# Erişkin Doğumsal Kalp Hastalarında Kardiyovasküler Fonksiyonun Değerlendirilmesinde O2-vuru - Kalp Hızı Eğim Açısı Farkı O2-Pulse - Heart Rate Inclination Angle Difference (IAD) in Assessing Cardiovascular Function in Patients with Adult Congenital Heart Disease

**Ferit Onur Mutluer[1], Nilüfer Çetiner[2], Volkan Çamkıran[3], Alpay Çeliker[4]**

1Yeditepe Üniversitesi Hastanesi, Kardiyoloji Ana Bilim Dalı, İstanbul, Türkiye

2Koc Üniversitesi Hastanesi, Pediatrik Kardiyoloji Ana Bilim Dalı, İstanbul, Türkiye

3Göztepe Medical Park Hastanesi, Kardiyoloji Ana Bilim Dalı, İstanbul, Türkiye

4VKV Amerikan Hastanesi, Pediatrik Kardiyoloji Ana Bilim Dalı, İstanbul, Türkiye

***ÖZ***

***GİRİŞ ve AMAÇ****: Kardiyopulmoner stres testi (KPT) erişkin doğumsal kalp hastalarının (EDKH)'nin yönetiminde önemli rol oynar. Bu çalışmada amacımız, egzersize kronotropik ve inotropik yanıtları intergre eden yeni bir parametre olan O2-vuru - Kalp hızı eğim açı farkının (EAF) EDKH'nın değerlendirilmesindeki rolünün değerlendirilmesidir.*

***YÖNTEM ve GEREÇLER****: EDKH ve sağlıklı kontroller prospektif olarak bu çalışmaya dahil edilmiştir. Katılımcılara sırasıyla transtorasik ekokardiyografi ve bisiklet ergometri üzerinde rampa protokolünde KPT uygulanmıştır. Her hastada standart KPT parametrelerine ek olarak EAF hesaplanmıştır.*

***BULGULAR:*** *EDKH olan 21 hasta (ortalama yaş 28 ± 12, 14 %66 erkek) ve 79 sağlıklı kontrol (ortalama yaş 34 ± 6, %100 erkek) bu çalışmaya dahil edilmiştir. Hastalar, sağlıklı kontrollere göre önemli derecede düşük sistemik ventrikül ejeksiyon fraksiyonuna (60±8% ve 69±4%, p <.001) ve daha yüksek pulmoner arter basınçlarına (33±13 versus 21±5 mmHg, p<.001) sahipti. EDKH'de egzersiz süresi (7.4±4 ve 10.1±2.3 dakika, p=.007), maksimal oksijen tüketimi (VO2max) (1524±614 ve 2398±391, p<.001) ve EAF (-5.9±13.7 ver 1.2±13.1 °) düşükken dakika ventilasyon/dakika karbondioksit ventilasyonu (VE/VCO2) yüksekti (31±5.1 ve 28.8±3.3, p=.030). Univariable analizde, yaş (r=0.236,p=.18), EDKH tanısı (r=-0.205,p=.41), NT-proBNP (r=-0.870,p=.002), VO2max (r=0.334, p=.001) ve VE/VCO2 (r=-0.273, p=.006) EAF ile ilişkiliydi. Yaş, EDKH tanısı, LVEF ve VO2max'den bağımsız olarak EAF VE/VCO2 ile ilişkiliydi (β=-1.2, CI -1.892--0.508, R2=0.242).*

***TARTIŞMA ve SONUÇ:****Bu çalışmada, yeni bir KPT parametresi olan EAF'nin EDKH'de kardiyovasküler fonksiyonun değerlendirmesinde potansiyel bir rolü olabileceğini gösterdik. Bu rol daha büyük kohortlarda araştırılmalıdır****.***

***Anahtar Kelimeler:*** *kardiyopulmoner stres test, erişkin doğumsal kalp hastalığı, egzersiz testi*

***ABSTRACT***

***INTRODUCTION:*** *Cardiopulmonary stress test (CPT) plays important role in management of adult congenital heart disease (ACHD). Our aim in the current study is to investigate the role of a novel CPT parameter, O2-pulse-Heart rate inclination angle difference (IAD), that integrates chronotropic and inotropic responses to exercise, in the assessment of ACHD.*

