nonsignificant (**Supplemental Table 5**), with larger *P* values and wider CIs, further suggesting power limitations. The results should therefore be interpreted with these considerations in mind.

Echocardiography data are not systematically available in the Tromsø Study for all HF cases to determine HF subtype. Furthermore, we do not have detailed information on medication use.

The generalizability of our findings may be limited due to participant recruitment from a single municipality in northern Norway. Furthermore, the 66% to 79% attendance introduces a potential response bias, as nonattendees have been shown to be slightly younger, have lower education and income levels, and more likely to be male and/or single compared to attendees.[16,47]

We do not have information from primary care, meaning patients with AF treated by their general practitioner only, are not included as an AF case in our data. In addition, due to their transient presentation possible cases with paroxysmal or persistent AF may be missed which could lead to an underestimation of the true population prevalence of AF.

Conclusions

Our study provides new insights into the sex-specific relationship between AF subtypes and incident HF from a large, prospective community-based cohort. Regardless of sex, both AF subtypes were associated with an increased risk of HF, and for permanent AF, women showed higher relative risk than men. Smoking was a shared risk factor for HF in both sexes, while increased diastolic BP and hypertension were risk factors in women only, whereas being underweight or obese, or having low alcohol consumption were only risk factors

in men. Subsequent development of HF was associated with an increased mortality in both sexes.

16.Congenital Heart Disease Fetuses Have Decreased Mid-Gestational Placental Flow, Placental Malperfusion Defects, and Impaired Growth

Abstract

Background

Placental health may impact the development and outcomes of congenital heart disease (CHD). CHD fetuses have been shown retrospectively to have decreased placental blood flow.

Objectives

The purpose of this study was to determine if CHD fetuses with decreased placental blood flow have placental pathology at birth and if there is a relationship between placental blood flow, placental pathology, and outcomes.

Methods

We performed a prospective case-control study of 38 CHD fetuses, including 28 with single ventricle physiology and 36 controls. Demographic, clinical, and postnatal biometric data were collected. Umbilical venous volume flow (UVVF) was measured from 2nd trimester fetal echocardiograms. Placentas underwent standardized pathological analysis. Standard descriptive statistics and regression analyses were performed to analyze the relationship between UVVF, placental defects, and outcomes.

Results

CHD fetuses had a 15% decrease in mid-gestational UVVF indexed to fetal weight ($P < 0.01$), and a 27% reduction in UVVF as a proportion of fetal cardiac

output ($P < 0.01$) compared to controls. CHD fetuses had increased placental maternal vascular malperfusion (MVM) lesions (44% vs 18%, $P < 0.05$), especially high-grade MVM (39% vs 9.1%, $P = 0.05$), and a trend toward increased placental fetal vascular malperfusion lesions (42% vs 23%, $P = 0.10$). Placental MVM but not fetal vascular malperfusion lesions were associated with decreased birth weight in CHD fetuses ($P < 0.001$). There was no association between UVVF and placental pathologic findings or fetal growth.

Conclusions

CHD (particularly single ventricle) fetuses have decreased mid-gestational placental blood flow, increased placental malperfusion defects, and impaired fetal growth. Placental MVM may influence impaired fetal growth in CHD.

Introduction

The majority of congenital heart disease (CHD) remains unexplained by currently identified genetic or environmental factors. The maternal-fetal environment may impact the development of, and outcomes associated with, CHD.[1-3] Our understanding of the role of the placenta, despite its critical place in the uterine environment, is quite limited.

The fetal heart and placenta develop concurrently and share several key developmental pathways.[1] Placental and umbilical cord abnormalities are associated with an increased risk of fetal CHD.[4-6] Likewise, there is a known association between maternal hypertensive disorders of pregnancy and fetal CHD.[7,8] Specifically, abnormal vascular development and an imbalance between circulating angiogenic and antiangiogenic factors is implicated in the pathophysiology of both placental abnormalities and CHD.[9,10]

Our limited understanding of the placenta in CHD is in part due to the challenges of assessing the organ in utero. In CHD, traditional Doppler indices of placental blood flow such as umbilical artery (UA) flow and the

cerebroplacental ratio (CPR) can vary considerably[6,11,12] and are often normal.[13,14] Umbilical venous volume flow (UVVF) is a validated noninvasive Doppler-derived method to directly assess blood flow from placenta to fetus.[15] UVVF measurements are highly reproducible; however, additional studies are required to standardize the methodology.[16] UVVF is an early indicator of fetal growth restriction and uniquely reflects characteristics of the placenta rather than the fetus.[17,18] We previously demonstrated decreased mid-gestational UVVF parameters in CHD fetuses compared to controls.[19] In this work, we sought to determine whether CHD fetuses with impaired placental blood flow demonstrate distinct pathological features of the placenta at birth and explore their relationship with adverse clinical outcomes.

