

Reliability of Peak Exercise Stroke Volume Assessment by Impedance Cardiography in Patients with Residual Right Outflow Tract Lesions After Congenital Heart Disease Repair

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Abstract Global ventricular response to exercise may be useful in follow-up of patients with residual right outflow tract lesions after congenital heart disease repair. In this context, impedance cardiography is considered accurate for stroke volume (SV) measurement during exercise testing, however, to date, only partial assessment of its reliability has been reported. We retrospectively evaluated relative and absolute reliability of peak SV by impedance cardiography during exercise using intraclass correlation (ICC) and standard error of measurement (SEM) in this population. Peak SV was measured in 30 young patients (mean age 14.4 years \pm 2.1) with right ventricular outflow tract reconstruction who underwent two cardiopulmonary exercise tests at a mean one-year interval. SV was measured using a signal morphology impedance cardiography analysis device (PhysioFlow[®]) and was indexed to body surface area. ICC of peak indexed SV measurement was 0.80 and SEM was 10.5%. High heterogeneity was seen when comparing patients according to peak indexed SV; in patients with peak SV $<$ 50 ml/m² (15 patients), ICC rose to 0.95 and SEM dropped to 2.7%, while in patients with a

peak SV $>$ 50 ml/m² relative and absolute reliability decreased (ICC = 0.45, SEM = 12.2%). Peak exercise SV assessment by a PhysioFlow[®] device represents a highly reliable method in patients with residual right outflow tract lesions after congenital heart disease repair, especially in patients with peak SV $<$ 50 ml/m². In this latter group, a peak SV decrease $>$ 7.3% (corresponding to the minimum “true” difference) should be considered a clinically-relevant decrease in global ventricular performance and taken into account when deciding whether to perform residual lesion removal.

Keywords Congenital heart disease · Reliability · Cardiopulmonary exercise test · Stroke volume · Signal morphology impedance cardiography

Introduction

Pulmonary regurgitation and stenosis are common residual lesions reported in patients after tetralogy of fallot repair or in patients with other congenital heart diseases (CHD) undergoing right ventricular outflow tract reconstruction. To ensure pulmonary valve replacement is performed before the occurrence of irreversible myocardial damage, cardiac evaluation of these patients is focused on right ventricle function assessment, particularly, in terms of ventricular volumes and ejection fraction on magnetic resonance imaging (MRI). However, resting right ventricular function parameters are load-dependent; and thus they do not only reflect the intrinsic contractility of the right ventricle in patients with pure pulmonary regurgitation.

Right ventricular response to exercise may represent an additional tool to evaluate intrinsic ventricular contractility. We recently highlighted the usefulness of maximal

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oxygen pulse, a surrogate of global ventricular response, in addition to resting MRI imaging, when deciding the timing of pulmonary valve replacement in patients with isolated pulmonary regurgitation [1]. However, the value of this measure is limited by its dependency on both peak stroke volume (SV) and peak arteriovenous oxygen difference. Direct noninvasive measurement of systemic SV at the peak of cardiopulmonary tests represents a more reliable indicator of global ventricular response. We thus opted to measure systemic SV by signal morphology impedance cardiography analysis (PhysioFlow[®]) during cardiopulmonary exercise testing. As our studied population includes patients in a growth phase, the measure was indexed to body surface area. Peak indexed systemic SV reflects global ventricular performance and is affected by any degree of right ventricular function decrease. As a small degree of interdependence between SV and heart rate may be observed [2], cardiac index was also considered. This noninvasive method is well correlated with the Fick method in most cardiac diseases and its reliability has already been evaluated in normal adult and pediatric populations at maximal effort [3, 4]. Nonetheless, it is important to keep in mind that this is only a partial assessment of reliability, since the issue of absolute reliability was not addressed. Absolute reliability provides an index of the expected trial-to-trial noise in the data. This information is crucial in the decision-making process, since it enables clinicians to determine whether an observed change during follow-up falls within the range of measurement error or whether it reflects a true clinically-relevant change. The aim of this study was thus to provide an exhaustive assessment of the reliability of peak indexed SV and peak cardiac index in patients with right ventricular outflow tract lesions, in order to improve its clinical application in the context of pulmonary valve replacement.