***METHODS:*** *ACHD patients and healthy controls were enrolled prospectively for this observational study. Participants underwent transthoracic echocardiography and CPT on a bicycle ergometer with a ramp protocol, respectively. IAD was calculated in addition to standard CPT parameters in each patient.*

***RESULTS:*** *Twenty-one patients with ACHD (mean age: 28 ± 12 years, 14 male, 66 %) and 79 healthy controls (mean age: 34 ± 6, male 100 %) were included in the study. Patients had significantly lower systemic ventricle ejection fraction (60±8% versus 69±4%, p <.001) and higher systolic pulmonary artery pressure (33±13 versus 21±5 mmHg, p<.001). Execise duration (7.4±4 versus 10.1±2.3 minutes, p=.007), maximal oxygen consumption (VO2max) (1524±614 versus 2398±391, p<.001) and IAD (-5.9±13.7 versus 1.2±13.1°) were lower while VE/VCO2 was higher (31±5.1 versus 28.8±3.3,p=.030) in ACHD patients. In univariate analysis, age (r=0.236,p=.18), diagnosis of ACHD (r=-0.205,p=.41), NT-proBNP (r=-0.870,p=.002), VO2max (r=0.334,p=.001) and VE/VCO2 (r=-0.273, p=.006) were associated with IAD. IAD was independently associated with VE/VCO2 when adjusted by age, diagnosis of ACHD, LVEF and VO2max (β=-1.2, CI -1.892--0.508, R2=0.242)*

***DISCUSSION AND CONCLUSION****: In this study, we demonstrated that the novel CPT parameter IAD might have a potential role in assessing cardiovascular function in patients with ACHD. This role should be further investigated in larger cohorts.*

***Keywords:*** *cardiopulmonary stress test, adult congenital heart disease, exercise test*

***İletişim / Correspondence:***

*Dr. Ferit Onur Mutluer*
*Yeditepe Üniversitesi Hastanesi, Kardiyoloji Ana Bilim Dalı, İstanbul, Türkiye*
*E-mail: onurmd@gmail.com*
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*Doi: 10.5505/ktd.2021.84669*
*Ferit Onur Mutluer: 0000-0001-9114-9529*
*Nilüfer Çetiner: 0000-0001-6827-5527*
*Volkan Çamkıran 0000-0003-1908-0648:*
*Alpay Çeliker: 0000-0001-7887-1963*

## INTRODUCTION

As a consequence of advances in surgical and interventional treatments, ACHD population has been continuously growing (1). Despite improvements in management, this patient population is not only at risk of developing long-term complications but also due to restrictions in daily activity, carries a risk of developing acquired heart disease in the long run (2). Previous studies demonstrated that majority of the ACHD patients has a false perception of good functional status that is inconsistent with their objectively assessed functional status (3, 4). Improved risk stratification and objective assessment of the functional status is for this reason of paramount importance in this patient cohort.

CPET emerged as a diagnostic modality that allows assessment of the cardiovascular, f the underlying malformation. It was previously shown that, in addition to being an objective correlate of functional status at maximal exercise, this parameter also has prognostic significance (7). O2-pulse is a surrogate of stroke volume, and is found by dividing the instantaneous VO2 by instantaneous HR. While O2-pulse time curve provides information on inotropic response to exercise, HR-time curve is important in determining the chronotropic response. These two curves together demonstrate cardiovascular response to exercise stress and often assessed together.

O2-pulse curve is often found depressed in situations in which stroke volume is fixed or decreased with exercise (ie. ischemia, aortic stenosis, Fontan circulation) and the O2-pulse curve might beecome steeper when there is chronothropic incompetence. HR response to exercise often becomes blunted when there is chronotropic incompetence due to autonomic dysfunction, sinus node dysfunction, beta blockade or inappropriate pacemaker rate response (8). Although both curves are often represented on the 9 panel plot in CPET analyses, a parameter integrating these two parameters regarding to two important aspects of cardiovascular function is lacking.