Methods

Study design

This was a single-center prospective case-control study performed in the Children's Hospital of Philadelphia's (CHOP) Fetal Heart Program and approved by the CHOP Institutional Review Board (IRB# 17-014630). Patients were consecutively enrolled from February 2018 to October 2019. Maternal-fetal dyads who obtained a fetal echocardiogram at CHOP's Fetal Heart Program either for clinically indicated screening or follow-up for CHD were eligible to participate in the study. Inclusion criteria for controls were fetal gestational age of 18 to 28 weeks, no structural heart disease on fetal echocardiogram, and consent to transfer the placenta to CHOP after delivery. Exclusion criteria for all subjects were multiple gestation, major extracardiac congenital abnormalities (such as congenital diaphragmatic hernia), significant fetal arrhythmia, hydrops fetalis, and the presence of hemodynamically significant maternal CHD (moderate or greater complexity).[20] All eligible dyads were approached for study participation. Enrolled fetuses with CHD included those with single ventricle (SV) CHD (n = 28), tetralogy of Fallot (n = 9), and D-transposition of the great arteries (n = 1). Thirty-six control fetuses were

enrolled. Mothers of 11 cases were simultaneously enrolled in a prospective randomized clinical trial of vaginal natural progesterone therapy vs placebo (**NCT02133573**) to evaluate the effect on neurodevelopment for fetuses with CHD. Placebo or progesterone was administered twice daily between 28 and 39 weeks gestation. Randomization of overlapping study subjects remained blinded to this study's investigators.

The majority of SV CHD were single right ventricle lesions, including hypoplastic left heart syndrome (n = 24) and its variants, such as double outlet right ventricle with mitral atresia (n = 2), and severely right-dominant unbalanced complete atrioventricular canal defects (n = 1). One patient with tricuspid atresia and unobstructed normally related great arteries was included in the SV category. All cases underwent prenatal and/or postnatal genetic evaluation.

Fetal echocardiograms were performed via standard protocol which included assessment of fetal biometry, umbilical vein and artery Doppler tracings, and cardiac rhythm and anatomy. Echocardiographic findings from 2nd trimester studies were compared between cases and controls, however all follow-up fetal echocardiograms performed for cases were included to evaluate longitudinal changes in UVVF. Measurements determined to be inaccurate due to inadequate 2nd trimester image quality were excluded. Controls had single studies performed with no follow-up. Other requisite data collection prior to delivery occurred via medical record review and no additional prenatal visits were required. Medical record review included maternal demographics, fetal gestational age and sex, pregnancy history, maternal medical history, and any known fetal genetic diagnoses. All cases were delivered in either the Special Delivery Unit at CHOP or at the University of Pennsylvania, and placentas were collected at delivery. Control subjects were provided shipment supplies for return of their placentas from delivery hospitals. Postnatal information was obtained from the medical record, or for controls, from a delivery information

sheet with delivery course and neonatal biometrics filled out by the mother's obstetrician. A fraction of controls were lost to follow-up and did not return their placentas and/or provide postnatal medical information. Controls received compensation of $25 for participation in and completion of the study.

UVVF and combined cardiac output measurements

UVVF was calculated as previously published.[19] Briefly, the umbilical vein was visualized in a free loop in the longitudinal plane and 3 measurements of the diameter of the vessel were averaged. Spectral Doppler of the umbilical vein was obtained at an angle of insonation of <20°. Due to the laminar flow pattern in the umbilical vein, the mean velocity is equal to half the maximum velocity. The cross-sectional area of the umbilical vein multiplied by the mean velocity of flow yields the rate of blood flow, UVVF, in mL/min. Interobserver reliability for UVVF measurements by this study's investigators was previously reported as high,[19] and these measurements are included in the standard fetal echocardiogram protocol at CHOP. Measurements were obtained at the time of the study but reviewed for adequacy and accuracy by R.J., D.Y.H., and Z.T.

Combined cardiac output (CCO) was assessed by multiplying the calculated area of both outflow tracts by the velocity-time integral determined by spectral Doppler for both the right and left ventricles and combining the values. In the case of single outflow tracts, only that value was used.

