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Risk of Cancer in Young and Older Patients with Congenital Heart Disease and the Excess Risk of Cancer by Syndromes, Organ Transplantation and Cardiac Surgery: Swedish Health Registry Study (1930-2017)

Venu Amula, MD

Commentary from Dr. Venu Amula (Salt Lake City, UT, USA) on the following article:
Risk of Cancer in Young and Older Patients with Congenital Heart Disease and the Excess Risk of Cancer by Syndromes, Organ Transplantation and Cardiac Surgery: Swedish Health Registry Study (1930-2017)
Christina Karazisi, Mikael Dellborg, Karin Mellgren, Kok Wai Giang, Kristofer Skoglund, Peter Eriksson, Zacharias Mandalenakis. Lancet Reg Health Eur. 2022 May 29;18:100407. doi: 10.1016/j.lanepe.2022.100407. eCollection 2022 Jul. PMID: 35663362

Take-Home Points

1. There is a 23% increased risk of cancer in young and older patients with Congenital Heart Disease when compared to matched controls without Congenital Heart Disease (CHD).
2. The risk is higher in children and those who were born in later birth cohorts.
3. The risk remains elevated after excluding patients with genetic syndromes and transplant recipients.

Overall, congenital cardiac surgery was not associated with an increased risk of cancer except in children who underwent cardiac surgery during the first year of life.

Karazasi et al. performed an observational case-control study using the Swedish health registry to investigate the risk of cancer in young and older patients with CHD and to evaluate the excess risk of cancer by syndromes, organ transplantation, and cardiac surgery. With the increasing survival of patients with congenital heart disease, they are at risk of acquired cardiovascular conditions and other diseases such as cancer. However, limited studies exist quantifying such a risk in patients with congenital heart disease compared to the general population.

The authors of this study used data from the Swedish National Inpatient Register, the Swedish National Outpatient Register, and the Swedish Cause of Death Register. Inclusion criteria included patients born between 1930 and 2017 with a diagnosis of CHD. ICD codes were used for diagnosis. Each patient with CHD was matched by sex and birth year with ten controls without CHD from the general population, identified from the Swedish Total Population Register. Follow-up times for CHD and control populations were

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estimated from birth until the event (cancer), death, or the end of the study period (31, December 2017), whichever occurred first. Incidence rates were reported as per 10,000 person-years and were estimated as the number of events divided by the total follow-up time of the population. Incidence rate ratio (IRR) was defined as the relative difference between CHD and the control population, with 95% confidence intervals (CI) Cox proportional hazard regression models used to obtain hazard ratios (HR) with 95% CIs. For all models, the control population was considered the reference population.

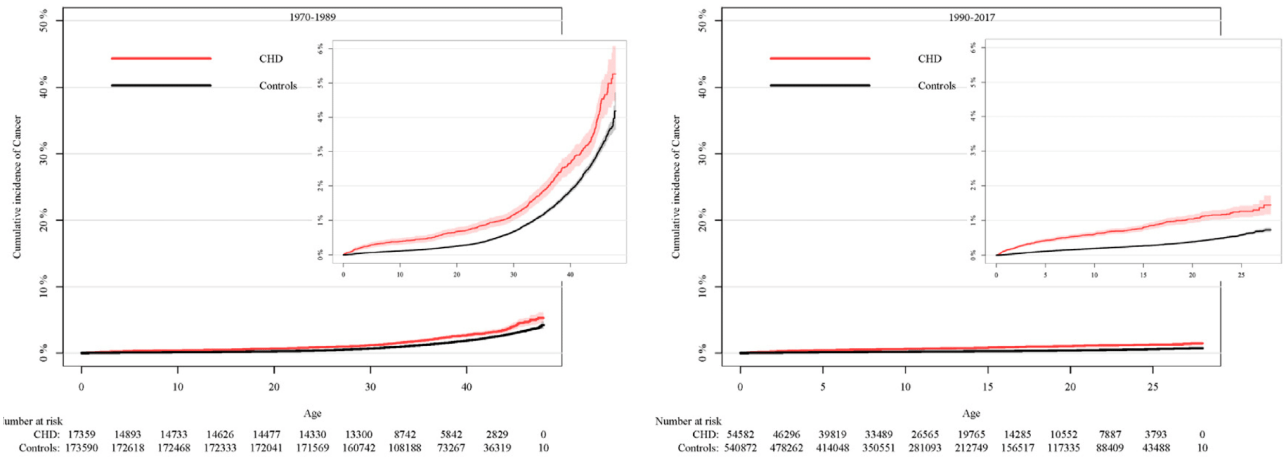
The authors identified 89,542 patients born between 1930 and 2017 who were registered with the diagnosis of CHD and 890,472 controls who were matched by birth year and sex. As noted in the table below, the baseline characteristics were similar in cases and controls. After a median follow-up time of 58.8 years for CHD patients and 61.3 years for controls, 4.5% of patients with CHD and 4.0% of the control population developed cancer. The cancer risk was 23% more in patients with CHD than in controls. The increased risk was maintained after excluding patients with syndromes and organ transplant recipients. When studying the cumulative incidence of cancer according to the birth cohort, the incidence of cancer was significantly higher in the CHD population from the youngest birth cohorts.

Characteristic	CHD	Controls
All patients, No (%)	89,542 (9·1%)	890,472 (90·9%)
Male	45,372 (50·7%)	453,720 (51·0%)
Female	44,170 (49·3%)	436,752 (49·0%)
Birth cohort		
1930–1949	7026 (7·8%)	70,260 (7·9%)
1950–1969	10,575 (11·8%)	105,750 (11·9%)
1970–1989	17,359 (19·4%)	173,590 (19·5%)
1990–2017	54,582 (61·0%)	540,872 (60·7%)
Age at event*		
Mean, years (SD)	52·6±22·1	57·4±17·6
Median, years (IQR)	58·8 (42·4–69·0)	61·3 (49·0–69·8)

***Table 1*: Characteristics of the study population.**
*cancer, death or end of the study period (31 December 2017).
CHD = congenital heart disease. SD = standard deviation. IQR = interquartile range.

