Abstract Highlights

The following selected highlights showcase intriguing and relevant abstracts presented at the European Society of Cardiology (ESC) Congress 2023, which were centred around congenital heart disease.

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Novel Insights on Right Ventricular Adaptation to Systolic Flow

MYOCARDIAL work (MW) represents an innovative methodology that integrates global longitudinal analysis with non-invasive assessment of ventricular pressure, enabling a comprehensive evaluation of ventricular performance. While this approach has been applied to the subpulmonary right ventricle (spRV), its application to the systemic right ventricle (sRV) remains unexplored.

The researchers extracted MW indexes from ventricular pressure-strain loops in a cohort of 48 patients with sRV. This cohort comprised of 32 individuals with transposition of the great arteries following atrial switch repair, and 16 with congenitally corrected transposition of the great arteries. The mean age of this group was 38.5±10 years, and it consisted of 56% males. Additionally, a control group of 20 healthy volunteers with spRV was included for comparative purposes.

Echocardiographic parameters and analysis of global longitudinal strain (GLS) revealed compromised systolic function in the sRV group. This included findings such as Tricuspid Annular Plane Systolic Excursion (TAPSE), measuring 12.3±3 mm, an S wave of 6.9±2 cm/s, fractional area change at 29.0% (23–35), GLS at -13.4±3.0%, RV septum GLS at -12.0±4.0%, and RV free-wall GLS at -14.8±4.0%.

The MW indexes were found to be below the normal reference values typically reported for the left ventricle. This included the global work index (GWI), measuring 1,056±331 mmHg% and the global constructive work (GCW) at 1490±269 mmHg%. On the other hand, global wasted work (GWW) and global work efficiency (GWE) showed mild increases at 245.5±162.0 mmHg% and 87.0±9.0%, respectively.

> **"Global wasted work (GWW) and global work efficiency (GWE) showed mild increases."**

The researchers observed that the sRV free-wall contributed more significantly to global performance compared to the septum. Specifically, GWI for the septum was 879±318 mmHg%, while for the free-wall, it was 1,241±412 mmHg% ($p<0.0001$). Similarly, GCW for the septum was 1,348±287 mmHg%; whereas for the free-wall, it was 1,626±377 mmHg% ($p<0.0001$). Interestingly, the analysis of segmental pressure-strain loops revealed higher wasted work values in dyssynchronous segments.

In comparison to spRV, MW indexes of performance were notably higher in sRV (spRV GWI: 349.3±99.0 mmHg%; $p<0.0001$, and spRV GCW: 451.1±104.0 mmHg%; $p<0.0001$). This difference likely signified the adaptation of the sRV to increased afterload. However, in response to chronic exposure to systemic pressure, there was a significant increase in both GWW and GWE in sRV compared with spRV (spRV GWW: 43.1±22.0 mmHg%; $p<0.0001$, and spRV GWE: 92.4±4.0; $p=0.0005$).

The authors concluded that evaluating MW in sRV patients is feasible, as it can offer valuable insights into ventricular global as well as segmental performance and efficiency; the findings are indicative of the sRV's adaptation to systemic loading. ●

Non-invasive Pressure Flow Plots in Patients of Fontan

IN PATIENTS who have had the Fontan procedure, the slope of pulmonary artery pressures, measured invasively, plotted against cardiac output (CO) during exercise has prognostic significance. A research team, led by Aleksandra Cieplucha, Katholieke Universiteit (KU) Leuven, Belgium, proposed a methodology to calculate peripheral venous pressure (PVP)/CO slopes in a non-invasive way, utilising echocardiography combined with cardiopulmonary exercise testing (CPET), and simultaneous peripheral venous pressure measurements. Overall, the team aimed to assess PVP/CO slopes and their relationship with peak O_2 consumption in patients.