Placental pathology and analysis

All placentas were examined in the pathology department at CHOP utilizing a systematic protocol, including recording the trimmed placental weight, membrane insertion, gross appearance, dimensions of the placental disc, and umbilical cord characteristics. Histologic samples included sections of membranes, umbilical cord, and at least 3 full-thickness sections of nonlesion placental parenchyma. Macroscopic and microscopic lesions were described

according to the 2016 Amsterdam Placental Workshop Group[21] and Freedman et al placental phenotypic classification systems[22] (**Supplemental Table 1**). Microscopic examination was performed by a single perinatal pathologist for all placentas (R.L.), blinded to CHD type, UVVF values, and outcomes.

Statistical analysis

Continuous variables are presented as median (IQR). Categorical parameters are described as frequency (N) and percentage (%). Controls were compared to all CHD and SV cases using chi-squared/Fisher's tests and *t*-test/Wilcoxon tests depending on the variable type and distribution. $P \leq 0.05$ was considered statistically significant. Linear and logistic regressions were performed to analyze the relationship between UVVF indexed to fetal weight (UVVF/Wt), placental defects, and outcomes. Following the exclusion of one patient with an outlier UVVF/Wt measurement, quantile regression was applied to: 1) assess the relationship between UVVF/Wt and gestational age; and 2) evaluate deviation from a healthy reference population. The optimal model for this study population was based on the Akaike information criterion and included both linear and quadratic terms.

All statistical analyses were conducted using R software, version 4.2.3 (R Development Core Team). R package rms was used for quantile regression and R package ggplot2 was used for figure generation.

Results

Subjects

A total of 38 fetal cases, the majority with SV CHD, as well as 36 fetal controls were included. The characteristics of the study population are shown in **Table 1**. The median gestational age of the cases was slightly higher than those of the controls (23 weeks vs 21 weeks; $P < 0.001$). Maternal age was slightly lower in cases compared to controls. There was no difference in the distribution of

maternal race, comorbidities, medication exposure, or fetal sex between cases and controls. While only present in few subjects, there was no difference in prevalence of maternal hypertension, preeclampsia, or maternal aspirin use between groups. Simple, or class I maternal CHD[20] was present in 4 controls (1 small VSD s/p spontaneous closure in childhood, 1 VSD s/p repair in childhood with no residual disease, 1 mild mitral valve prolapse, and 1 double aortic arch s/p neonatal repair), and in 1 case (small VSD s/p spontaneous closure). There was an increased prevalence of maternal diabetes in the control group, which may be due to diabetes being an indication for surveillance fetal echocardiography. One case was diagnosed postnatally with Rubinstein-Taybi syndrome. No other genetic anomalies were identified in cases or controls at the time of medical record review.

Table 1Characteristics of the Study Population

	Controls (n = 36)	All CHD (n = 38)	*P* Value[a]	Single Ventricle (n = 28)	*P* Value[b]
Fetal gestational age (wk)	21.0 (20.0-22.0)	23.0 (22.3-26.8)[c]	**<0.001**	23.0 (22.8-25.0)[d]	**<0.001**
Maternal age (y)	32.0 (29.8-35.0)	30.0 (26.0-33.0)[e]	**0.022**	31.0 (27.0-34.0)	0.209
Maternal race			0.565		0.507
African American	3 (8.3%)	1/31 (3.2%)		0/22 (0%)	
Asian	3 (8.3%)	6/31 (19%)		4/22 (18%)	
Caucasian	28 (78%)	21/31		16/22 (73%)	

Table 1Characteristics of the Study Population

	Controls (n = 36)	All CHD (n = 38)	*P* Value[a]	Single Ventricle (n = 28)	*P* Value[b]
		(68%)			
Hispanic	1 (2.8%)	2/31 (6.5%)		1/22 (4.5%)	
Other	1 (2.8%)	1/31 (3.2%)		1/22 (4.5%)	
Fetal sex			0.532		0.539
Female	7/17 (41%)	12/37 (32%)		9 (32%)	
Male	10/17 (59%)	25/37 (68%)		19 (68%)	
Maternal comorbidity	19 (53%)	15 (39%)	0.251	12 (43%)	0.431
Chronic hypertension	3 (8.3%)	2 (5.3%)	0.670	2 (7.1%)	>0.999
Preeclampsia/Gestational hypertension	1 (2.8%)	3 (7.9%)	0.615	2 (7.1%)	0.577
Diabetes	10 (28%)	1 (2.6%)	**0.002**	0 (0%)	**0.003**
Autoimmune disease	0 (0%)	2 (5.3%)	0.494	2 (7.1%)	0.188
Maternal CHD	4 (11%)	1 (2.6%)	0.194	1 (3.6%)	0.375
Obesity	0 (0%)	2 (5.3%)	0.494	2 (7.1%)	0.188
Renal disease	0 (0%)	0 (0%)		0 (0%)	
Smoker	0 (0%)	0 (0%)		0 (0%)	
Aspirin use	5 (14%)	3 (7.9%)	0.474	2 (7.1%)	0.454
Antihypertensive	0 (0%)	1 (2.6%)	>0.999	1 (3.6%)	0.438

Table 1Characteristics of the Study Population

	Controls (n = 36)	All CHD (n = 38)	*P* Value [a]	Single Ventricle (n = 28)	*P* Value [b]
medication use					

CHD = congenital heart disease.