Methods

Patients

Patients undergoing CHD repair that involved right ventricular outflow and who had two consecutive cardiopulmonary exercise tests with an interval of approximately one year were considered for inclusion. Patients were excluded if they had an additional residual cardiac lesion or left ventricular dysfunction, if they performed specific exercise training between assessments, received additional therapy, or displayed any changes in their cardiac conditions at rest at rest during the one year of follow-up.

Cardiopulmonary Exercise Test

Cardiopulmonary exercise tests were performed using an ergocycle (Ergoline, Germany). Initial mechanical power was set at 15 watts and increased by 10–15 watts every 60 s until volitional exhaustion. Oxygen uptake (VO_2) and related parameters were determined continuously on a breath-by-breath basis using an automated cardiopulmonary exercise system (Sensor Medics system 290, Anaheim, California), calibrated according to the manufacturer's recommendations. Measurements were displayed every 20 s during the test. As proposed by Duncan et al., the primary criterion for reaching maximal VO_2 was a plateau in VO_2 despite an increase in power output [5]. In the absence of a plateau, a secondary criterion included a respiratory exchange ratio of 1.10 or greater, and a maximal heart rate $> 90\%$ of theoretical maximal heart rate [5]. Reference values were based on Wasserman et al. [6].

Noninvasive Stroke Volume Measurement

Cardiac output (Q) and SV were determined noninvasively during the exercise test using a thoracic bioelectrical impedance device (PhysioFlow[®], PF-05 Lab1, Manatec Biomedical). This method has been validated in both adults [3, 7] and children [4]. The peak SV was defined as the SV value measured at the peak of effort and was indexed to body surface area. The PhysioFlow[®] principle (Signal-Morphology-ICGTM) assumes that variations in impedance (DZ) of a high-frequency (75 kHz), low-magnitude (1.8 mA) alternating current across the thorax during cardiac ejection, result in a specific waveform that can then be used to calculate SV. DZ thus describes fluid velocity and is a smooth wave that corresponds with the systole as indicated by ECG tracing. The first mathematical derivative of DZ (dZ/dt) describes fluid acceleration, and the peak of DZ should correspond to the baseline of dZ/dt . PhysioFlow[®] relies on a morphological analysis of the dZ/dt signal and the algorithm does not require basal thoracic impedance measurement (Z0). The electrodes were positioned on the neck, the back at the level of the xiphoid on the left-hand sided of the spine, the left-hand side lower ribs and the right clavicle. Systolic and diastolic blood pressures were measured at rest in a seated position, and entered in the autocalibration process of the Physioflow[®].

Statistical Analysis

Standard statistical methods were used for the calculation of means and standard deviations. Normal Gaussian distribution of the data was verified by the Shapiro–Wilk test, and homoscedasticity by a modified Levene Test. Systematic bias, which refers to a general trend for

measurements to be different in a particular direction between repeated tests [8], was assessed with a student's *t* test for dependent samples. The magnitude of the difference was assessed by the Hedges' *g* (*g*), and was considered small ($0.2 < |g| \leq 0.5$), moderate ($0.5 < |g| \leq 0.8$), or large ($|g| > 0.8$) [8]. Relative reliability, which represents the degree to which individuals maintain their position in a sample with repeated measurements [9], was assessed with the intraclass correlation coefficient (ICC model [1, 2]). Absolute reliability, which is the degree to which repeated measurements vary for individuals, was assessed with the standard error of measurement (SEM). The ICC and SEM were computed from the breakdown of a two-way ANOVA (trials x subjects) with repeated measures, as presented elsewhere [10]. We considered an ICC over 0.90 as very high, between 0.70 and 0.89 as high and between 0.50 and 0.69 as moderate [11]. Currier et al. proposed that an ICC value higher than 0.80 was acceptable for clinical practice [12]. SEM can also be used to determine the minimum difference to be considered real (MD), which represents the limit under which the observed difference is within what we might expect to see in repeated testing purely due to noise in the measurement [13]. Statistical significance was set at $p < 0.05$ for all analyses. All calculations were made with Statistica 6.0 (Statsoft, Tulsa, OK).