Adult patients post-Fontan procedure who attended the outpatient clinic at KU Leuven were included in the study. All included patients underwent CPET-echo-PVP, where the peripheral intravenous line connected to the pressure transducer was zeroed at the mid-axillary level. Bloodwork was performed with the PVP/CO slope, calculated as a linear approximation using linear regression analysis from pressure-flow plots. Finally, univariable regression analysis was performed, permitting the identification of potential determinants of PVP/CO slope.

Overall, 20 patients (mean age 30.5±10.4; 11 [55%] females; and 15 dominant left ventricle [75%]) were included in the study with a N-terminal pro B-type natriuretic peptide of 297±235 pg/mL. Each participant performed staged exercise tests, achieving a workload of 102±30 Watts with a peak O_2 consumption of 19.2±3.8 mL/kg/min. CO, heart rate, and PVP all increased during exercise. Furthermore, stroke volume index increased from baseline to peak exercise in nine patients (45%). The average PVP/CO slope was 2.21±1.53 mmHg/L/min, with the value exceeding 3 mmHg/L/min in five (25%) patients. The researchers also identified potential determinants of PVP/CO slope, including peak O_2 consumption, peak workload during exercise; N-terminal pro B-type natriuretic peptide, New York Heart Association (NYHA) Functional Classification; and rest-to-peak change in tissue-Doppler e' of the lateral wall of dominant ventricle.

To conclude, CPET-echo-PVP could be a reliable method in identifying determinants of exercise limitation in patients who have had the Fontan procedure. The PVP/CO slope, reflecting total pulmonary resistance, is related to peak O_2 consumption, diastolic function, and heart rate reserve. The authors suggest that as it reflects hydraulic load to the systemic venous system, it may be an important target in patients.

"The team aimed to assess PVP/CO slopes and their relationship with peak O_2 consumption in patients."

Systemic Right Ventricle: Echocardiographic Variables Associated with Mortality

IMPAIRED subpulmonary left ventricle (LV) function in adult patients with a systemic right ventricle (sRV) is associated with heart or heart-lung transplantation and mortality, according to an abstract presented at the ESC Congress 2023, which took place in Amsterdam, the Netherlands, between 25th–28th August.

Authors from the Royal Brompton and Harefield Hospitals, London, UK, reviewed data from 120 adult patients with an sRV who had echocardiography performed between 2011–2019, to evaluate the correlation and relative prognostic power of subpulmonary LV function in this cohort. Of patients included, 60.0% were male, the average age was 43.5±12.1 years, 37.5% had congenitally corrected transposition of the great arteries, 66.4% were receiving ≥1 heart failure therapy, and 79.0% had heart failure classified as New York Heart Association (NYHA) Functional Class I/II. The study endpoints were transplantation or death, and the median follow-up duration was 4.9 years.

Subpulmonary LV function was determined using 4-chamber global longitudinal strain (GLS), fractional area change (FAC), and free-wall longitudinal strain (FWLS). Linear regression and Cox regression were used to assess the correlation between the subpulmonary LV function echocardiographic variables and the association between these variables and transplantation or mortality, respectively.

The analysis identified that 52.5% displayed, at a minimum, moderate systolic sRV dysfunction at baseline (median SRV FAC: 27.0%) and 81.7% of all patients had visually preserved subpulmonary LV function (LV FAC: 47.0%). Median values for GLS and LV FWLS were -15.2% and -19.9%, respectively. The correlation between LV FAC and GLS was noted to be weak (r=0.25).

Out of the 120 patients enrolled in the study, three patients underwent either a heart or heart-lung transplant, and 24 patients died. Whilst LV FWLS was not found to be a predictor of transplantation or death, univariable Cox analysis revealed that GLS and LV FAC were predictors (/5%; hazard ratio: 1.60; 95% confidence interval: 1.10–2.31; p=0.0100; and /5%; hazard ratio: 0.55; 95% confidence interval: 0.47–0.65; p<0.0001), respectively. However, LV GLS was not found to be a predictor on bivariable analysis. Despite this, the authors suggested that LV FAC and GLS should be included as part of a comprehensive echocardiographic assessment, highlighting that LV FACS has better prognostic value in this patient cohort.