	HR (95% CI)		p-value
	All patients	Excluding patients with syndromes and organ transplant recipients	(all vs excluded patients)
Study population	1·23 (1·19–1·27)	1·18 (1·14–1·22)	<0·001 / <0·001
Age group			
0–17 years	3·21 (2·90–3·56)	2·42 (2·15–2·73)	<0·001 / <0·001
18–39 years	1·34 (1·21–1·48)	1·24 (1·12–1·38)	<0·001 / <0·001
40+ years	1·11 (1·07–1·15)	1·11 (1·07–1·15)	<0·001 / <0·001
Birth cohort			
1930–1949	1·03 (0·98–1·08)	1·03 (0·98–1·08)	0·20 / 0·25
1950–1969	1·33 (1·25–1·42)	1·32 (1·24–1·40)	<0·001 / <0·001
1970–1989	1·76 (1·59–1·96)	1·62 (1·45–1·81)	<0·001 / <0·001
1990–2017	2·88 (2·57–3·22)	2·16 (1·89–2·47)	<0·001 / <0·001

***Table 2*: Cancer risk in patients with congenital heart disease compared with matched controls, according to age and birth cohort.**
HR = hazard ratio. CI = confidence interval.



GRAPHS *Cumulative incidence of cancer risk by birth cohort: Birth cohorts 1970–1989 and 1990-2017. This study is of utmost importance and raises several important questions. The reasons for such an increased cancer risk remain elusive, but several are plausible. Genetic predisposition, increased exposure to low ionizing radiation as a part of diagnostic and therapeutic procedures, and early thymectomy with immune dysregulation are possible explanations without any direct evidence incriminating them. The association of higher cancer risk with younger birth cohorts does follow the increased surgical and catheter-based intervention trends in recent periods. Longitudinal studies involving large populations may provide more insight, but in the meanwhile, cardiologists should be aware of this higher risk and engage in heightened surveillance of young patients.*

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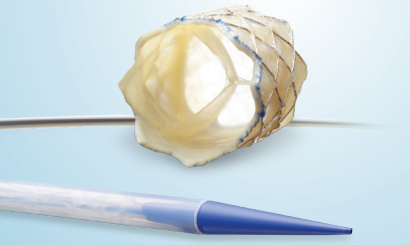

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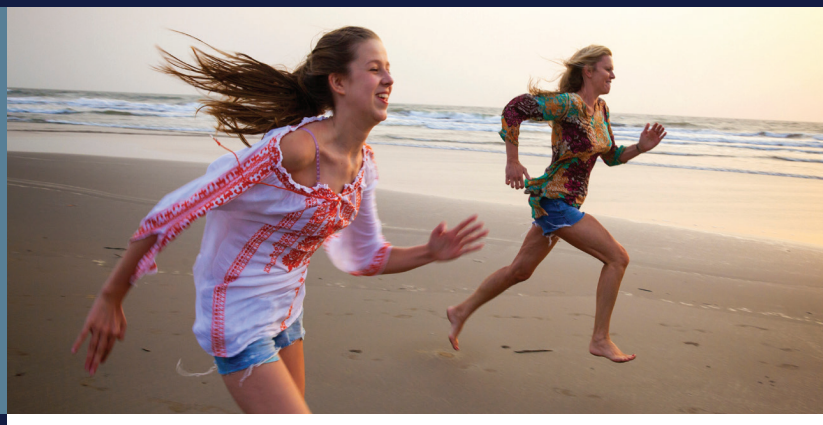

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*The term "stent fracture" refers to the fracturing of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.

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- Patients with regurgitant prosthetic right ventricular outflow tract (RVOT) conduits or bioprostheses with a clinical indication for invasive or surgical intervention, OR
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Contraindications

- Venous anatomy unable to accommodate a 22 Fr size introducer sheath
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Potential Complications/Adverse Events: Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, pain, swelling or bruising at the catheterization site. Potential device-related adverse events that may occur following device implantation include the following: stent fracture.* stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

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For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

The Melody Transcatheter Pulmonary Valve and Ensemble II Transcatheter Delivery System has received CE Mark approval and is available for distribution in Europe.

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Short- and Medium-Term Outcomes for Patent Ductus Arteriosus Stenting in Neonates ≤2.5 Kg with Duct-Dependent Pulmonary Circulation

Konstantin Averin, MD

Commentary from Dr. Konstantin Averin (Glen Oaks, NY, USA) on the following article:
Short- and Medium-Term Outcomes for Patent Ductus Arteriosus Stenting in Neonates ≤2.5 kg with Duct-Dependent Pulmonary Circulation
Nasef MA, Shahbah DA, Batlivala SP, Darwich R, Qureshi AM, Breatnach CR, Linnane N, Walsh KP, Oslizlok P, McCrossan B, Momenah T, Alshahri A, Abdulhamed J, Arafat A, Tamimi OA, Diraneyya OM, Goldstein BH, Kenny D. Catheter Cardiovasc Interv. 2022 Oct;100(4):596-605. doi: 10.1002/ccd.30351. Epub 2022 Jul 29.PMID: 35904221

Take-Home Points

- Stenting the patent ductus arteriosus in infants ≤ 2.5 kg with DDPBF is technically feasible and achieves short-term outcomes comparable to or better than surgical systemic-to-pulmonary shunting.
- There is a relatively high incidence of morbidity with this procedure, especially related to arterial access.