Our aim in the current study is to determine the utility of a novel CPET parameter O2pulse-HR curve inclination angle difference (IAD) in assessing the dynamic integrated cardiovascular response to exercise in patients with ACHD.

pulmonary, musculoskeletal and metabolic systems in an integrated and dynamic manner (5). This test occupies a central role in contemporary management of ACHD and provides invaluable information with regard to functional status, long-term prognosis, need for medication change or requirement for a transcatheter or surgical intervention. There are several different parameters obtained from CPET. In addition to aiding in determining the functional status, these parameters allow identifying the etiology underlying the functional limitation in ACHD patients (6).

Maximal VO2 consumption (VO2max) is the most commonly utilized parameter with CPET and is a surrogate of cardiac output. VO2max is decreased in varying degrees in patients with ACHD and the degree of the decrease is often correlated with the complexity and severity o

## MATERIALS AND METHODS

### Study population

This prospective cohort study was conducted in 2015 on ACHD patients admitted to our ACHD excellence center and underwent CPET as part of their management. Healthy adult male patients who admitted to our cardiology outpatient clinic for another clinical research project acted as the control group. These patients were recruited with an advertisement and consisted of participants without cardiovascular symptoms, and had normal laboratory and cardiovascular work-up results The decision to perform a CPET was made by the physician on the clinical grounds. Subjects were excluded when they met any of the following criteria: uncontrolled arrhythmia or heart failure, inability to perform the exercise test or noncompliance with the bicycle ergometry, a diagnosis of chronotropic incompetence with inability to increase heart rate to 85 % of the predicted maximal heart rate during exercise. Patients were classified according to the anatomy-physiology classification proposed in the latest ACC-AHA ACHD guidelines (9). The study was approved by the local ethical committee. Informed consent was obtained from the participants prior to enrollment in the study. The study was conducted in accordance with the Helsinki declaration.

**Clinical assessment**

The standard clinical assessment included physical examination, ECG, and standard transthoracic echocardiography. An extended protocol with sequential segmental analysis was implemented for transthoracic echocardiography, as recommended by the literature (10).

**Cardiopulmonary Exercise Stress Testing**

Patients underwent symptom-limited CPET (Carefusion, Vyntus CPX, Germany) with a ramp protocol on bicycle ergometer. Continuous respiratory gas, ECG and sphygmomanometer analysis were performed during the exercise protocol. An exercise protocol consisting respectively of 3 minutes of rest, exercise, 3 minutes of active recovery at the rate of the starting workload and 7 minutes of recovery was used. Exercise ramp protocol was set up with 15 Watt/min increments for healthy controls and 7, 10 or 15 Watt/min increments for ACHD patients, according to anatomic and physiologic severity of the lesions, at physician's discretion. A pedalling rate of 60-80 per minute was assured. Spirometry analysis was performed before and after the exercise protocol.

The endpoints for symptom-limited exercise stress test were: attainment of >85 % of the maximal heart rate, a respiratory exchange ratio of >1.1 or inability of the patient to continue with the protocol due to exhaustion. The analysis output was represented according to the 9-panel plot. A modification was performed to represent both HR and O2-pulse on the same panel (11). VO2max, VO2/kg, VE/VCO2, O2-pulse and HR values were extracted to standard spreadsheets for calculation of the study parameter IAD. O2-pulse-HR curve angle difference was calculated from the instantaneous O2pulse and heart rate values at the beginning of the exercise protocol and at the beginnnig of the active recovery period. The inclination angles of the HR-time and O2-pulse time curves were calculated from the slopes with the reverse tangent function. IAD was calculated by subtracting the HR inclination angle from O2-pulse inclination angle (Figure 2B).