Values are median (IQR) or n (%). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 31 for fetal gestational age for all CHD subjects.

d n = 24 for fetal gestational age for single ventricle subjects.

e n = 37 for maternal age for all CHD subjects.

Placental blood flow

On manual review, 7 cases lacked adequate image quality for an accurate calculation of second trimester UVVF. At the time of fetal echocardiography, the median fetal weight for cases was higher than controls, in the setting of slightly higher median gestational age (**Table 2**). Accordingly, absolute UVVF was not different between cases and controls. When UVVF was indexed to fetal weight (UVVF/Wt), it was significantly decreased in all cases, as well as the SV subgroup, compared to controls. UVVF as a proportion of cardiac output (UVVF/CCO), reflecting the proportion of fetal circulation returning to the placenta, was significantly decreased in all cases, as well as the SV subgroup, compared to controls. While still within the normal range, there was an increased mean UA pulsatility index (UA PI), and a decreased mean uterine

artery PI (UtA PI) in cases compared to controls. The middle cerebral artery PI (MCA PI) and CPR were not different (**Table 2**). UVVF/Wt slowly declined throughout the late 2nd trimester and 3rd trimester in cases who underwent at least one follow-up study (n = 23) (**Figure 1**). Compared to published norms,[23] average UVVF/Wt values for cases were decreased compared to the 50th percentile for healthy fetuses in the 2nd trimester, however continued to trend slightly lower than normal in later gestation.

Table 2Placental Blood Flow Characteristics

	Controls (n = 36)	All CHD (n = 31)	*P* Value [a]	Single Ventricle (n = 24)	*P* Value [b]
Fetal weight (g)	437 (340-546)	629 (530-756)	**<0.001**	646 (528-830)	**<0.001**
CCO (mL/min/kg)	394 (345-472)[c]	442 (321-542)	0.574	371 (321-471)	0.555
UVVF (mL/min)	51 (38-68)	61 (47-84)	0.147	59 (44-80)	0.333
UVVF/Wt (mL/min/kg)	113 (98-145)	96 (79-115)	**0.007**	87 (74-108)	**0.001**
UVVF/CCO (%)	30 (24-39)[c]	22 (18-30)	**0.006**	23 (20-31)	**0.045**
MCA PI	1.67 (1.55-1.79)[c]	1.78 (1.55-1.93)	0.261	1.77 (1.49-1.89)	0.660
UA PI	1.23 (1.16-1.36)	1.36 (1.27-1.48)	**0.020**	1.33 (1.28-1.39)	0.091
UTA PI	0.96 (0.78-1.24)	0.78 (0.66-1.00)	**0.017**	0.80 (0.67-0.99)	**0.038**
CPR	1.36 (1.17-1.52)[c]	1.29 (1.10-1.50)	0.404	1.30 (1.14-1.46)	0.413

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

CCO = combined cardiac output; CPR = cerebroplacental ratio (MCA/UA); MCA = middle cerebral artery; PI = pulsatility index; UA = umbilical artery; UTA = uterine artery; UVVF = umbilical venous volume flow; other abbreviation as in **Table 1**.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 35 for CCO, UVVF/CCO, MCA PI, and CPR for controls.

Umbilical Venous Volume Flow/Wt Throughout Gestation in Congenital Heart Disease Fetuses

UVVF/Wt (ml/min/kg) was measured from serial fetal echocardiograms across gestational age (GA) in CHD fetuses. 95% (p95), 50% (p50), and 5% (p5) are represented by solid lines using a quantile regression with linear and quadratic terms. p5 = 9.35* GA - 0.20* GA^2 - 44.54. p50 = 14.68* GA – 0.27* GA^2 - 100.97. p95 = 6.14* GA – 0.15* GA^2 +83.73. Gray shading represents 95% confidence interval of the p50. Gray dashed lines represent the previously published 5% (p5 [ref]), 50% (p50 [ref]), and 95% (p95 [ref]) regression model of UVVF/Wt over gestation in healthy fetuses.[23] Average UVVF/Wt for cases was decreased compared to the reference 50th percentile for healthy fetuses in the 2nd trimester, however continued to trend slightly lower than normal in later gestation. CHD = congenital heart disease; UVVF = umbilical venous volume flow.