Stenting of the patent ductus arteriosus (PDA) has become an accepted alternative to a surgical systemic-to-pulmonary shunting (SPS) in patients with ductal dependent pulmonary blood flow (DDPBF). Infants who are ≤ 2.5 kg are at highest risk for SPS, so PDA stenting is an attractive option in this patient population. The authors sought to assess procedural and short-term outcomes in infants ≤ 2.5 kg undergoing PDA stenting for DDPBF using data from four large cardiac centers.

FIGURE 1

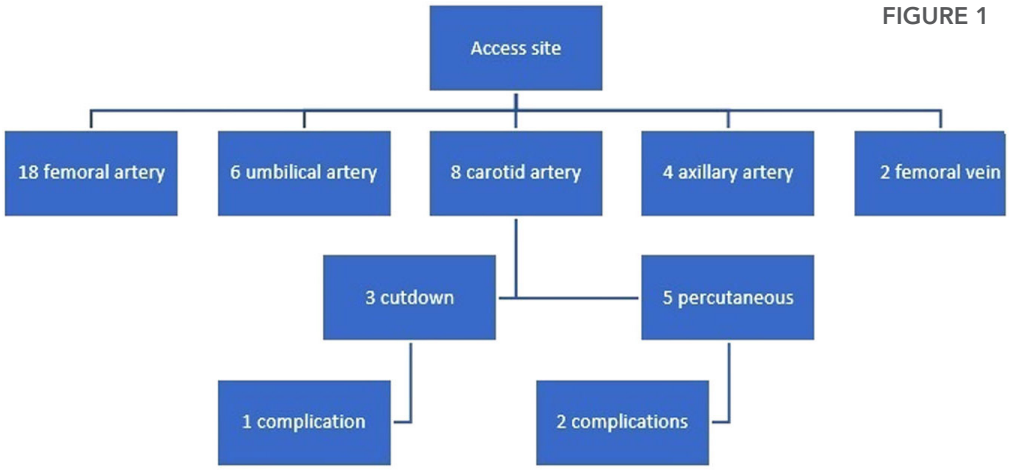
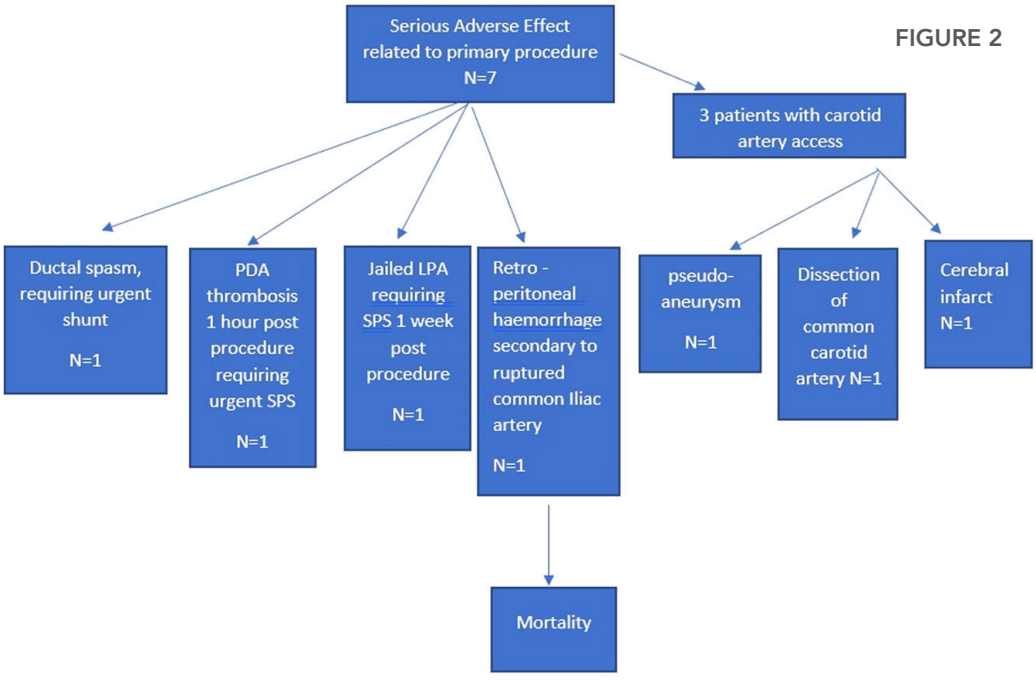


FIGURE 2



From March 2007 to February 2020, 38 patients – median age at procedure 10 days (IQR 6-15), median procedural weight 2.2 kg (IQR 2-2.4 kg) (11 under 2.0kg) – underwent PDA stenting. There were a variety of diagnoses, but a majority had pulmonary atresia or pulmonary stenosis (71%). A majority (79%) of the PDA's had complex anatomy with a tortuosity index of II or III. In 47% of patients, the procedure was performed via the femoral artery, while the carotid artery was used in eight (21%), umbilical artery in six, axillary artery in four, and femoral vein in two **(Figure 1)**.

Patient outcomes are summarized in **Figure 3**. Successful stent implant was achieved in 92% of initial procedures (35/38) with no procedural deaths. There was a high incidence (18%, 7/38) of serious adverse events related to the primary procedure **(Figure 2)** – most commonly related to carotid and femoral artery access. The thirty-day survival for the entire cohort was 97%. Twenty patients required reintervention.

The authors conclude that PDA stenting in infants ≤ 2.5 kg is feasible and effective. The authors should be commended for providing important data on a challenging procedure in a very challenging patient population. Despite the relatively high risk of access-related complications, it is interesting that none of the patients who underwent axillary artery access had any complications related to this. Recognizing that this was one of the access sites used least frequently, further investigation as to whether the axillary artery may be a safer approach for this procedure is warranted. This study highlights the need for additional data to inform decision making around PDA stenting.

