higher in the MVT and NSVT groups than NVT group, respectively. Although there was no significant difference among the groups in degree of prolapse, mean BE (median; IQR) was significantly higher in the MVT and NSVT groups than NVT group (16.7 ± 2.6 [15; 15 to 19], 18.5 ± 5.1 [18.5; 15 to 20], 14.1 ± 4.2 [14.0; 10 to 16]; $p = 0.03$). All patients had a higher mean regional strain in the posterolateral trident (basal and midposterior and posterolateral wall segments) compared with the basal and midseptal segments (-24 ± 5% vs. -15 ± 4% $p < 0.01$). Univariate logistic regression identified potential predictors of VT (lateral wall PSI, BE, and Pickelhaube spike). Empirical optimal cutoff points for these variables for VT were identified through receiver operator characteristics analyses (Liu method) and sensitivity, specificity, and area under the curve determined (**Figure 1**). Multivariate logistic regression showed lateral wall PSI ≥4.5% and BE to be statistically significant ($p < 0.05$).

Our observations indicate that mean Pickelhaube spike, BE, and basal and midlateral wall PSI tend to be higher in patients with malignant arrhythmogenic MBMVP. The Pickelhaube sign represents a marker of myocardial stretch caused by tugging of prolapsing mitral leaflets in systole on papillary muscles and adjacent myocardium, thus altering myocardial deformation in these segments (PSI). In contradistinction to a previous report of CMR LGE (LV fibrosis) in MBMVP syndrome (1), we found CMR evidence of LGE in only 33% of patients. This may be because fibrosis occurs at a later stage in the disease. Thus, tissue Doppler and STE can identify patients at risk of malignant ventricular arrhythmias in MBMVP earlier, before development of fibrosis.

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Impact of Age and Sex on Cardiovascular Magnetic Resonance Measurements

After Tetralogy of Fallot Repair

Although cardiovascular magnetic resonance (CMR) imaging measurements are known to differ between sexes and according to age in the normal heart, little is known about measurement variability in patients with congenital heart disease (CHD). Yet, aggregate CMR data, without adjustment for sex or age, are now used for risk stratification and to guide timing for intervention in select CHD populations. In those with repaired tetralogy of Fallot (rTOF), CMR data provide a cornerstone for management that is virtually unparalleled in other forms of heart disease—congenital or acquired. Although an understanding of the range of CMR values in patients with rTOF is essential because this information may direct clinical care, little has been published on this topic to date. Therefore, in this study, we examined cross-sectional CMR measurements, stratified by age and sex, in a large, multinational cohort of patients with rTOF and significant pulmonary regurgitation (PR).

Children and adults with rTOF, at least moderate PR and a contemporary CMR examination were prospectively recruited in Canada, Europe, and Asia as part of the CORRELATE (Comprehensive Outcomes Registry Late After Tetralogy of Fallot Repair) study. Those with a bioprosthetic pulmonary valve (PV) were excluded. Institutional review board approval was obtained from each participating site. Participants provided written informed consent. Subjects were divided into quartiles by age: younger than 18 years; 18 to 24 years; 25 to 39 years; and 40 or older years. An experienced central reader blinded to clinical data completed all CMR analyses. Our CMR methods were previously published (1). Univariate tests explored the relationship of CMR parameters by

TABLE 1 CMR Measurements* and Pulmonary Valve Interventions Stratified by Age and Sex Categories†