Placental pathology

Thirty-nine percent of control subjects were lost to follow-up and did not provide their placenta or postnatal data for analysis. Placentas from 2 cases who delivered at an outside institution were not available for analysis. In those

analyzed, there was no significant difference between placental weight in cases compared to controls (**Table 3**). There was also no difference in the ratio of placental weight to birth weight (PW:BW), an indicator of placental efficiency. Notably, 44% of all cases and 41% of SV cases had lesions associated with maternal vascular malperfusion (MVM) compared to 18% of controls (P = 0.041, P = 0.088). In particular, cases had significantly more high-grade MVM lesions compared to controls (39% cases vs 9.1% controls, P = 0.049). Lesions associated with fetal vascular malperfusion (FVM) were found in 42% of total cases, and 41% of SV cases, compared to 23% of controls, however this finding was not statistically significant (P = 0.141, P = 0.181). There was no difference in the prevalence of other placental abnormalities between groups, including umbilical cord abnormalities, chronic inflammation, increased villous vascularity, or other significant pathology (massive perivillous fibrin deposition, delayed villous maturation, or chorangiosis). There was a nonsignificant trend toward an increased prevalence of acute inflammatory lesions in the control placentas (P = 0.055).

Table 3Placental Pathology in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value [a]	Single Ventricle (n = 27)	*P* Value [b]
Placenta weight (g)	442 (428-473)	426 (332-490)	0.332	412 (335-493)	0.300
PW:BW	0.13 (0.12-0.14)[c]	0.13 (0.11-0.15)	0.820	0.12 (0.11-0.15)	0.574
Cord abnormality	6 (27%)	11 (31%)	0.790	5 (19%)	0.510
Acute inflammation (AI)	13 (59%)	12 (33%)	0.055	11 (41%)	0.201

Table 3Placental Pathology in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value[a]	Single Ventricle (n = 27)	*P* Value[b]
AI grade			0.115		0.376
0	9 (41%)	24 (67%)		16 (59%)	
1	11 (50%)	9 (25%)		8 (30%)	
2	2 (9.1%)	3 (8.3%)		3 (11%)	
Chronic inflammation (CI)	10 (45%)	23 (64%)	0.169	17 (63%)	0.220
CI grade			0.382		0.444
0	12 (55%)	13 (36%)		10 (37%)	
1	6 (27%)	13 (36%)		9 (33%)	
2	4 (18%)	10 (28%)		8 (30%)	
Maternal vascular malperfusion (MVM)	4 (18%)	16 (44%)	**0.041**	11 (41%)	0.088
MVM grade			**0.049**		0.063
0	18 (82%)	20 (56%)		16 (59%)	
1	2 (9.1%)	2 (5.6%)		1 (3.7%)	
2	2 (9.1%)	14 (39%)		10 (37%)	
Fetal vascular malperfusion (FVM)	5 (23%)	15 (42%)	0.141	11 (41%)	0.181
FVM grade			0.295		0.449
0	17 (77%)	21 (58%)		16 (59%)	
1	3 (14%)	11 (31%)		8 (30%)	
2	2 (9.1%)	4 (11%)		3 (11%)	

Table 3Placental Pathology in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value[a]	Single Ventricle (n = 27)	*P* Value[b]
Increased villous vascularity	3 (14%)	6 (17%)	>0.999	5 (19%)	0.715
Other pathologies[d]	7 (32%)	14 (39%)	0.587	13 (48%)	0.247

PW:BW = placental weight: birth weight ratio; other abbreviation as in **Table 1**.

Values are median (IQR) or n (%). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c n = 18 for PW:BW for controls samples.

d Other pathologies include presence of hemosiderosis, massive perivillous fibrin deposition, delayed villous maturation, chorangiosis, or isolated small for gestational age placenta (<10th percentile).

Clinical outcomes

There was no difference in birth gestational age between cases and controls (**Table 4**). All cases, as well as the SV subgroup, demonstrated significantly decreased birth weight compared to controls ($P = 0.026$ for all CHD, $P = 0.050$ for SV). Birth length was also decreased in cases however there was significant attrition (75%) due to loss to follow-up in controls for this outcome (**Table 4**). There was 1 intrauterine fetal demise at term in a case. All other cases survived to 30 days if inpatient or index hospital discharge, whichever came first.