This article was originally published by The CHiP Network and can be view on the following site:

https://thechipnetwork.org/short-and-medium-term-outcomes-for-patent-ductus-arteriosus-stenting-in-neonates-%e2%89%a42-5-kg-with-duct-dependent-pulmonary-circulation/

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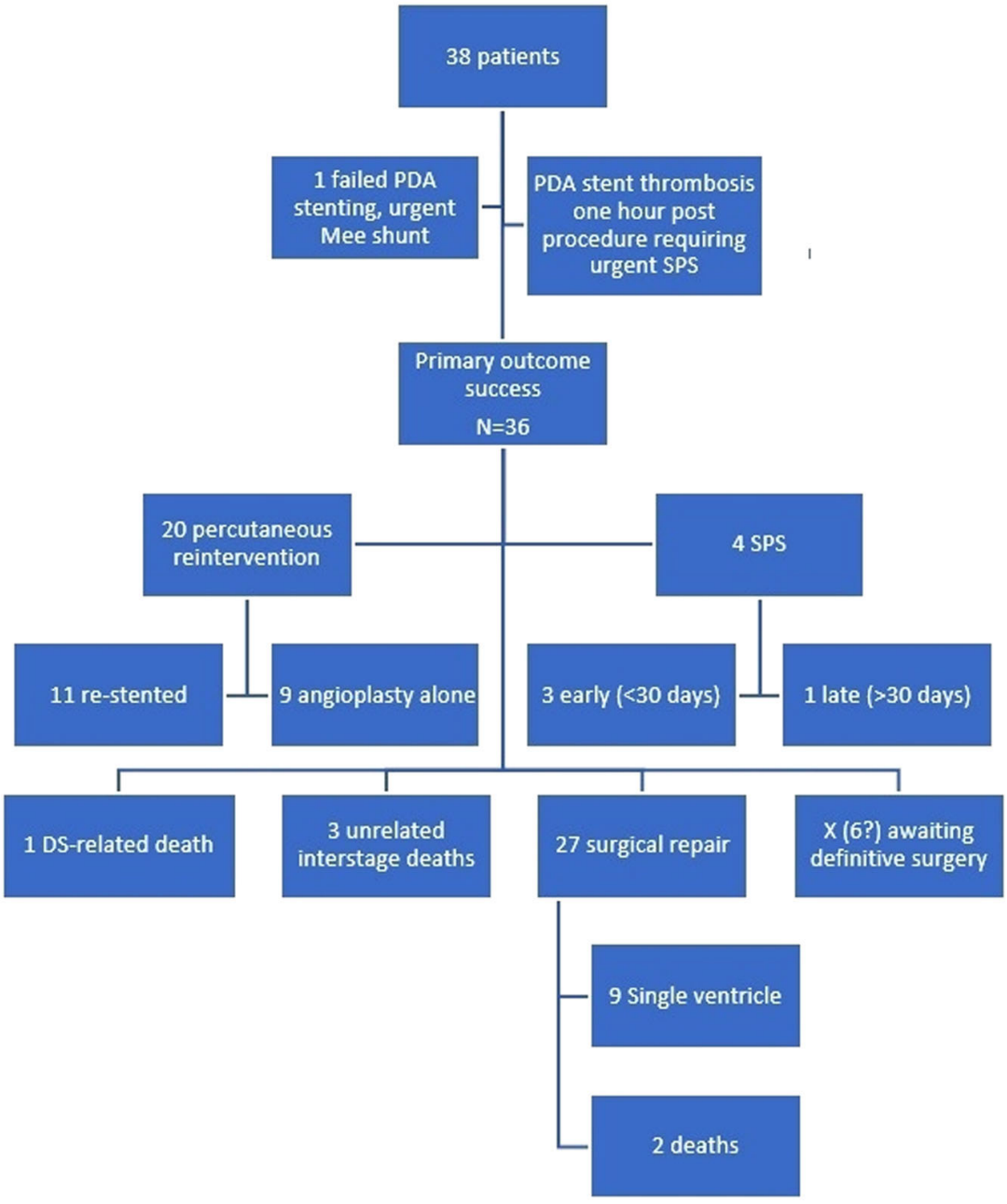

FIGURE 3

Peak Oxygen Uptake on Cardiopulmonary Exercise Test is a Predictor for Severe Arrhythmic Events During Three-Year Follow-Up in Patients with Complex Congenital Heart Disease

Timothy Roberts, MD

Commentary from Dr. Timothy Roberts (Melbourne, Australia) on the following article:
Peak Oxygen Uptake on Cardiopulmonary Exercise Test Is a Predictor for Severe Arrhythmic Events during Three-Year Follow-Up in Patients with Complex Congenital Heart Disease
Von Sanden F, Ptushkina S, Hock J, Fritz C, Hörer J, Hessling G, Ewert P, Hager A, Wolf CM.J Cardiovasc Dev Dis. 2022 Jul 4;9(7):215. doi: 10.3390/jcdd9070215. PMID: 35877577

Take-Home Points

- Risk stratification for sudden cardiac death (SCD) and primary prevention ICD therapy in patients with complex Congenital Heart Disease is challenging.
- This single-centre retrospective study of 1194 patients with complex CHD evaluated the ability of a range of measurements collected during routine cardiopulmonary exercise testing (CPET) to aid in the risk assessment of SCD over a three-year follow-up period.
- Severe arrhythmia was documented in 97 patients (8.1 %/3 years), with independent risk factors being older age and low peak oxygen uptake (VO2peak) on multivariate analysis.
- The authors, thus, suggest considering age and VO2peak in the risk stratification of SCD and the individualized decision for primary prevention ICD implantation in patients with complex CHD.
- The data from this study has a number of limitations and will not result in a significant change in clinical practice, however it does endorse the large body of literature supporting the use of CPET in the overall risk stratification of patients with CHD.

Patients with complex CHD carry a lifetime elevated risk for severe arrhythmia and sudden cardiac death (SCD), with up to 26% of CHD deaths attributed to SCD. International guidelines specific to CHD patients and indications for primary prevention ICD are limited, and improving the risk stratification process is desperately needed.