**Statistical analysis**

The data distribution was tested using histograms and the Shapiro-Wilk test. Continuous data were presented as mean ± standard deviation (SD). Categorical data was presented as frequencies and percentages. For comparison of normally distributed continuous between two groups with the Student's t-test. For comparison of frequencies the $\chi 2$-test was used. Univariable analysis was performed with Spearman's correlation and univariable linear regression analysis. Parameters for multivariable analysis were selected at a significance of p<.20. Multivariable linear regression analysis was used for determining independent predictors of IAD. Two-tailed tests were used for correlation analysis. All statistical analyses were performed using SPSS statistics version 26 and Graphpad Prism 9. A p value of less than 0.05 was considered statistically significant.

## RESULTS

**Study population**

Twenty-one patients with ACHD and 79 healthy controls were enrolled in this study (mean age = 28 □ 12 versus 34 □ 6 years, p=.032, 33 % versus 100 % male, p <.001). While 7 of the patients (24 %) had an anatomically severe lesion, 4 patients (13 %) had severe physiology according to AHA/ACC classification. Systemic ventricle ejection fraction (EF) was lower ( 60□8 % versus 69□4 %, p<.001) and systolic pulmonary artery pressure was higher (33□ 13 versus 21□5 mmHg) in patients. Baseline characteristics of the study participants are demonstrated in Table 1. The detailed distribution of cardiac lesions in the study patients is demonstrated in Supplementary Table 1.

**Cardiopulmonary exercise stress testing parameters**

CPET parameters are demonstrated in Table 2. Exercise duration was lower (7.4□4 versus 10.1□2.3 minutes, p=.007) in ACHD patients, as well as VO2max (1524□614 versus 2398□391 ml/min, p<.001) and VO2max indexed to body weight (VO2max/kg) (24□6 versus 28.8□3.3, p<.001). VE/VCO2 was significantly higher (31□5.1 versus 28.8□3.3, p=.020) and IAD was

significantly lower (-5.9 □ 13.7 □ versus 1.2 □ 13.1 □).

**Predictors of IAD**

Table 1 and Figure 1 demonstrate results of univariable analysis. Age (r=0.236, p=.18), diagnosis of ACHD (r=-0.236, p=.41), NT-Pro-BNP (-0.870, p=.002), VO2max (r=0.334, p=.001), VE/VCO2 (-0.273, p=.006) significantly correlated with IAD in univariable analysis. VE/VCO2 independently predicted IAD when adjusted by age, diagnosis of ACHD, EF, and VO2max (β=-1.2, 95 % CI: -1.892--0.508, p=0.001). NT-proBNP values were available only in 9 patients, and unavailable in healthy controls. This parameter was excluded from the multivariable model for this reason

**Table1. Baseline characteristics of the study participants**

| | Patients (n=21) | Controls (n=79) | p |
|---|---|---|---|
| **Age** | **28 ± 12** | **34 ± 6** | **.032** |
| **Gender (Male, n[%])** | **14 (33 %)** | **79 (100 %)** | **<.001** |
| **Body Mass Index** | 22.7 ± 4.2 | 21 ± 1 | .079 |
| **Anatomic Severity Classification** | | | |
| **Group 1**<br>**Group 2**<br>**Group 3** | (11, 38 %)<br>(11, 38 %)<br>(7, 24 %) | -<br>-<br>- | |
| **Physiologic Severity Classification** | | | |
| **I**<br>**II**<br>**III**<br>**IV** | *10 (35 %)*<br>*8 (29 %)*<br>*7 (23 %)*<br>*4 (13 %)* | -<br>-<br>-<br>- | |
| **ECG** | | | |
| **Conduction disturbance**<br>**None**<br>**LBBB**<br>**RBBB**<br>**Pre-excitation** | <br>15<br>4<br>11<br>1 | <br>79<br>0<br>0<br>0 | <.001 |
| **Resting Heart Rate (bpm)** | 88 ± 16 | 94 ± 13 | .081 |
| **Permanent Pacemaker**<br>**Pacemaker dependent rhythm** | 5 (16.1 %)<br>0 | 0<br>0 | |
| **ECHOCARDIOGRAPHY** | | | |
| **Systemic Ventricle Ejection Fraction** | *60 ± 8* | *69 ± 4* | *<.001* |
| **Systolic Pulmonary Artery Pressure** | *33 ± 13* | *21 ± 5* | *<.001* |
| **NT-ProBNP (ng/mL)** | *25 (13-143)* | - | |