Table 4Clinical Outcomes in Cases Vs Controls

	Controls (n = 22)	All CHD (n = 36)	*P* Value [a]	Single Ventricle (n = 27)	*P* Value [b]
Gestational age at delivery (wk)	39.2 (38.5-39.6)[c]	38.9 (38.3-39.6)	0.236	39.0 (38.3-39.7)	0.437
Birth weight (g)	3,358 (3,165-3,742)[c]	3,145 (2,873-3,462)	**0.026**	3,160 (2,905-3,502)	**0.050**
Birth length (cm)	51.4 (49.5-52.5)[c]	48.4 (47.1-50.0)[d]	0.012	48.9 (48.0-51.0)[e]	0.048
Head circumference (cm)	35.0 (33.8-35.5)[c]	33.5 (32.5-34.5)[d]	0.086	33.5 (32.5-34.5)[e]	0.177

Abbreviation as in **Table 1**.

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

a *P* value comparison between all CHD subjects and controls.

b *P* value comparison between single ventricle subjects and controls.

c Controls: n = 18 for gestational age at delivery and birth weight. n = 9 for birth length. n = 8 for head circumference.

d All CHD: n = 34 for birth length. n = 33 for head circumference.

e Single ventricle: n = 25 for birth length and head circumference.

When comparing fetuses with evidence of either MVM or FVM to those without, there was no significant difference in the mid-gestational UVVF/Wt of cases or controls (**Table 5**). However, there was significantly decreased birth weight in

cases with evidence of either MVM or FVM compared to cases without, which was not present in the control group, though in the setting of 39% attrition of controls for this outcome. Univariable linear regression demonstrated that for cases, the presence of either MVM or FVM lesions was associated with a 382g decrease in birth weight (P = 0.029), a relationship not seen in the control group (P = 0.692) (**Table 6**). Decreased birth weight in cases compared to controls appeared to be related to MVM lesions in particular but was independent of the presence of FVM lesions (**Figure 2**). Accordingly, the presence of MVM lesions was associated with a 531g decrease in birth weight for all CHD (P < 0.001), and 403g decrease in birth weight for SV cases (P = 0.017). There was no significant relationship between MVM lesions and birth weight in the control group, or between FVM lesions and birth weight for any subjects (**Table 6**). There was no significant difference in median intensive care unit length of stay (ICU LOS) in cases with evidence of either MVM or FVM compared to cases without (**Table 5**). Regression analyses did not demonstrate a significant relationship between mid-gestational UVVF/Wt and clinical outcomes (data not shown).

Table 5The Influence of Placental Malperfusion Defects on UVVF and Outcomes

	Controls			**All CHD**		
	MVM/FVM Absent	**MVM/FVM Present**	***P* Value**	**MVM/FVM Absent**	**MVM/FVM Present**	***P* Value**
	(n = 11)	**(n = 9)**		**(n = 11)**	**(n = 18)**	
UVVF/Wt (ml/min/kg)	99.7 (93.2-133.5)	119.1 (113.1-161.7)	0.056	88.2 (83.4-106.9)	96.7 (71.3-118.2)	0.982
	(n = 12)	**(n = 6)**		**(n = 12)**	**(n = 24)**	
Birth weight	3,402	3,282	0.750	3,480	3,130	**0.039**

Table 5The Influence of Placental Malperfusion Defects on UVVF and Outcomes

	Controls			All CHD		
	MVM/FVM Absent (n = 11)	MVM/FVM Present (n = 9)	*P* Value	MVM/FVM Absent (n = 11)	MVM/FVM Present (n = 18)	*P* Value
(g)	(3,110-3,726)	(3,206-3,891)		(3,064-3,749)	(2,766-3,258)	
				(n = 12)	(n = 23)	
ICU LOS (d)				14.5 (10.0-20.5)	17 (10.3-30.0)	0.444

Values are median (IQR). **Bold** text indicates $P \leq 0.05$.

FVM = fetal vascular malperfusion; ICU LOS = index hospitalization ICU length of stay; MVM = maternal vascular malperfusion; other abbreviations as in **Tables 1** and **2**.