Cardiopulmonary exercise testing (CPET) provides a well-established marker of cardiopulmonary function in children and adults with CHD and has not been mentioned in 2015 and 2020 guidelines as a tool for SCD risk stratification. The aim of this study was to evaluate measurements obtained during CPET as predictors for the occurrence of severe arrhythmias during a three-year follow-up.

The study design was that of a single-centre retrospective analysis of patients with complex CHD (univentricular heart, Ebstein's anomaly, Tetralogy of Fallot, truncus arteriosus communis, and transposition of the great arteries post arterial switch operation or Senning/Mustard procedure) undergoing CPET between 2009 and 2014. A symptom-limited customized ramped upright bicycle CPET protocol was used until exhaustion (respiratory exchange ratio > 1.0). The highest 30-second interval of oxygen uptake during exercise was defined as peak oxygen uptake (VO2peak). Data collected on the date of CPET were: demographics (age, gender, body mass index), VO2peak, anaerobic threshold (VO2at), ventilatory efficiency (VE/VCO2 slope), respiratory exchange ratio at peak exercise, and pulse oximetric saturation at peak exercise (SpO2max). Medical charts and available Holter recordings, ICD-, pacemaker- and event-recorder readings were reviewed within a follow-up time of three years after CPET. Systemic ventricular function by transthoracic echocardiography was added to the analysis if assessed within 12 months of the index CPET. Primary endpoint was survival without severe arrhythmia events (SAE), chiefly SCD, aborted SCD, appropriate ICD discharge, ICD anti-tachycardia pacing for VT, hospital admission for acute ventricular arrhythmia, cardiac syncope caused by ventricular arrhythmia, and the occurrence of non-sustained VT on Holter, event-recorder, pacemaker, or ICD recordings. Data analyses were performed using SPSS with appropriate statistical considerations. Univariate and backwards stepwise multivariable logistic regression models were used to identify parameters associated with SAE within three years. Time-to-event analysis was conducted via univariable and backwards stepwise multivariable Cox regression analysis. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic ability of VO2peak to predict SAE.

In total, 1,194 patients (663 male) were included in the study. Median age was 25.9 years (IQR 17.4–34.6 years), median BMI was 22.4 (IQR 19.8–25.6) kg/m2. Underlying diagnosis was:

- Univentricular heart (UVH) in 205
- Ebstein's anomaly (EBS) in 135
- Tetralogy of Fallot (TOF) in 469
- Truncus arteriosus communis (TAC) in 51
- Transposition of the great arteries, arterial switch operation (TGA ASO) in 149
- Transposition of the great arteries, Senning/Mustard procedure (TGA SM) in 185

Transthoracic echocardiogram was available in 1,148 patients. Peak performance was reached by 1,075 patients during CPET. Three years of follow-up were completed in 1,101 patients (92.2 %). Holter recordings were available in 445 patients (38.1 %). During follow-up, ICD's were present in 42 patients, 145 patients had a pacemaker, and event-recorders were used in three patients; of these totals, 27 pacemakers and 17 ICDs were implanted during follow-up, including five ICD-upgrades to preexisting pacemakers. Twenty-seven patients (2.3 %) died during follow-up:

- SCD diagnosed in 2 patients
- Non-SCD in 16
- Unclear cause of death in 9

Severe arrhythmic events occurred in 97 of 1,194 patients (8.1 %), with no statistically significant differences found between the distinct anatomical groups. Non-sustained VT was the most frequent SAE, while sustained VT was documented in eight patients (**Table 2**).