Results

A total of 30 patients were eligible. Cardiac, anthropometric, and physiological characteristics of the patient population are presented in Tables 1 and 2. The mean interval between the two exercise tests was 1.2 years \pm 0.4. Mean ages at the first and second measures were 14.4-years-old \pm 2.1 and 15.6-years-old \pm 2.1, respectively (Table 2). Parameters of cardiopulmonary exercise testing and reliability of SV at the two time points are presented in Tables 2 and 3. No time effect (or systematic bias) was apparent for any of the exercise test parameters ($p > 0.05$; $-0.21 \leq g \leq 0.26$) (Table 2).

Relative reliability of the overall sample was high for both peak indexed SV and peak cardiac index (ICC = 0.80 for both). However, when analyzing patients according to the peak SV, relative reliability was very high (ICC > 0.87) in patients with a peak indexed SV < 50 ml/m² (*N* = 15), while it was poor (ICC < 0.50) in patients with a peak indexed SV > 50 ml/m² (*N* = 15), especially in patients with SV \geq 70 ml/m² (Table 3; Fig. 1).

Absolute reliability of the overall sample ranged from 10.5% (peak indexed SV) to 13.9% (peak cardiac index). Once again, we found a high heterogeneity according to the peak indexed SV, since SEM was large (from 12.2 to

Table 1 Cardiac characteristics of the population

Population (30 patients)	
Initial congenital heart defect	
Tetralogy of fallot	15
Tetralogy of fallot with pulmonary atresia	9
TGA, VSD and pulmonary stenosis	3
Left ventricular outflow tract obstruction	2
Pulmonary atresia	1
Type of RV outflow tract repair	
Plasty/reconstruction	16
RV-PA conduit	10
Secondary pulmonary valve replacement	4
Residual lesions	
Pulmonary stenosis with RV pressure > 50 mmHg	4
Moderate to severe pulmonary regurgitation	11
Mixed lesion	10
None	5

PA pulmonary artery, *RV* right ventricle, *TGA* transposition of the great arteries, *VSD* ventricular septal defect

16.3%) in patients with higher values, while it was acceptable in patients with low peak SV (2.7 to 7%). This difference inevitably impacted the MD, since the observed difference required in order to exceed the noise in the measurement during repeated testing, ranged from 7.3 to 33.6% for peak indexed SV, and from 21.1 to 45.2% for peak cardiac index (Table 3).

Discussion

Noninvasive SV measurement at peak exercise may be a useful clinical tool for detecting right ventricular dysfunction in patients with volumic and/or barometric overload. High reliability is essential for clinical application of such a technique. Our study demonstrated high reliability in the overall population of patients with residual right outflow tract lesions after CHD repair (ICC = 0.80), and notably in the group of patients with peak SV below 50 ml/m² (ICC = 0.95). This result is in agreement with a previously published study by Shultz et al. This group showed that PhysioFlow[®] displays high relative reliability for evaluating SV in light-to-moderate intensity exercise (ICC = 0.896, $p < 0.05$) with a small difference between visits (mean difference $-2.93 \text{ ml} \pm 9.90$) [14]. In a more recent study, Velsman et al. evaluated the reproducibility of peak SV in an exercise test in 20 children [4]. In their study, when three tests were analyzed together, typical error expressed as a coefficient of variation was 9.3% with an ICC of 0.86.

Table 2 CPET parameters

	Test 1 (mean ± SD)	Test 2 (mean ± SD)	Hedge's g
Patients characteristics			
Age	14.4 ± 2.1	15.6 ± 2.1 ^a	0.57
Weight	48.3 ± 14	51.8 ± 12.6	0.48
Height	154.1 ± 31.7	164.2 ± 10.8	0.43
Peak exercise CEPT parameters			
Load (W)	66 ± 17	70 ± 13	0.26
VO ₂ (ml min/Kg)	1.50 ± 0.43	1.59 ± 0.42	-0.21
VO ₂ (% TV)	74 ± 13	72 ± 17	-0.13
HR (b/min)	164 ± 26	165 ± 23	-0.04
HR (% TV)	79 ± 13	80 ± 11	0.08