	Comparison of Age Quartiles 1, 2, 3, 4 Male/Females		Quartile 1 <18 yrs			Quartile 2 18–24 yrs			Quartile 3 25–39 yrs			Quartile 4 >40 yrs		
	Male	Female	Male	Female		Male	Female		Male	Female		Male	Female	
	p Value	p Value	(n = 69)	(n = 60)	p Value	(n = 68)	(n = 60)	p Value	(n = 83)	(n = 74)	p Value	(n = 81)	(n = 51)	p Value
Age at CMR (yrs)	**<0.001**	**<0.001**	14 ± 2	15 ± 2	0.17	21 ± 2	22 ± 2	0.05	32 ± 4	32 ± 4	0.62	51 ± 8	50 ± 7	0.79
RVEDVi (ml/m^2)	0.844	**0.002**	164 ± 41	136 ± 24	**0.00001**	169 ± 36	138 ± 26	**<0.00001**	167 ± 49	155 ± 38	0.09	164 ± 46	150 ± 38	0.07
RVESVi (ml/m^2)	0.237	**<0.001**	89 ± 27	69 ± 16	**<0.00001**	94 ± 21	73 ± 17	**<0.00001**	98 ± 36	86 ± 24	**0.02**	98 ± 34	86 ± 32	**0.04**
RV stroke volume (ml)	**<0.001**	**<0.001**	111 ± 29	97 ± 22	**0.003**	141 ± 32	105 ± 22	**<0.00001**	134 ± 36	116 ± 31	**0.001**	130 ± 37	109 ± 27	**0.0005**
RV EF (%)	**<0.001**	**<0.001**	46 ± 5	49 ± 6	**0.001**	44 ± 5	47 ± 6	**0.0008**	42 ± 7	45 ± 6	**0.01**	40 ± 7	43 ± 8	**0.02**
LVEDVi (ml/m^2)	**0.0008**	0.115	91 ± 14	82 ± 14	**0.0002**	94 ± 19	78 ± 12	**<0.00001**	88 ± 18	82 ± 14	0.06	82 ± 20	78 ± 14	0.15
LVESV (ml/m^2)	0.323	0.406	41 ± 9	36 ± 8	**0.002**	44 ± 12	34 ± 8	**<0.00001**	41 ± 14	36 ± 8	**0.002**	40 ± 14	34 ± 9	**0.008**
LV stroke volume (ml)	**<0.001**	**0.001**	77 ± 20	68 ± 16	**0.005**	95 ± 23	71 ± 13	**<0.00001**	90 ± 22	79 ± 18	**0.0006**	85 ± 27	75 ± 17	**0.02**
LV EF (%)	**0.001**	0.863	56 ± 7	56 ± 5	0.62	54 ± 6	57 ± 6	**0.002**	53 ± 8	57 ± 6	**0.001**	51 ± 8	57 ± 7	**0.00007**
PR fraction (%)	0.208	0.632	38 ± 13	39 ± 13	0.74	38 ± 15	41 ± 11	0.33	38 ± 14	42 ± 15	0.14	42 ± 16	42 ± 15	0.98
RV mass: volume ratio	**<0.001**	**<0.001**	0.24 ± 0.04	0.23 ± 0.03	**0.04**	0.22 ± 0.04	0.22 ± 0.03	0.78	0.22 ± 0.03	0.21 ± 0.04	**0.04**	0.22 ± 0.04	0.20 ± 0.03	0.05
RV mass (g/m^2)	**0.041**	0.538	38 ± 7	31 ± 6	**<0.00001**	36 ± 7	30 ± 6	**<0.00001**	36 ± 8	31 ± 7	**0.0002**	35 ± 9	30 ± 8	**0.002**
LV mass: volume ratio	**<0.001**	**0.019**	0.58 ± 0.09	0.53 ± 0.08	**0.001**	0.60 ± 0.10	0.55 ± 0.10	**0.009**	0.64 ± 0.13	0.53 ± 0.10	**<0.00001**	0.70 ± 0.18	0.58 ± 0.10	**0.00002**
LV mass (g/m^2)	0.155	0.319	52 ± 7	43 ± 7	**<0.00001**	55 ± 8	42 ± 6	**<0.00001**	55 ± 10	43 ± 6	**<0.00001**	56 ± 12	45 ± 8	**<0.00001**
RA area (cm^2/m^2)	**0.011**	**<0.001**	11 ± 3	11 ± 2	0.24	12 ± 3	11 ± 3	0.24	12 ± 4	12 ± 3	0.86	13 ± 4	13 ± 4	0.91
LA area (cm^2/m^2)	**0.004**	**<0.001**	10 ± 2	9 ± 2	0.38	9 ± 2	10 ± 2	0.15	9 ± 3	10 ± 3	**0.043**	11 ± 4	11 ± 3	0.21
RVOT diastole (mm/m^2)	0.11	0.408	19 ± 6	18 ± 7	0.96	19 ± 7	20 ± 6	0.52	18 ± 7	21 ± 8	0.12	21 ± 6	21 ± 8	0.89
RVOT systole (mm/m^2)	**0.038**	0.251	18 ± 4	18 ± 5	0.92	19 ± 7	20 ± 6	0.91	18 ± 7	21 ± 8	**0.04**	21 ± 8	21 ± 7	0.96
Referral for PVR (n) stratified by sex within each age quartile at follow-up time, months (IQR)			n = 17/69 22 (11–38)	n = 5/60 23 (1–38)		n = 25/68 35 (19–49)	n = 6/60 26 (12–38)		n = 22/83 26 (11–41)	n = 23/74 32 (16-43)		n = 22/81 28 (11–47)	n = 12/51 37 (20–46)	

Values are mean ± SD or median (interquartile range). Statistical significance is shown in **bold**. *All CMR measurements were indexed to body surface area according to the Mosteller formula. †In a linear regression model designed to evaluate the impact of ethnicity (white vs. non-white) on CMR measurements (RVEDVi, RVESVi, RVEF, LVEF, RV mass and LV mass) ethnicity did not impact CMR values, even after adjustment for sex and age.

CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EDVi = end-diastolic volume indexed; EF = ejection fraction; ESV = end-systolic volume; ESVi = end systolic volume indexed; LA = left atrium; LV = left ventricle; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RA = right atrium; RV = right ventricle; RVOT = RV outflow tract.

age and sex using parametric Student's *t*-tests and analysis of variance, or nonparametric Student's *t*-tests and Kruskal-Wallis tests, as appropriate. Tukey's post hoc honestly significant difference was used. A 2-tailed p value <0.05 was considered statistically significant. The Benjamini-Hochberg false discovery rate controlling procedure to adjust for multiple comparisons was used. The intraclass correlation coefficient assessed variability of measurements between observers and within an observer (>1 month between measurements). Analyses were conducted using R version 3.5.0 (R Foundation, Vienna, Austria) and SPSS version 24.0 (IBM, Armonk, New York).

We studied 546 subjects (55% were men; age 29.5 ± 14.2 years). CMR characteristics are shown in Table 1; intraclass correlation coefficient values for all measurements were good to excellent (0.88 to 0.99). With

advanced age in women, changes were apparent throughout the right heart and included increased indexed right ventricular end-diastolic (RVEDVi) and end-systolic volumes (RVESVi), decreased RV ejection fraction (EF), and increased right atrial (RA) dimensions. Conversely, there were no significant differences in left ventricular (LV) volumes or LVEF in females across age quartiles. Following testing for multiple comparisons, there were no significant changes to these findings. Post-hoc analyses on variables of interest in females (RVEDVi, RVESVi, RVEF, and RA area) revealed statistically significant differences in the quartile of middle-aged women (25 to 39 years) compared with 1 or both of the older and/or younger quartiles of females for each parameter. In contrast in males, both RVEDVi and RVESVi measurements were similar across age quartiles. Although LVEDVi was decreased in advanced male age, LVESVi did not differ. The biventricular EF incrementally decreased with increasing age in males.

To our knowledge, this was the largest prospective rTOF CMR study of high-risk patients with significant PR. Our multinational cohort consisted of a balanced representation of children, young adults, middle-aged adults, and older adults across the 4 age quartiles, which enhanced generalizability (as opposed to previous data reported from a single country with younger subjects) (2). Our results confirmed that male and female hearts with rTOF were distinct, and adaptive response of cardiac dimensions and systolic function to chronic volume overload appeared to vary according to age and by sex.

At more advanced ages, women displayed more extensive change within the right heart. Older adult women had larger RV volumes, whereas the extent of RV dilation did not differ significantly in older males versus younger males, which suggested that age might be a more important consideration for timing of PV intervention in females to mitigate irreversible RV remodeling in older women with larger RV volumes. Following post hoc analysis of indexed values for right heart dimensions and systolic function, consistent differences were noted in the quartile of middle-aged women (25 to 39 years) compared with younger or older females. These findings agreed with widely established observations that morbidity and mortality accelerate during middle age in populations of adults with CHD.

Current guidelines propose volume thresholds, regardless of sex or age, in which PV intervention can be considered in the asymptomatic individual (specifically, RVEDVi >160 ml/m^2 and RVESVi >80 ml/m^2) (3). In the era of precision medicine, targeted therapies tailored to the individual are rapidly replacing the historical "one size fits all" approach. With the knowledge that females with rTOF have smaller hearts at baseline but may be more susceptible to RV enlargement and RV systolic dysfunction with advancing age, one must question whether referral for intervention should incorporate sex and age variables. We suggest that our data may carry the potential to further inform risk stratification and timing of PV intervention in rTOF.

