Methods and Results

829 TOF patients underwent whole exome sequencing (WES), the largest cohort of non-syndromic TOF patients reported to date. The prevalence of unique, deleterious variants was determined; defined by their absence in the Genome Aggregation Database (gnomAD) and a scaled combined annotation-dependent depletion (CADD) score of 20. Clustering analysis of variants revealed that two genes, NOTCH1 and FLT4, surpassed thresholds for genome-wide significance (assigned as $P<5 \times 10–8$), after correction for multiple comparisons. NOTCH1 was most frequently found to harbour unique, deleterious variants. 31 variants were observed in 37 probands (4.5%; 95% confidence interval [CI]:3.2–6.1%) and included seven loss-of-function variants, 22 missense variants and two in-frame indels. Sanger sequencing of the unaffected parents of seven cases identified five de novo variants. Three NOTCH1 variants (p.G200R, p.C607Y and p.N1875S) were subjected to functional evaluation and two showed a reduction in Jagged1-induced NOTCH signalling. FLT4 variants were found in 2.4% (95% CI:1.6–3.8%) of TOF patients, with 21 patients harbouring 22 unique, deleterious variants. The variants identified were distinct to those that cause the congenital lymphoedema syndrome Milroy disease. In addition to NOTCH1, FLT4 and the well-established TOF gene, TBX1, we identified potential association with variants in several other biologically plausible candidate genes.

Conclusion In summary, the NOTCH1 locus is the most frequent site of genetic variants predisposing to non-syndromic TOF, followed by FLT4. Together, variants in these genes are found in almost 7% of TOF patients.

Conflict of Interest None

140 OBESITY AS A MODIFIABLE RISK FACTOR IN REPAIRED TETRALOGY OF FALLOT

[1]Mark Philip Cassar*, [2]Elizabeth Orchard, [3]Alex Jones, [4]Stefan Neubauer, [5]Lucy Hudsmith, [6]Oliver Rider. *[1]Royal Berkshire Hospital, Reading; [2]John Radcliffe Hospital, Oxford; [3]John Radcliffe Hospital, Oxford; [4]Oxford University; [5]Queen Elizabeth Hospital, Birmingham; [6]John Radcliffe Hospital, Oxford*

10.1136/heartjnl-2019-BCS.137

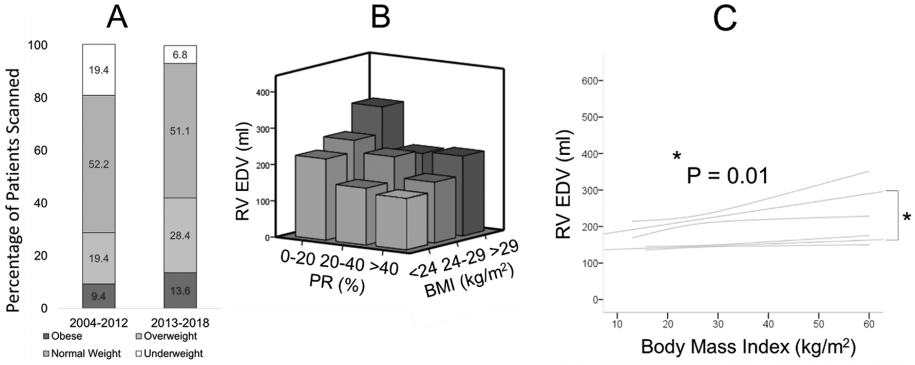
Introduction In modern society, obesity is an increasingly prevalent, and now widely recognised, risk factor for almost all cardiovascular diseases, exerting independent adverse effects on the cardiovascular system. Despite this, the effects within adult congenital heart disease are not well documented but are becoming increasingly important.

Methods We collected data from 155 patients (aged 7–76 years) with repaired tetralogy of Fallot (rTOF), scanned between 2004 and 2018 in OCMR. Anthropometric data (height, weight, age) were recorded. All patients had CMR imaging (1.5T) to determine right ventricular (RV) cavity size (end diastolic volume; EDV; ml) and phase contrast flow imaging to determine pulmonary regurgitation severity (PR, %). The association of obesity with RVEDV in rTOF was determined by linear regression and compared to the relationship seen in the normal heart (n=722) using dummy variable regression.

Results Comparing rTOF patients scanned in the period 2013–2018 (n=67) to those of 2002–2012 (n=88) showed a substantial increase over time in the proportion of rTOF patients who were either overweight (19.4% to 28.4%) or obesity (9.4% to 13.6%, figure A). In parallel, the proportion of patients who were underweight declined (19.4% to 6.8%). As height (167±13 vs 166±11cm, p=0.66) and age (32±15 vs 28±14 yr, p=0.16) did not differ between the groups, the 6 kg greater average weight in the later population can be attributed to fat mass. Strikingly, 42% of rTOF patients scanned in the last five years were either overweight or obese, highlighting this is a significant clinical problem.

In rTOF, RV dilatation was associated with increased BMI, regardless of the presence or severity of PR (figure B). Although dilatation of the RV was associated with higher BMI in the normal population, the degree of RV cavity dilatation is over four-fold greater in rTOF (RVEDV rTOF +21 ml, vs. normal heart +5 ml per 10 BMI points increase, p<0.01, figure C). In comparison, although obesity results in LV cavity dilation in both rTOF and normal hearts, there was no difference in the degree of cavity dilatation (LVEDV rTOF +8 ml vs +6 ml per 10 BMI points increase, p=0.79 for comparison). This suggests that the RV dilatory response to obesity in rTOF is disproportionate, being not only over two-fold greater than the dilatory response of the LV within rTOF patients, but also four-fold higher than that seen in the normal heart.