Table 6Univariable Linear Regression Modeling of the Association Between Presence of Placental Malperfusion Lesions and Birth Weight (g)

	Controls (n = 18)	*P* Value	All CHD (n = 36)	*P* Value	Single Ventricle (n = 27)	*P* Value
Predictor						
MVM/FVM	81.42 (−346.70 to 509.53)	0.692	−381.75 (−726.59 to −36.91)	**0.031**	−230.00 (−599.73 to 139.73)	0.212
MVM	−14.87 (−559.08 to	0.955	−531.56 (−829.27 to	**<0.001**	−403.47 (−729.76 to	**0.017**

Table 6Univariable Linear Regression Modeling of the Association Between Presence of Placental Malperfusion Lesions and Birth Weight (g)

	Controls (n = 18)	*P* Value	All CHD (n = 36)	*P* Value	Single Ventricle (n = 27)	*P* Value
	529.35)		−233.85)		−77.17)	
FVM	145.13 (−393.67 to 683.94)	0.576	62.34 (−290.41 to 415.10)	0.722	189.46 (−168.31 to 547.23)	0.286

Values are beta coefficient and (95% CI). Three separate univariable linear regressions were applied to each patient population. The independent variable was presence of MVM/FVM lesions, presence of MVM lesions, or presence of FVM lesions. For all models, birth weight (g) was the dependent variable. **Bold** text indicates $P \leq 0.05$.

Abbreviations as in **Tables 1** and **5**.

Impaired Fetal Growth in Congenital Heart Disease Occurs Exclusively With Maternal Vascular Malperfusion Lesions

(A) CHD fetuses but not controls demonstrate significantly decreased birth weight (3,480 g vs 3,130 g; $P = 0.04$) in the presence of PMP lesions. Decreased birth weight in CHD fetuses is seen only in the presence of MVM lesions (3,340 g vs 2,905 g; $P < 0.001$) (B), and not FVM lesions (3,140 g vs 3,160 g; $P = 0.7$) (C). FVM = fetal vascular malperfusion; MVM = maternal vascular malperfusion; PMP = placental malperfusion; other abbreviation as in **Figure 1**.

Discussion

We previously demonstrated in a retrospective study that fetuses with CHD have decreased mid-gestational placental blood flow, however correlation with

placental pathology could not be performed.[19] In this prospective cohort, we demonstrate that CHD fetuses, specifically those with SV physiology, have decreased mid-gestational placental blood flow, a high prevalence of placental malperfusion (PMP) defects, and impaired fetal growth resulting in lower birth weight at similar gestational age compared to normal fetuses (see **Central Illustration**). CHD fetuses had on average only 22%, rather than the normal 30%, of fetal CCO returning from the placenta, which we hypothesize, may be due to increased placental resistance. The effect of redistribution of fetal blood flow is unclear, as cerebral blood flow reflected by absolute mid-gestational CPR was not different. Assessment of middle cerebral artery PI and CPR *z*-scores may better reflect the distribution of fetal blood flow given varying fetal gestational ages. The increased mid-gestational UA PI in cases may also reflect increased placental resistance, however decreased flow through the UA despite increased placental resistance may normalize the UA PI, and thus UVVF may be a more reliable indicator of placental flow. The significance of decreased UtA PI in cases is unclear but suggests that placental resistance was not sufficiently elevated at mid-gestation to result in elevated UtA Doppler parameters. Our work confirms that abnormal placental blood flow in fetuses with CHD can be detected as early as mid-gestation.

Placental Malperfusion in Fetal Congenital Heart Disease

Fetuses with CHD have decreased blood flow from the placenta to fetus through the umbilical vein, as measured in second trimester fetal echocardiograms by umbilical venous volume flow. In the setting of unchanged cardiac output, decreased umbilical flow is suggestive of increased placental resistance. These fetuses have a higher incidence of placental malperfusion lesions at birth. Placental maternal vascular malperfusion lesions, in particular, are associated with decreased fetal growth in CHD. Abbreviation as in **Figure 1**.

We have undertaken a rigorous analysis of placental pathology in CHD based on standardized placental phenotypic classification systems.[21,22] An increased

frequency of MVM and FVM defects has been reported in CHD.[24-26] The frequency of our placental findings in CHD is similar to published reports,[26,27] however reported frequencies vary widely due to variable patient and control populations, and criteria for placental pathologic diagnosis. FVM can occur secondary to umbilical cord obstruction or flow alterations in CHD which could result in decreased placental blood flow and stasis.[28] MVM is due to defective placental implantation in early pregnancy resulting in inadequate maternal spiral artery remodeling and disrupted intervillous flow.[25] We did not find a significant difference in umbilical cord abnormalities, as has been previously reported in CHD,[29,30] or in the frequency of chronic inflammatory lesions, which when severe, can be a cause of FVM.[21] The trend toward increased low-grade acute inflammation in controls likely reflects induction of most CHD mothers prior to the onset of natural labor, while most control mothers labored naturally.[31]