The team concluded that in adults with an sRV, impaired subpulmonary LV systolic function was strongly associated with death and heart or heart and lung transplantation.

"In adults with an sRV, impaired subpulmonary LV systolic function was strongly associated with death."

Value of Left Ventricular Strain-Volume Loops as Biomarkers

SIGNIFICANT characteristics of left ventricular (LV) strain-volume (SV) loops have been observed between patients with bicuspid aortic valve (BAV) and healthy controls. This evidence is compelling for its potential in providing new insights in cardiac haemodynamics and in detecting LV remodelling at an early stage, as well as being a promising new prognostic marker. The current research is sourced from an abstract presented at the ESC Congress 2023, which took place in Amsterdam, the Netherlands, between 25th–28th August.

Patients with BAV were compared with healthy controls, grouped based on age and sex, and apical two, three, and four chamber views were used to measure LV global longitudinal strain and volume, in order to construct SV-loops. Univariable Cox regression was employed to assess the composite endpoint of all-cause mortality, heart failure, and supraventricular and ventricular arrhythmias. A total of 113 patients were included, with mean age of 32 years, and 40% female. Median aortic jet velocity was 2.3 m/s and 21 patients (19%) experienced moderate aortic regulation. Sslope was significantly lower in patients with BAV (0.21% /mL [interquartile range (IQR): 0.17-0.28] versus 0.27% /mL [IQR: 0.24–0.34]; p<0.001), as was ESlope (0.19% /mL [IQR: 0.12–0.25] versus 0.29% /mL [IQR: 0.21–0.43]; p<0.001). Greater uncoupling was seen in patients with BAV for both early (0.48±1.29 versus 0.05±1.21; p=0.018) and late diastolic (0.66±1.02 versus -0.07±1.07; p<0.001).
In a median follow-up period of 9.9 years, 17 patients experienced a primary endpoint. Echocardiographic parameters associated with the primary endpoint were early diastolic uncoupling (hazard ratio [HR]: 1.82; p=0.009), E/e' ratio (HR: 1.29; p<0.001), ESslope (HR: 0.55; p=0.030), and LV end-systolic volume (HR: 1.05; p=0.030).

The researchers showed support for the capabilities of this technique, through the significant differences in SV-loop characteristics observed between patients with BAV and healthy controls in this investigation. SV-loops as biomarkers are presented as valuable tools for cardiologists, and clinicians can expect to see more research emerge on this topic soon, as this work translates into practice. ●

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Haemodynamic Consequences of High Risk Anatomical Features

RESEARCHERS from the Netherlands presented key results from their study in patients with anomalous aortic origin of a coronary artery (AAOCA) at the ESC Congress 2023. The study aimed to evaluate the haemodynamic consequences of the high-risk anatomical features in AAOCA through fractional flow reserve (FFR), a technique that assesses further risk stratification of myocardial ischaemia and sudden cardiac death.

The prospective cohort study took place in a tertiary AAOCA referral centre, and included patients with the condition who had undergone diagnostic work-up according to the MuSCAT trial. This spanned from July 2020–January 2023, and included 30 patients (57% female), with a mean age of 48.7±15.3 years at the time of AAOCA diagnosis. Researchers detailed that CT angiography (CTA) of the intraluminal space, and orifice geometry using intravascular ultrasound were applied to assess the presence and length of the intramural segment.

Results showed that 90% of patients presented with an anomalous aortic origin of the right coronary artery. FFR adenosine levels, measured in all patients, reflected significant correlations to the following: hypoplasia of the proximal segment on CTA (R=0.400; p=0.029); the inter-luminal space at 2 mm from the ostium on CTA (R=0.517; p=0.003); the length of the intramural course on CTA (R=0.500; p=0.005); the orifice shape on intravascular ultrasound (IVUS; R=0.460; p=0.011); and the minimal lumen area on IVUS (R=0.371; p=0.044).