***Supplementary table 1. Distribution of the patients within the anatomical and physiological subgroups***

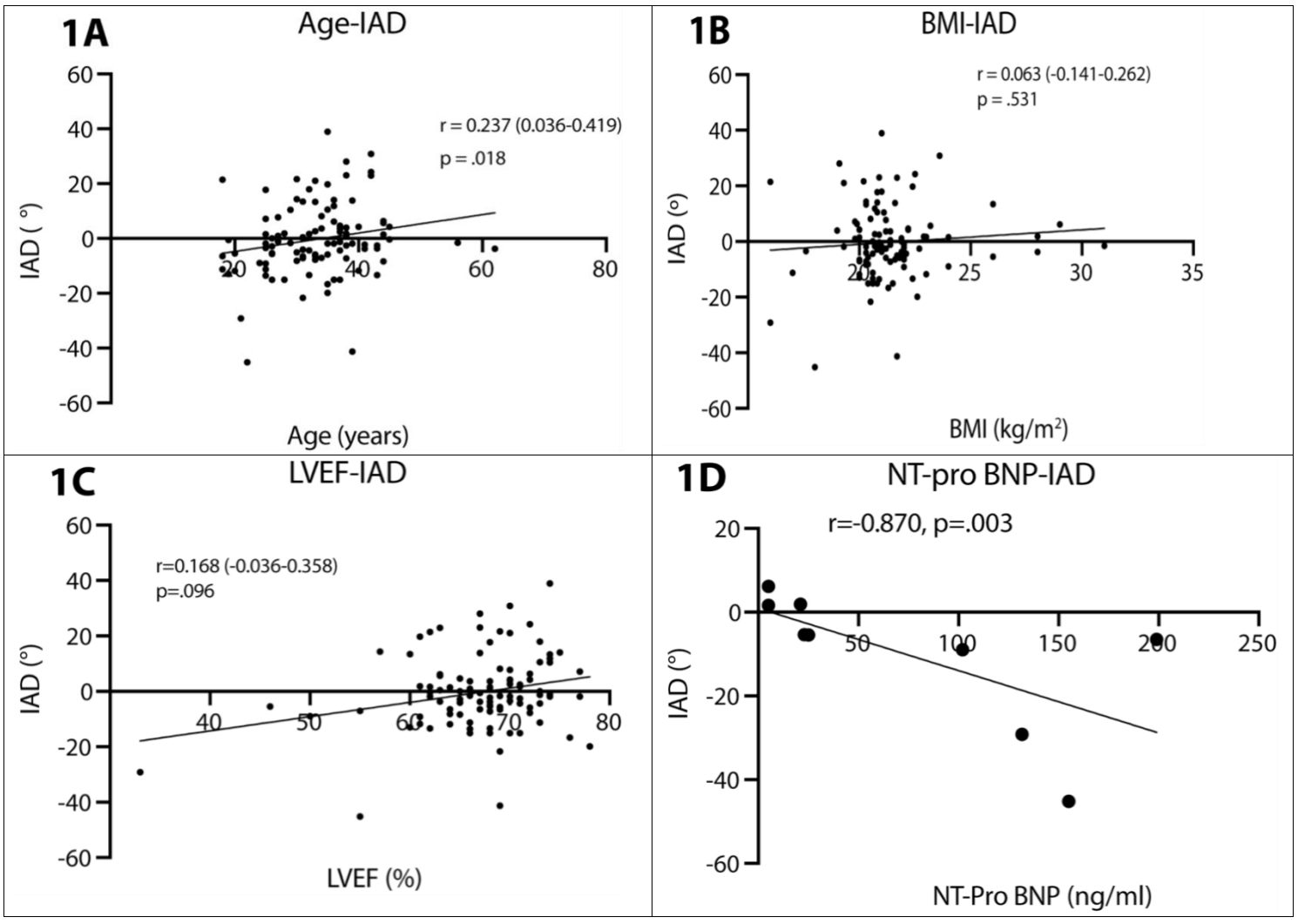
***Table 2. Cardiopulmonary exercise testing parameters in patients and controls***