VO₂ oxygen uptake, HR heart rate, %TV percent of theoretical value

^aDifferent from test 1 (p < 0.05)

Table 3 Reliability of peak cardiac index and peak indexed stroke volume

	Test 1 (mean ± SD)	Test 2 (mean ± SD)	Hedge's g	ICC	SEM (%)	MD (%)
All patients (n = 30)						
Peak SV (ml/m ²)	53.6 ± 12.8	52.8 ± 13.2	-0.06	0.80	10.5	28.9
Peak CI (L/mn/m ²)	8.7 ± 2.7	8.6 ± 2.3	-0.04	0.80	13.9	38.2
Patients with peak SV ≤ 50 ml/m ² (n = 15)						
Peak SV (ml/m ²)	44.1 ± 4.7	43.6 ± 5.2	-0.1	0.95	2.7	7.3
Peak CI (L/mn/m ²)	7.2 ± 1.5	7.0 ± 1.3	-0.08	0.87	7	21.1
Patients with peak SV ≥ 50 ml/m ² (n = 15)						
Peak SV (ml/m ²)	63.1 ± 10.2	61.8 ± 11.2	-0.12	0.45	12.2	33.6
Peak CI (L/mn/m ²)	10.5 ± 2.4	10.3 ± 1.7	-0.09	0.50	16.3	45.2

There is no statistical difference between test 1 and test 2

CI cardiac index, ICC Intraclass correlation coefficient, MD minimum difference to be considered real, PU parameter unit, SEM standard error of measurement, SV indexed stroke volume

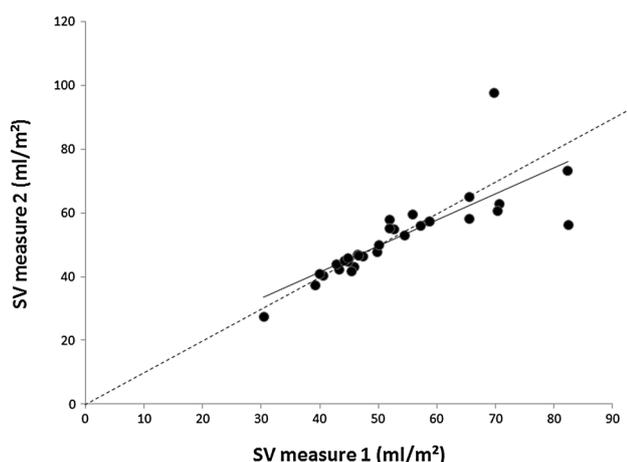


Fig. 1 Relationship between the two measures of peak SV. Correlation coefficient (Pearson test) $r = 0.80$, $p < 0.0001$; dotted line: identity line; solid line: regression line

Among other available methods for detecting right ventricular dysfunction, the Fick principle is currently the gold standard [15]. However, as an invasive technique (such as requiring hemodynamic catheterization), this method cannot always be used in clinical practice because rare but serious complications may develop [16]. Stress echocardiography and exercise/stress MRI are noninvasive options for left SV response assessment. Recent evaluations of reproducibility of exercise echocardiography in small patient cohorts have reported ICCs ranging from 0.91 to 0.94 for Doppler-determined SV in children and adults [17, 18]. While these values are slightly higher than those observed in our overall population, they are comparable with the ICC of our population with SV < 50 ml/m². SV measurement by stress MRI and echocardiography has also demonstrated good reliability [19], although to our knowledge, ICCs have not been reported in the literature for these methods. Nonetheless, these investigations do not permit maximal effort, and unavailability of stress MRI