The researchers concluded that FFR was significantly reduced in high-risk anatomical features of increased hypoplasia of the proximal segment on CTA, lower inter-luminal space at 2 mm from the ostium on CTA, longer intramural course on CTA, increased slit-like orifice shape on IVUS, and lower minimal lumen area on IVUS, which all appear as haemodynamically relevant in the pathophysiology of AAOCA.

"Results showed that 90% of patients presented with an anomalous aortic origin of the right coronary artery."

Non-Cardiac Surgery Risk Stratification in Adult Congenital Heart Disease

ADULTS with congenital heart disease (ACHD) often undergo multiple surgeries throughout their lives. Data regarding the specific risk of non-cardiac surgery and the subsequent impact of this on the severity of ACHD outcome are limited. A research team, led by Alicia Jeanette Fischer, University of Münster, Germany, aimed to assess frequency and outcome of non-cardiac surgery and to identify patients with ACHD specifically at risk.

All ACHD cases admitted for non-cardiac surgery between 2011–2018 in Germany were included in the study. Non-cardiac surgery was categorised as either low, medium, or high risk based on a risk score validated for patients without congenital heart disease. Demographic data as well as medical data regarding diagnoses, in-hospital complications, and mortality were analysed, with the primary endpoints investigated being major adverse cardiovascular events, major infection, major bleeding, thromboembolism, and in-hospital death. Outcomes in the ACHD cohort were compared to those of a propensity score matched cohort of non-ACDH.

Overall, 13,041 ACHD were included in the analysis, with 72%, 21%, and 7% categorised as having simple, moderate, and complex heart defects, respectively. Low-risk surgery was performed for 23.0% of simple ACHD cases, while intermediate and high-risk surgery was performed for 31.1% and 45.0%, respectively.

In the medium complexity ACHD cohort, 35.8% received low-risk, 42.3% intermediate-risk, and 21.8% high-risk surgery. Finally, regarding complex ACHD, 42.4% underwent low-risk, 41.2% intermediate-risk, and 16.4% high-risk surgery. Simple ACHD cases more frequently presented with typical cardiovascular risk factors, such as dyslipidaemia, diabetes, and arterial hypertension, compared with other categories of ACHD severity at the time of non-cardiac surgery ($p<0.001$ for all). Compared with a propensity score matched cohort, patients with congenital heart disease more frequently met the endpoints, depending on complexity of the disease and pre-defined risk of surgery. Following adjustment on multivariable logistic regression analysis, moderate and severe complexity was associated with adverse outcomes. Specifically, risk for death was increased in moderately complex (odds ratio: 1.44; 95% confidence interval: 1.15–1.81; $p=0.001$) and severely complex ACHD (odds ratio: 2.28; 95% confidence interval: 1.63–3.20; $p<0.001$) when compared with a non-ACHD cohort. Finally, compared to low-risk surgeries, mid- and high-risk surgeries increased the risk of death, yielding odds ratios of 7.66 and 8.03, respectively.

To conclude, ACHD are at increased risk of adverse outcomes when undergoing non-cardiac surgery. This risk increases with the complexity of disease and surgical risk classifications were also associated with a much higher adverse outcome in patients undergoing high-risk procedures.