Interestingly, decreased birth weight in cases compared to controls was only observed in the presence of MVM lesions but was independent of FVM lesions. MVM lesions in controls were not associated with decreased birth weight in our cohort though the number of control samples with MVM was small, suggesting a possible multifactorial etiology for decreased birth weight in CHD. No change in birth weight was seen in the setting of FVM lesions for cases or controls. MVM and FVM lesions are associated with intrauterine growth restriction,[25,28] a common finding in CHD.[24-27,32] Some retrospective studies lacking control groups have not implicated other placental pathologies in low birth weight in CHD,[33,34] however low placental weight *z*-score at birth and low placental volume by magnetic resonance imaging have been associated with decreased fetal growth in CHD in other studies.[5,35] A direct association specifically between PMP and birth weight in CHD is rarely interrogated.[33,36,37] Our data suggest that the mechanisms underlying MVM may act in synergy with the impaired fetal hemodynamics and/or alterations in systemic oxygenation in fetal CHD to impair fetal growth. While we had

hypothesized that UVVF might be a mid-gestational marker of PMP, our analyses revealed no significant association between mid-gestational UVVF and placental pathologic findings or measures of fetal growth. Nevertheless, we demonstrate tangible evidence of altered fetal-placental circulation in CHD. Better understanding of the role of abnormal placental blood flow in CHD could inform the future use of therapeutic agents in utero such as aspirin, known to improve placental perfusion in maternal preeclampsia.[38]

There are several limitations to this study. The small sample size resulted in the study likely being underpowered to achieve statistical significance where clinically meaningful differences may exist. The study may have been underpowered to determine the nature of the relationship between UVVF, placental abnormalities, and many of our study outcomes. Due to technical issues or loss to follow-up, some data were not available for all subjects. High rates of attrition for control subjects' placental and outcomes data could introduce bias, affecting the validity of these outcomes. As UVVF was measured at mid-gestation, there may be additional factors not accounted for that affect placental development between mid-gestation and delivery. Our study demonstrated several significant findings despite a number of factors which may have biased this study toward the null hypothesis. Control subjects were recruited from referrals due to clinical indications for screening fetal echocardiograms, and thus do not fully represent low risk, normal pregnancies. Eleven cases may have received vaginal progesterone (randomization was blinded) as part of an unrelated clinical trial evaluating the effect of progesterone on neurodevelopment in CHD, an outcome not analyzed in our study. Vaginal progesterone has been associated with vasodilation and improved Doppler flow parameters in utero,[39] which could have biased our results toward the null hypothesis with regard to UVVF. Its impact on PMP lesions at birth is unknown. The frequency of placental abnormalities in our prospective control population may be higher than in more commonly used retrospective control populations, as several indications for fetal

echocardiography (ie, diabetes) may increase the risk of abnormal placental pathology. Similarly, the presence of maternal CHD, present in 4 controls and 1 case, has been associated with PMP and decreased birth weight. However, when stratified based on CHD severity according to the 2018 American Heart Association/American College of Cardiology guidelines,[20] several studies have not found a robust association between "simple" maternal CHD, similar to that found in our study subjects, and PMP or impaired fetal growth.[40,41] Comparison of our control subjects with and without both maternal diabetes and CHD revealed no significant differences in maternal or fetal characteristics, placental blood flow, placental pathology, or outcomes (**Supplemental Tables 2 to 5**). Any predisposition to placental defects or poor growth due to maternal diabetes or CHD would most likely bias our results toward the null hypothesis; however, we were able to detect meaningful comparative increases in placental pathology in our cohort. Our findings are most relevant to fetuses with SV CHD and may not be generalizable to other CHD subgroups. Future work comparing placental blood flow and pathology between right and left-sided obstructive lesions will be of great interest, as the degree of fetal brain and placental hypoxia varies.[42] Additional studies in a larger cohort are necessary to determine the relationship between abnormal UVVF parameters and placental pathology at birth, and whether they are associated with additional outcomes of interest such as abnormal neurodevelopment and increased mortality, which have been associated with placental abnormalities in CHD.[2,43]

Conclusions

In this prospective study, we demonstrate that fetuses with CHD, specifically SV CHD, have decreased mid-gestational placental blood flow, increased frequency of PMP defects, and impaired fetal growth. In addition, a rigorous and systematic evaluation of the placenta in fetal CHD demonstrates an association between decreased fetal growth and the presence of placental MVM

lesions but not FVM lesions. Our study did not demonstrate significant associations between impaired mid-gestational UVVF and placental pathologic findings. Despite this, decreased UVVF reflects tangible evidence of abnormal in utero fetal placental blood flow in CHD. There remain significant unknowns regarding the abnormal fetal circulation, its relationship to placental abnormalities in CHD, and how they may contribute to outcome disparities which warrant future investigation. Understanding the mechanism underlying PMP in CHD is of great interest and could inform novel therapeutic targets.