| | *Patients* | *Controls* | *p* |
|---|---|---|---|
| ***Exercise Duration (minutes)*** | *7.4 ± 4* | *10.1 ± 2.3* | *.007* |
| ***Maximal Heart Rate (bpm)*** | *157 ± 23* | *161 ± 18* | *.339* |
| ***SaO2 at peak exercise (%)*** | *98 ± 5* | *97 ± 9* | *.939* |
| ***VO2max (ml/min)*** | *1524 ± 614* | *2398 ± 391* | *<.001* |
| ***VO2max/kg (ml/min.kg)*** | *24 ± 6* | *31 ± 6* | *<.001* |
| ***VE/VCO2*** | *31 ± 5.1* | *28.8 ± 3.3* | *.020* |
| ***IAD(°)*** | *-5.9 ± 13.7* | *1.2 ± 13.1* | *.030* |

***SaO2: Arterial oxygen saturation, VO2max: maximal oxygen consumption, VE: minute ventilation, IAD: VO2p-HR inclination angle difference***

*Table 3. Predictors of O2 pulse- heart Rate inclination angle difference*

| | r | p | USβ | p | β | p |
|---|---|---|---|---|---|---|
| **Age (years)** | **0.236** | **.018** | **0.335** | **.050** | 0.307 | .069 |
| **Sex (male)** | 0.025 | .804 | 3.461 | .514 | | |
| **BMI (kg/m2)** | 0.063 | .532 | 0.522 | .396 | | |
| **Patients (versus controls)** | **-0.205** | **.041** | **-7.106** | **.030** | 8.744 | .223 |
| **Anatomy classification** | -0.085 | .474 | -2.856 | .498 | | |
| **Physiology classification** | 0.028 | .904 | -0.826 | .790 | | |
| **Systolic Blood Pressure (mmHg)** | -0.41 | .685 | 0.017 | .878 | | |
| **NT-proBNP (ng/ml)** | **-0.870** | **.002** | **-0.149** | **.051** | | |
| **LVEF (%)** | **0.168** | **.096** | **.514** | **.014** | 0.119 | .623 |
| **SPAB (mmHg)** | 0.108 | .295 | -0.34 | .834 | | |
| **VO2max (ml/min)** | **0.334** | **.001** | **.008** | **.001** | 0.006 | .055 |
| **VO2/kg max (mil/min.kg)** | **0.142** | **.158** | **0.434** | **.041** | | |
| **VE/VCO2** | **-0.273** | **.006** | **-1.412** | **<.001** | **-1.200** | **.001** |
| **SAO2max (%)** | 0.033 | .753 | .189 | .234 | | |