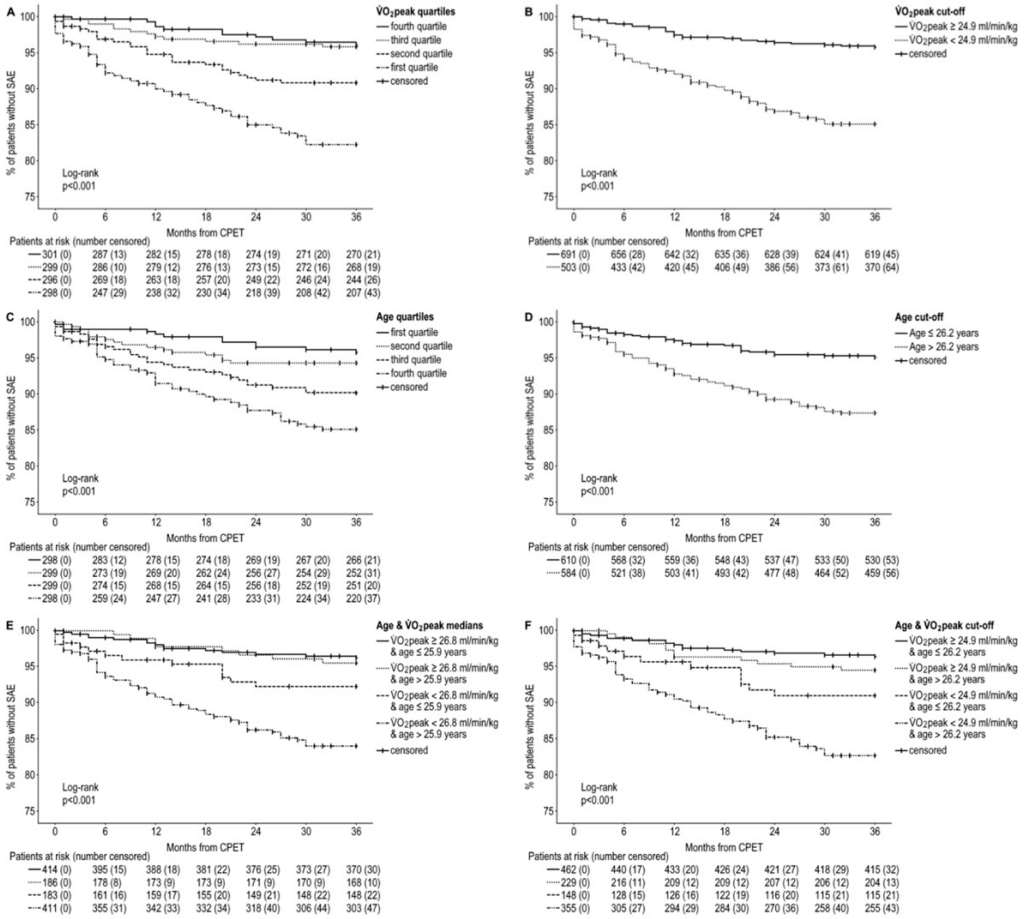

Figure 1. Kaplan–Meier SAE-free survival for $\dot{V}O_2$peak and age. (**A**) Kaplan–Meier SAE-free survival for quartiles of $\dot{V}O_2$peak, (**B**) Kaplan–Meier SAE-free survival for patients reaching or failing the ROC cut-off value for $\dot{V}O_2$peak (24.9 mL/min/kg), (**C**) Kaplan–Meier SAE-free survival for quartiles of age at CPET, (**D**) Kaplan–Meier SAE-free survival for patients exceeding or not exceeding the ROC cut-off value for age (26.2 years) at CPET, (**E**) Kaplan–Meier SAE-free survival separated by medians of age and $\dot{V}O_2$peak, (**F**) Kaplan–Meier SAE-free survival separated by ROC cut-off values for age at CPET (26.2 years) and $\dot{V}O_2$peak (24.9 mL/min/kg); SAE: Severe arrhythmic event, $\dot{V}O_2$peak: Peak oxygen uptake, ROC: Receiver operating characteristic, CPET: Cardiopulmonary exercise testing.

TABLE 2 *Clinical variables associated with SAE in multivariable analysis were age at CPET (OR, 1.029; 95 % CI, 1.00901.049; p=0.004) and VO2peak (OR, 0.951; 95 % CI, 0.921-0.982; p=0.002). VE/VCO2 slope, RERmax, SpO2max, gender, and type of CHD did not correlate significantly in the logistic regression model.*

ROC curve analysis identified VO2peak (AUC, 0.687; 95 % CI, 0.631-0.743; p < 0.001) and age (AUC, 0.659; 95 % CI, 0.602-0.715; p < 0.001) as independent predictors for SAE in CHD patients, with potential cut-off values for VO2peak at 24.9 ml/min/mg (Youden's Index, 0.318; sensitivity 0.702; specificity 0.616) and age at 26.2 years (YI, 0.242; sensitivity 0.711; specificity 0.531). Lower VO2peak values in the second and first quartiles were associated with a decrease in SAE-free survival (90.7% and 82.2%). Patients with VO2peak above the cut-off value of 24.9 ml/min/kg presented with more frequent 3-year survival without SAE than patients with lower VO2peak than cut-off (95.8% vs. 85.1%). Age above the cutoff value of 26.2 years led to less frequent 3-year survival without SAE (87.4% vs. 95.1%).

Table 2. Occurrence of severe arrhythmic events (total and separated in CHD groups).

[n/N[%]]	Total	UVH	EBS	TOF	TAC	TGA ASO	TGA SM	*p*-Value
Severe arrhythmic event	97/1194(8.1)	18/205(8.8)	15/135(11.1)	41/469(8.7)	1/51(2.0)	8/149(5.4)	14/185(7.6)	0.291 [χ^2]
SCD equivalent	15/1194(1.3)	2/205(1.0)	3/135(2.2)	8/469(1.7)	0/51(0.0)	1/149(0.7)	1/185(0.5)	0.588 [χ^2]
SCD	2/1194(0.2)	0/205(0.0)	1/135(0.7)	1/469(0.2)	0/51(0.0)	0/148(0.0)	0/186(0.0)	0.593 [χ^2]
Aborted SCD	6/1194(0.5)	1/205(0.5)	1/135(0.7)	2/169(0.4)	0/51(0.0)	1/149(0.7)	1/185(0.5)	0.990 [χ^2]
ICD-ATP	8/1194(0.7)	2/205(1.0)	1/135(0.7)	5/469(1.1)	0/51(0.0)	0/149(0.0)	0/185(0.0)	0.549 [χ^2]
Appropriate ICD-discharge	6/1194(0.5)	1/205(0.5)	1/135(0.7)	4/469(0.9)	0/51(0.0)	0/149(0.0)	0/185(0.0)	0.661 [χ^2]
Hospitalisation/Syncope	21/1194(1.8)	2/205(1.0)	2/135(1.5)	13/469(2.8)	0/51(0.0)	2/149(1.3)	2/185(1.1)	0.400 [χ^2]
Hospitalisation	11/1194(0.9)	1/205(0.5)	1/135(0.7)	7/469(1.5)	0/51(0.0)	1/149(0.7)	1/185(0.5)	0.697 [χ^2]
Syncope	14/1194(1.2)	1/205(0.5)	2/135(1.5)	8/469(1.7)	0/51(0.0)	1/149(0.7)	2/185(1.1)	0.695 [χ^2]
sVT/nsVT in device	83/1194(7.0)	17/205(8.3)	12/135(8.9)	33/469(7.0)	1/51(2.0)	7/149(4.7)	13/185(7.0)	0.481 [χ^2]
sVT in device	8/1194(0.7)	2/205(1.0)	1/135(0.7)	4/469(0.9)	0/51(0.0)	0/149(0.0)	1/185(0.5)	0.859 [χ^2]
nsVT in device	82/1194(6.9)	17/205(8.3)	12/135(8.9)	32/469(6.8)	1/51(2.0)	7/149(4.7)	13/185(7.0)	0.475 [χ^2]