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Ferumoxytol MR Angiography

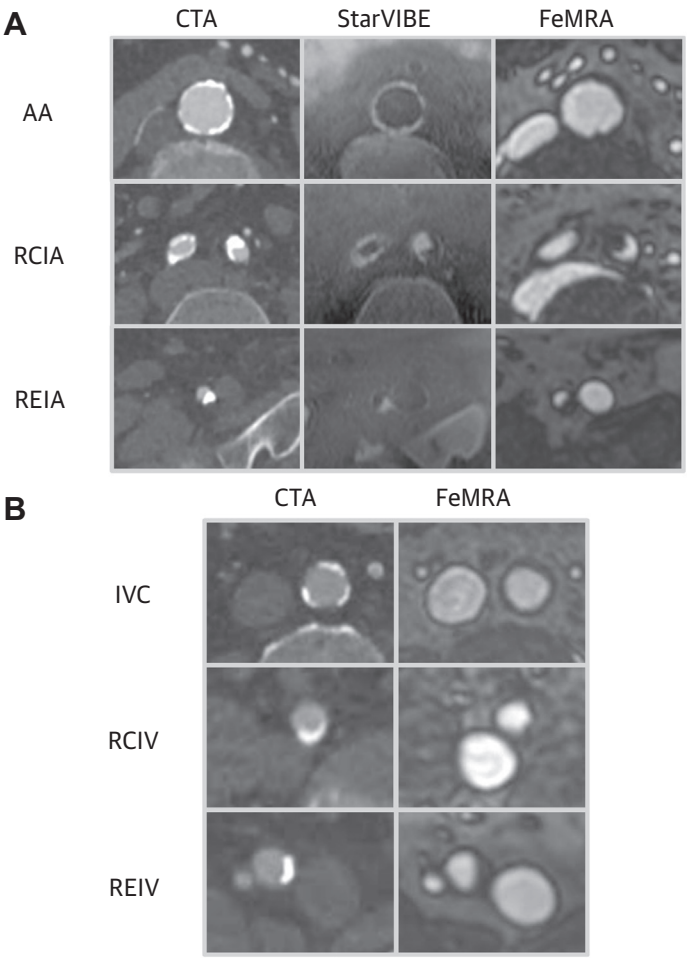
A Novel Technique for Assessing Iliac Vasculature in Potential Kidney Transplant Recipients

Although kidney transplantation is the treatment of choice for suitable patients with end-stage kidney disease, approximately 25% of chronic kidney disease (CKD) patients have peripheral arterial disease (PAD) (1). Computed tomography angiography (CTA) can identify patients requiring revascularization procedures before transplant listing; however, its use has been limited because of the risk of nephrotoxicity in patients with residual renal function. Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, Massachusetts) is an iron oxide nanoparticle used for treatment of iron deficiency anemia that has superparamagnetic properties, with high r1 relaxivity and a long intravascular half-life. We compared ferumoxytol-enhanced magnetic resonance angiography (FeMRA) with CTA in an assessment of potential kidney transplant recipients using anatomic and signal parameters as surrogates of diagnostic quality.

We prospectively enrolled 36 patients (age 54 ± 11 years; 61% male; 47% with diabetic nephropathy) who had FeMRA and CTA of aortoiliac vasculature on the same day. The study was approved by the institutional review board (North of Scotland Research Ethics Committee reference: 16/NS/0099). CTA was performed with a 320-detector row computed tomography scanner (Aquilion One Vision edition, Canon/Toshiba, Tustin, California) after injection of 100 cc of iodine contrast (Omnipaque 350). Cardiac magnetic resonance studies were performed on a 3.0-T Prisma magnetic resonance scanner (Magnetom, Siemens Healthineers, Erlangen, Germany) after infusion of 3 mg/kg of ferumoxytol based on data from a dose-finding study (2). For detection of arterial calcification, a specific cardiac magnetic resonance sequence (3-dimensional free-breathing [StarVIBE] fast low-angle shot [FLASH]) was performed before ferumoxytol administration.

CTA and FeMRA images were synchronized using anatomic landmarks, and pre-specified arterial and venous cross sections (overall 216) were selected for comparative analysis. Regions of interest were used for the infrarenal abdominal aorta, right common iliac artery, right external iliac artery, inferior vena cava, right common iliac vein, and right external iliac vein to estimate the: 1) arterial diameter; 2) vein diameter; 3) area of calcification; and 4) luminal enhancement (Figure 1). Two independent readers (S.S., P.H.B.) assessed the FeMRA (new technique), and a third reader (D.B.) assessed the CTA (standard technique). Interclass correlation coefficients (ICC) with 95% confidence intervals (CIs) were performed to test intra-reader and inter-reader consistency of agreement, and mean differences (and 95% CI) were estimated.

FIGURE 1 Method for the Comparative Analysis Using Arterial and Venous Cross Sections



(A) Arterial cross-sections at the level of infra-renal abdominal aorta (AA), right common iliac artery (RCIA) and right external iliac artery (REIA) used for comparisons between computed tomography (CTA) and StarVIBE/ferumoxytol-enhanced magnetic resonance angiography (FeMRA). Note the consistency in the presence and conformity of calcifications between CTA and StarVIBE and the intraluminal filling defects in FeMRA, which correspond to calcified plaques. **(B)** Venous cross-sections at the level of inferior vena cava (IVC), right common iliac vein (RCIV), and right external iliac vein (REIV) used for comparisons between CTA and FeMRA.