Conclusion Obesity is becoming more prevalent in rTOF patients and is related to disproportionate dilatation of the RV, at all levels of pulmonary regurgitation. The reasons for this are unknown but are likely to be related to the additional stroke volume demands of obesity imposed in the setting of a congenitally pathological ventricle. Chronic PR and existing RV dilatation contribute too. Given the relationship between RV dilatation, symptoms and the need for surgical intervention, this should logically be detrimental in rTOF. It follows then that treatment strategies that



Abstract 140 Figure 1

reduce RV cavity size in rTOF may be beneficial. As such, obesity is a promising and modifiable therapeutic target in rTOF.

Conflict of Interest None

141 CRYPTOGENIC STROKE AND PATENT FORAMEN OVALE DEVICE CLOSURE: THE IMPORTANCE OF MULTI-DISCIPLINARY DECISION-MAKING

[1]Sashiananthan Ganesananthan*, [1]Carven Yee Shean Chin, [1]Katie W.L. Kwan, [1]Timothy Woo, [1]Zong Xuan Lee, [2]Tom Hughes, [2]Peter Groves. *[1]Cardiff University School Of Medicine; [2]University Hospital UK*

10.1136/heartjnl-2019-BCS.138

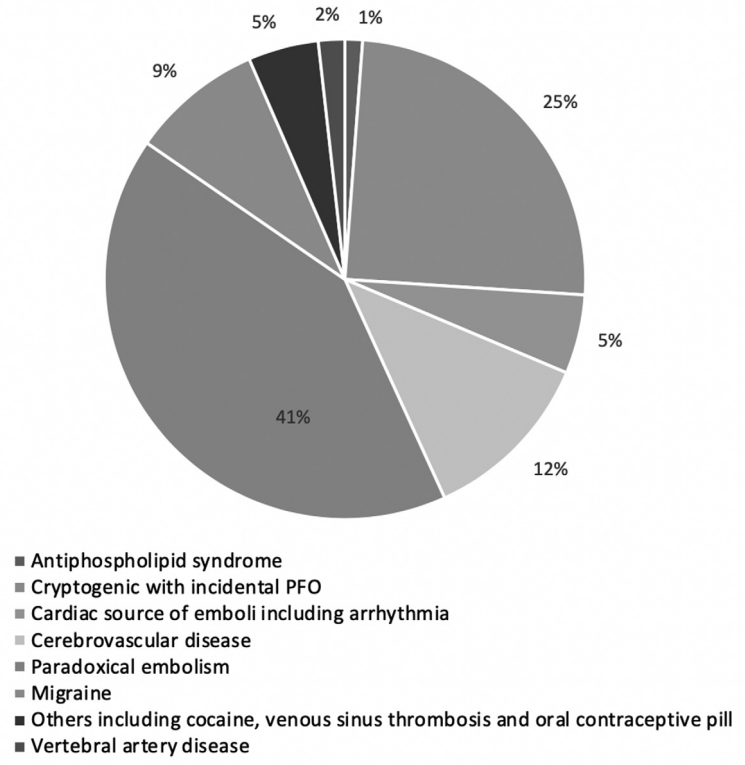
Introduction There is a high prevalence of patent foramen ovale (PFO) in patients with cryptogenic stroke; paradoxical embolism may be implicated in some but not all of these. Percutaneous device PFO closure reduces the risk of recurrent emboli but the success of this treatment is dependent on appropriate patient selection. The work-up of patients with cryptogenic stroke and PFO is best undertaken by a multi-disciplinary team (MDT).

Aim The aim was to evaluate the impact of a methodical approach to MDT investigation and work-up of patients with cryptogenic stroke and PFO on the final diagnosis and selection of patients for device PFO closure in a UK centre.

Methods The study was done in a single tertiary cardiac centre providing a PFO device closure service to a population of 1.3 million. Consecutive patients referred to the service between March 2011 and January 2017 were studied. Assessment included clinical consultation and expert review of all cardiac imaging (TOE and bubble contrast TTE), brain imaging (CT, DWI MRI, CT angiography), thrombophilia and arrhythmia investigations. Information about the MDT conclusions was obtained from meeting minutes, electronic and paper patient records.

Results 171 patients [51% female, mean age of 42 years (SD: ±16)] were assessed. The median number of MDT discussions was 1 per patient (range 1–5). Referral was with a cerebral infarct in 82%, transient cerebral ischaemia in 12% and peripheral emboli in 6%. Brain imaging confirmed the presence of cerebral infarction in 74% of patients. Cardiac imaging confirmed the presence of a PFO in 88%, an ASD in 5% and both in 4%; the intra-atrial septum was intact in 3%. One 'high risk' echo marker for paradoxical embolism was present in 44% of patients; an atrial septal aneurysm (23%), large right-to-left shunt (20%) or spontaneous shunt (43%). Clinically significant atrial arrhythmia was detected in 5% and thrombophilia testing was abnormal in 5% with lupus anticoagulant being positive in 62% of this subgroup. The final diagnoses are summarized in the figure 1. Paradoxical embolism was proposed if there was cerebral infarction typical of thrombo-embolism in the absence of vascular disease or arrhythmia and in the presence of PFO or ASD with a 'high-risk' ECHO marker. Based on these criteria, device closure was recommended in 41% of patients. The remainder received treatment appropriate to their diagnosis: antiplatelet therapy in 36%, anti-coagulants in 10% and no treatment in 15%.

Conclusion In patients with cryptogenic stroke who have a PFO, paradoxical embolism is implicated in the minority. Methodical work-up of patients by an MDT results in a range of diagnoses most of which are unrelated to the PFO. While clinical follow-up is required in all patients included



Abstract 141 Figure 1 Final diagnosis from PFO MDT