CHD: Congenital heart disease, UVH: Univentricular heart, EBS: Ebstein's disease, TOF: Tetralogy of Fallot, TAC: Truncus arteriosus communis, TGA: Transposition of the great arteries, ASO: Arterial switch operation, SM: Senning/Mustard, SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, ATP: Antitachycardia pacing, sVT: Sustained Ventricular Tachycardia, nsVT: Non-sustained ventricular Tachycardia, device:

PEAK OXYGEN UPTAKE ON CARDIOPULMONARY EXERCISE TEST

This article was originally published by The CHiP Network and can be view on the following site:
https://thechipnetwork.org/peak-oxygen-uptake-on-cardiopulmonary-exercise-test-is-a-predictor-for-severe-arrhythmic-events-during-three-year-follow-up-in-patients-with-complex-congenital-heart-disease/

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Section Editor
ACHD Journal Watch
The CHiP Network
Melbourne, Australia

Res Cordis et Mentis: Peccatum Omissionis

Neil Wilson, MBBS, DCH, FRCPCH, FSCAI

In 1995, perhaps, 1996, at the Royal Hospital For Sick Children in Glasgow, Scotland. An interesting name for a hospital as an American friend once teased me. "So, do you have hospitals for well children in Scotland too"? Good point.

Wednesday morning outpatient clinic was quite busy with 18 patients booked. No fellow, third-year medical student. We'd been enjoying the clinical signs and repartee, and with plenty of outstanding experienced echo tech support, things were moving smoothly. It's about 9.30am. In comes Jamie, a chubby nine-month-old baby boy, accompanied by his mom.

I had seen Jamie three months earlier. He was referred then by his family practitioner because of a heart murmur and some (insignificant as I thought) episodes of pallor and screaming. He was pink, and too lively to tolerate the pulse oximeter for a meaningful reading. I wasn't concerned about a cyanotic lesion. Sure enough, he had widespread systolic murmurs throughout the precordium and well heard into the back. EKG wasn't the best quality, perhaps debatable right ventricular hypertrophy with a splintered rSr pattern. Echo, well, no way was Jamie going to entertain that notion though we did see enough to confirm normal situs and connections and no major structural intracardiac lesions. Main pulmonary artery debatably small. I settled on a clinical diagnosis of bilateral branch pulmonary artery stenosis. He was indisputably well. Growth well up the centile charts. I wasn't going to sedate him, but was confident we'd get better pictures in a few months time. So here we are…

Jamie, still chubby, now nine-months-old. Mom still relating these episodes of him becoming upset, pale and then settling down in a matter of minutes. He's in great shape sitting on mom's knee, very cooperative, clinical signs pink with saturations 94-95%. Active precordium, perhaps I could convince myself of a precordial heave, but we'll see. Widespread systolic murmurs as before. He's engaging and cooperative and in good shape for an EKG which unequivocally shows right axis deviation. Echo, he's a sweetheart on mom's lap. Excellent pictures. Right atrium and ventricle are unequivocally dilated, atrial septum is intact; in fact, I'd say a whiff of right to left through a PFO. Main pulmonary artery is small, we can see small branches too and the colour Doppler signal lights up with aliasing flow like the lungs are on fire. Tricuspid regurgitation is trivial to mild, not the best waveform but Doppler predicts more than 4 m/sec. I am immediately concerned about the episodes of pallor and screaming he'd had, which I had not hitherto felt relevant. I'm thinking RV ischaemia. Now longish chat with mom, complete with a hasty pencil sketch of a normal heart and side by side a drawing of what I thought was going on in Jamie's. I explain the rationale for admission right now and procedure of cardiac catheterisation the following day, "To get some more information about how severe these lung artery narrowings are." "Will he need an operation doctor?" asks mom. "Possibly," I responded, "but we'll have a better idea after the catheter test tomorrow."

Jamie and mom head directly from outpatients to the ward with Kate, the specialist cardiac nurse. I carry on with the clinic, dictate the letters and helped my student carry the enormous pile of 18 case notes to the secretary office. We walk up the five flights of stairs to the ward (it was in my running days). And there's Jamie on his mom's knee hoovering down an off yellow sludge of banana something. Both look settled and happy. I reward the student with lunch and spend the afternoon fiddling about with a presentation I am due to give at the Scottish Cardiac Society the coming weekend. I've got Jamie on my mind, he's fourth on the list tomorrow. I go down to the echo department and review the images of the following day's catheter cases. I can't see anything different with Jamie's pictures, but start thinking he might be a candidate for stents which are just beginning to take off in the congenital heart intervention armamentarium. I had done a handful of cases of branch pulmonary artery stents but in much bigger patients.

Sign out round about 6:15pm. Jamie is sitting in his cot chewing at a blue and red plastic toy. Happy enough, nothing to report. No mom to be seen. Nurse says "Mom left just after admission, I suppose she's gone home to see Jamie's older sister say hello and explain things to dad". Fair enough, understandable, she'll no doubt be back.

Not sure what I had for dinner that evening. I spent the post-prandial time irritating the kids about homework, pleading them to tidy bedrooms, the usual stuff.