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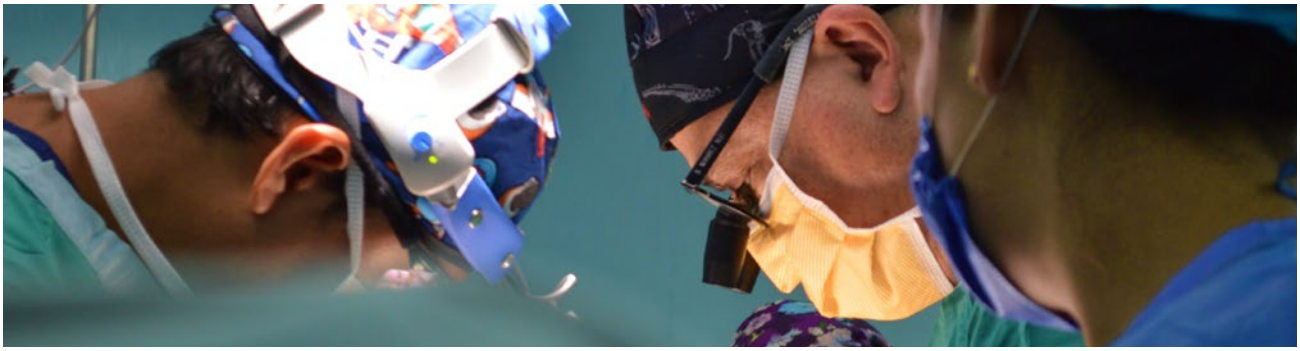

Predicting Low-Density Lipoprotein-Lowering Drug Impact on Congenital Heart Disease Risk

WITH the emergence of novel long-lasting low-density lipoprotein cholesterol (LDL) lowering therapies, such as silencing RNA treatments, which maintain clinical effects for up to 6 months post-administration, there is a significant likelihood that females of childbearing age could become pregnant during the drug's active period. In cases where clinical data is lacking, the Mendelian randomisation (MR) paradigm can be employed to forecast the impact of drug target perturbation using genetic data.

The research team sought to employ genetic data for the purpose of assessing the potential impact of LDL reduction through various drug targets, such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) on congenital heart disease. They extracted uncorrelated genome-wide significant variants ($p<5\times10-8$) related to LDL levels, along with their association estimates, both in the overall dataset and within the *HMGCR*, *NPC1L1*, and *PCSK9* gene regions (with a margin of +/- 10 kB).

The data were sourced from genome-wide association studies summary data from the UK Biobank, encompassing 469,897 individuals. Furthermore, gene-outcome association data were obtained from genome-wide association studies results derived from FinnGen 8th Release, involving 342,499 individuals, focusing on various congenital heart conditions including conotruncal defects; congenital malformations of the great arteries; septal defects; congenital diseases of the aortic or mitral valves; and the vertebral, anorectal, cardiovascular, tracheo-oesophageal, renal, and limb anomaly (VACTERL) association. To analyse the impact of drug targets on these conditions, a drug-target MR analysis was conducted using the inverse-variance weighted MR approach.

Genetically-proxied LDL reduction through PCSK9 was linked to increased odds of VACTERL association (odds ratio [OR]: 1.70; 95% confidence interval [CI]: 1.25–2.32; p<0.001), conotruncal defects (OR: 3.97; 95% CI: 1.37–11.53; p=0.011), and overall congenital heart disease of any type (OR: 1.49; 95% CI: 1.08–2.05; p=0.015). On the other hand, genetically-proxied LDL lowering via *HMGCR* was associated with higher odds of congenital malformations involving the great arteries (OR: 5.85; 95% CI: 1.07–31.84; p=0.041). However, it is important to note that genetically driven LDL reduction through *NPC1L1* drug targets did not reveal significant differences in the risk of congenital heart disease, albeit the statistical power for these analyses was somewhat limited.

These findings provide genetic evidence indicating that the utilisation of LDL-lowering medications during pregnancy might have the potential to influence the risk of congenital heart disease. The authors emphasise that these results are specifically relevant to medications capable of crossing the placental barrier and directly affecting foetal LDL metabolism. They affirm the findings should not be extended to deduce the indirect consequences of lowering maternal LDL.

These outcomes underscore the significance of exercising caution when contemplating statin use during pregnancy. Additionally, they propose that long-lasting PCSK9-inhibiting agents, like monoclonal antibodies and silencing RNA therapies, which possess the ability to traverse the placental barrier, should be employed with great care by females who are planning to conceive. ●

"A drug-target MR analysis was conducted using the inverse-variance weighted MR approach."