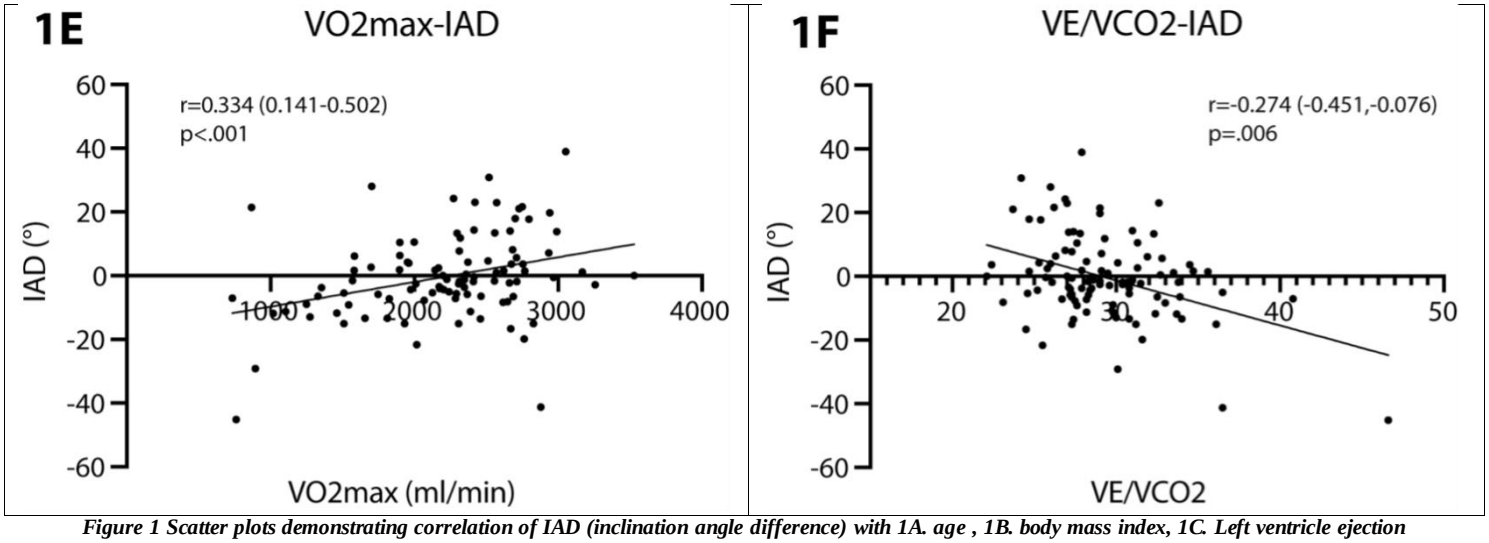



***Figure 1 Scatter plots demonstrating correlation of IAD (inclination angle difference) with 1A. age , 1B. body mass index, 1C. Left ventricle ejection fraction, 1D. NT-Pro-BNP, 1E. VO2max, 1F. VE/VCO2. BMI: body mass index, LVEF: left ventricle ejection fraction, VO2max: maximal oxygen consumption, VE/VCO2: maximal ventilation/maximal CO2 expiration***

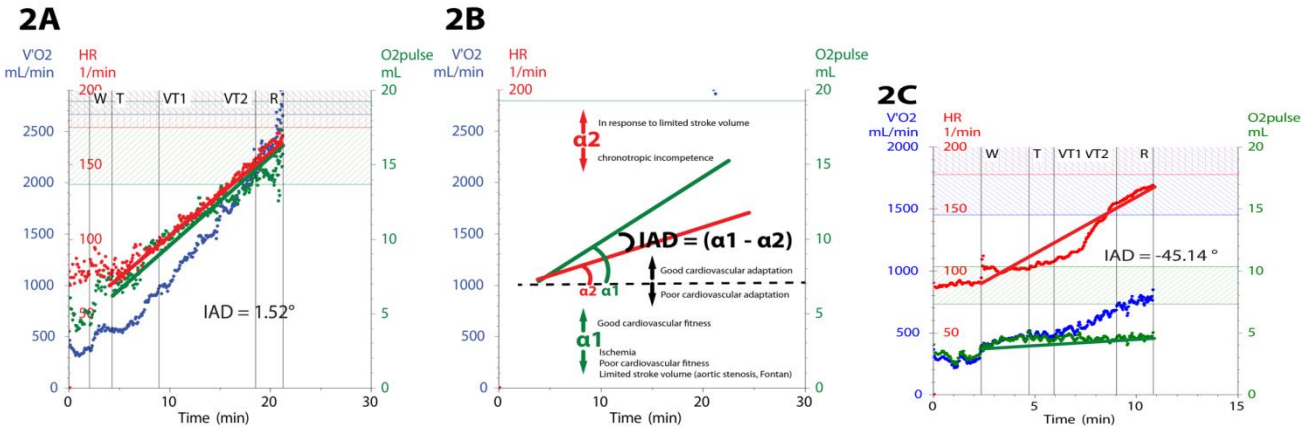



***Figure 2A. O2pulse-Heart rate curves in a patient with a small ASD closed with a device, Figure 2B. demonstration of interrelation of inclination angles of O2 pulse (α1), heart rate (α2) and inclination angle difference (IAD), Figure 2C. O2pulse-Heart rate curves in a patient with Fontan circulation.***