9.15pm, the phone rings. "Dr. Wilson, the baby you admitted from outpatients has arrested, the crash team (code team) are with him." I'm in the car speeding and feeling sick, "What the hell is going on, what have I done wrong?" Twenty minutes later I'm at the bedside. He's intubated, pulse oximeter is not reading. CPR looks effective though Jamie's body is grey, white, monitor shows electrical asystole. Empty glass ampoules of various drugs litter the mattress. We carry on with the CPR, more adrenaline, calcium etc, etc. We get an agonal rhythm eventually but can't get output. Forty minutes on I ask, "Where's mom?" "She's in the parent room at the end of the ward, she was with him when he started to get agitated and went pale and arrested." Another ten minutes, no output, back to asystole on EKG. Pupils are enormous and unresponsive. These are the days before available resuscitative ECMO. The anaesthesiologist eyes me and looks away. I read her mind, and indeed the minds of the rest of the team. "I think we should stop. OK? He's not coming back." I ask the team to continue CPR and I peel off to speak to mom adding that we'll stop after I had spoken to her. I get about halfway to the parent room from which I can hear loud distressed crying. A nurse hurries up from behind me. "Doctor Wilson, you probably ought to know, Mom's dad had a heart attack and died in the Western Infirmary (Adult hospital 400 yards across the road) this afternoon." Oh hell. Mom knows what's coming. Second time today. I can hardly get my words out. She's

now on the floor, face down distraught and almost screaming her tears. A slightly younger looking woman is beside her, kneeling, sobbing too and trying to get her arms round her sister. I can't stop saying, "I am so sorry, I am so sorry," though I am sure my words can't be heard through the crying. You can imagine what's going through my mind. Why didn't I sedate him for echo when I saw him for the first time three months ago? If I had, I might have catheterised him then, organised treatment and saved his life. Why did I ignore the potential significance of the episodes of agitations, crying, etc? Find me a six-month-old baby who doesn't appear to get upset for no reason… I am trying to rationalise to make myself feel better, but it doesn't work. After about 30 minutes, Mom and sister leave the parent room and come into the ward. More intense crying, then a moment of silence from both. Mom reaches into the cot and picks up her baby, her tears dropping on to her son's face as she rocks him, "Oh mah wee man, whit's all this aboot? First yer grandad now you…"

Post Script

Jamie's post mortem showed severe dilation and hypertrophy of the right ventricle with evidence of subendocardial ischaemia. He had a small main pulmonary artery with extensive bilateral branch pulmonary artery narrowings well beyond the hila, some arteries almost atretic. Liver normal macro and microscopically. Chromosomes…Normal.

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CHiP NETWORK
CONGENITAL HEART INTERNATIONAL PROFESSIONALS

CareDx's HeartCare Multimodality Service Receives Medicare Coverage for Heart Transplant Surveillance

HeartCare Combines Testing Using Both AlloMap Gene Expression Profiling and AlloSure Donor-Derived Cell-Free DNA

CareDx, Inc. (Nasdaq: CDNA), a leading precision medicine company focused on the discovery, development, and commercialization of clinically differentiated, high-value healthcare solutions for transplant patients and caregivers – today announced Medicare coverage for HeartCare, a multimodality testing service that includes both AlloMap® Heart and AlloSure® Heart, in a given patient encounter, for heart transplant surveillance. Coverage is effective April 1, 2023. AlloMap Heart and AlloSure Heart are also covered by Medicare individually.

"Today is a major milestone for heart transplant care and for the use of multimodality technologies to improve patient outcomes with HeartCare," said Reg Seeto, CEO and President of CareDx. "I could not be prouder of our organization's unwavering commitment to serving patients and leading transplant innovation. I want to thank MolDX for recognizing the critical clinical value of multimodality in heart transplant surveillance."

"Medicare's coverage of HeartCare reflects the growing scientific evidence supporting its use for routine graft surveillance in lieu of a biopsy. We have witnessed a significant reduction in the need for endomyocardial biopsies in our clinical practice by incorporating paired testing with AlloMap and AlloSure, which provides complementary information about allograft health," said Jeffrey Teuteberg, MD, Professor of Medicine, Section Chief of Heart Failure, Cardiac Transplantation, and Mechanical Circulatory Support, Stanford University.

Studies showed that multimodal testing with HeartCare, including both AlloMap and AlloSure, dramatically reduced dependency on endomyocardial biopsies (EMBs).[1,2] These publications showed a reduction in biopsies with HeartCare when compared to prior use of an AlloMap-only protocol, without impacting outcomes.[1,2] These studies also showed that when using HeartCare, a negative AlloMap result that accompanied a positive AlloSure result was associated with fewer biopsies than if every AlloSure result above threshold led to a biopsy.[1,2] When both tests were negative, 99.5% of biopsies were deferred.[1,2]

"Since the introductions of AlloMap gene expression profiling and AlloSure donor-derived cell-free DNA, followed by their subsequent incorporation in ISHLT guidelines, we've seen widespread adoption of these noninvasive testing services at leading heart transplant centers in the U.S.," said Eugene DePasquale, MD, Medical Director, Heart Transplant Program, Keck Medicine, USC. "The additive value of both biomarkers will lead to a new standard of care, from routine endomyocardial biopsies to noninvasive surveillance, using HeartCare as a robust strategy for the surveillance of heart transplant recipients."

The use of HeartCare has been supported by the new International Society for Heart and Lung Transplantation (ISHLT) guidelines recommending the use of AlloMap gene expression profiling (GEP) and donor-derived cell-free DNA (dd-cfDNA), as in AlloSure, in routine heart transplant surveillance: AlloMap has been in the ISHLT guidelines since 2010 and both in the 2022 update.[3] In a guide published in the Journal of the American College of Cardiology: Heart Failure, the transition from routine invasive EMBs to a less invasive acute rejection monitoring protocol was described for clinicians.[4]

AlloMap became commercially available in 2005 and has the distinction of being the only gene expression profiling test that has been FDA cleared for use in heart transplant patients.[5] In 2020, CareDx launched HeartCare, which includes both AlloMap GEP and AlloSure dd-cfDNA, to provide a comprehensive view of organ rejection by assessing immune quiescence and graft injury. HeartCare is currently used in over one in two newly-transplanted patients and in over 90% of heart transplant centers in the U.S.[5]

AlloMap Heart, AlloSure Heart, and HeartCare are covered by Medicare under MolDX LCD L38568 and will be listed on the Palmetto GBA Dex Exchange. HeartCare is covered for the first year, starting two months post-transplant.

For more information, please visit: CareDx.com.

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