equipment, a limited acoustic window, and difficulties in Doppler alignment limit their use in the clinic as previously noted [20]. Other noninvasive methods have been recently developed including a CO₂ rebreathing method although this has lower reliability than impedance cardiography with the PhysioFlow[®] [4]. This PhysioFlow[®] device has the advantages of enabling evaluation of SV during maximal exercise in an upright position and portability, has lower costs, and requires low technical expertise to acquire the results [4]. It demonstrated good accuracy compared with the Fick method during exercise in healthy subjects [3, 7] and in patients with cardiac failure [21], and also compared with the thermo-dilution method in patients with pulmonary hypertension [22]. One study showed a significant difference at rest between Fick method and Physioflow[®] device in young patients with CHD [23], however, the population included a very heterogeneous age (ranging from 0.4 to 17 years), displayed complex heart malformation, and had undergone palliative operations with possible poorly-mixed pulmonary blood flow or absence of a mixed venous blood chamber that could impact the reliability of the Fick measurement [23, 24]. A very recent study including a more homogenous population of patients with CHD demonstrated a high accuracy of PhysioFlow[®] at rest when compared to MRI [25].

In addition to relative reliability, our study also evaluated absolute reliability, providing crucial information for clinical pediatricians in terms of the MD value. This value represents the limit under which the observed difference could be attributed to noise associated with repeated testing. Peak SV measurement during exercise testing may be useful to evaluate global ventricular reserve in patients with CHD, especially those with residual right ventricular overload and we consider it an important parameter in patient follow-up [1]. In our study, the MD values of indexed SV and cardiac index were large in patients with high indexed SV ($> 50 \text{ ml/m}^2$), and were small (7.3 and 21% respectively) in patients with peak SV $< 50 \text{ ml/m}^2$. We have previously reported, as has Welsman et al., that values of SV $> 40 \text{ ml/m}^2$ ($50 \pm 10 \text{ ml/m}^2$) at peak exercise are normal [4, 26]. From our analyses, a decrease in peak SV $> 7.3\%$ in patients with peak SV $< 50 \text{ ml/m}^2$ can be considered a true degradation of global ventricular response and should be taken into account for treatment decisions. On the other hand, we found poor absolute reliability in patients with SV $> 50 \text{ ml/m}^2$ especially when peak SV exceeded 65 ml/m^2 . Naturally-occurring high SV at peak exercise has been described in healthy subjects in relation to high blood volume [27] and the high variability (within the normal range) observed in such patients may be explained in part by exacerbated blood volume variations.

While the sample size of 30 patients may be considered relatively small, it is nonetheless generally considered

sufficient for reproducibility studies (notably to obtain satisfactory 95% confidence intervals), an important point to keep in mind given that the primary objective of the study was to measure the ICC, SEM, and MD, and not to compare mean values. Another potential limitation of our study is the relatively long delay of one year between the two measures. Nonetheless, this study was performed in a routine care setting in which exercise tests were performed at least once annually in these patients in our institution. Despite this mean one-year interval, we were able to demonstrate high reliability between the two measures. In practice, this implies that measuring SV during exercise does not need to be performed more than once a year in a population of young adults. In a similar population suffering from tetralogy of fallot, Kipps et al. reported a decrease of peak VO₂ and oxygen pulse (the product of SV and arteriovenous oxygen difference), a surrogate of SV, of 1.4 and 1.8% per year, respectively (in peak percent of predicted value) [28]. However, the median age of their patients (23.6 years) was much higher than in our study. In this older population, the reduction in oxygen pulse over one year could be explained either by a reduction in cardiac performance (i.e., maximal SV) due to longer exposure to pulmonary leaking, or a reduction in arteriovenous oxygen difference promoted by a sedentary lifestyle.

Conclusion

The aim of this study was to provide an exhaustive assessment of the reliability of peak indexed SV and peak cardiac index in patients with right ventricular outflow tract lesions, in order to demonstrate its clinical usefulness in the context of pulmonary valve replacement. Taken together, our results show that both measures represent highly reliable methods of assessment in patients with residual right outflow tract lesions after CHD repair. The good absolute reliability allows implementation of these measures in clinical practice to detect abnormal decreases in global ventricular performance in overloading conditions. Further prospective studies are needed to clarify the role of this parameter in therapeutic decision-making for pulmonary valve replacement.

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Compliance with Ethical Standards

Conflict of interest Antoine Legendre, Damien Bonnet, Laurent Bosquet declares that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As a retrospective study, no formal consent was required.

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