## DISCUSSION

The findings from this study could be summarized as follows: IAD was decreased in ACHD patients compared with healthy controls. This novel parameter showed moderate level correlation with age, EF, VO2max and VE/VCO2 in univariate analysis. Additionally, it was associated with VE/VCO2 when adjusted by age, diagnosis of ACHD, EF, and VO2max. IAD allows integratively assessing cardiovascular inotropic and chronotropic response to exercise and might have additional role in management of ACHD.

ACHD patients have limited exercise capacity despite advances in management. This limitation is due to cardiovascular, pulmonary, musculoskeletal, or metabolic causes. In many patients, limited

exercise capacity is the result of a combination multiple factors. The patients often report falsely high functional class that is inconsistent with their objective findings (2). Conventional treadmill exercise stress test allows estimation of the presence and extent of the exercise limitation. However, management decisions are often made

based on the pathophysiology causing the limitation. CPET not only objectively quantifies the limitation, but also allows delineation of these pathophysiological mechanisms.

Among the established and validated CPET parameters, VO2max quantifies the overall cardiovascular exercise capacity as a function of cardiac output and arteriovenous difference in oxygen concentration. Any factor resulting in limited cardiac output, such as residual defects, or systolic dysfunction, failure to increase cardiac output in response to exercise all result in decreased VO2max levels. The two determinants of cardiac output, stroke volume and heart rate could be assessed separately from the O2-pulse and heart rate curves, respectively (12). Flattening of the O2pulse was previously shown to be predictive of myocardial ischemia (13). In studies on ACHD patients, however, when values were compared between patients with complete versus incomplete repair, the values didn't reach statistical significancen (14). Additionally, O2pulse might be unexpectedly high in patients with chronotropic incompetence and might be falsely low in patients with low oxygen extraction at the tissue level. As a result the use of O2 pulse in ACHD patients is relatively limited (6).

It is recommended that O2pulse should be assessed together with heart rate, because of the inter-relationship of these 2 parameters (8). IAD provided the assessment of interrelation of these 2 determinants of the cardiovascular function in this study. In this manner inotropic response was successfully assessed in relation to chronotropic response. This approach is important, because inotropic and chronotropic response to exercise are intertwined, impairment in one results in compensatory changes in the other. Provided that the chronotropic response is not compromised, we have shown that IAD correlated well with the validated parameters of ventilation perfusion efficiency, VE/VCO2 and VO2 max as well as EF. This finding suggests that not only heart rate or stroke volume response separately, but interrelation of these two might be important in determining the clinical condition of the patients with ACHD. Preserved IAD likewise might define a subset of ACHD patients with good myocardial adaptation to workload. That is, blunted myocardial inotropic response relative to heart rate (Figure 2C) might be associated with poor outcomes when compared with a patient with a preserved response (Figure 2A). This myocardial adaptation might also have prognostic implications in the long-term follow-up. This potential should be explored in larger cohorts of patients with follow-up data.

**Limitations of the study**

This study was performed on a small ACHD cohort consisting of a heterogenous mixture of patients from different severity classes. Similarly, healthy controls only consisted of male patients. Thus it was impossible to assess the role of sex on the distribution of the study parameter. Lastly, only patients with intact chronotropic response was enrolled in this study, a correction might be needed for patients with chronotropic incompetence. This should be separately investigated.

## CONCLUSION

IAD is a novel CPET parameter that assesses inotropic and chronotropic response to exercise at the same time. The significance and prognostic role of thies parameter should be assessed in further studies.

**Ethics Committee Approval:** Ethical approval was obtained.

**Conflict of Interest:** There is no conflict of interest.

**Funding:** There is no financial support.

**Informed Consent:** This a retrospective study

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