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Feasibility, reproducibility and accuracy of electrical velocimetry for cardiac output assessment in congenital heart disease

Alexander C. Egbe [a,*], Muhammad Wajih Ullah [a], Arslan Afzal [a], Keerthana Banala [a], Rahul Vojjini [a], Maria Najam [a], Karim Osman [a], Sahith Thotamgari [a], Donald J. Hagler [b]

[a] Department of Cardiovascular Medicine, Mayo Clinic Rochester, MN 55905, United States
[b] Division of Pediatric Cardiology, Mayo Clinic Rochester, MN 55905, United States

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A B S T R A C T

Background: Noninvasive cardiac output assessment is important for prognostication in patients with heart failure. Electrical velocimetry (EV), an impedance cardiography technique, can be used for noninvasive cardiac output assessment. The purpose of this study was to determine the feasibility, reproducibility and accuracy of cardiac output assessment by EV in adults with congenital heart disease (CHD).
Methods: Cross-sectional study of CHD patients that had simultaneous cardiac output assessment by Fick and EV (using Cardiotronic monitor, Osypka Medical). We divided the cohort into: Group 1 patients ($n = 54$) had hemodynamic assessment at rest only, while Group 2 patients ($n = 7$) had assessment both at rest and peak exercise.
Results: EV cardiac output assessment was feasible in 100% of the patients. There was good correlation between Fick-derived and EV-derived cardiac index ($r = 0.89$, $p < 0.001$) in Group 1. Among 26 patients in Group 1 that underwent cardiac output assessment pre- and post-intervention, there was no difference in the strength of correlation of Fick and EV cardiac output pre- and post-intervention (p-interaction 0.244) indicating good reproducibility of the technique. There was also modest correlation between Fick-derived and EV-derived cardiac index at rest ($r = 0.68$, $p = 0.032$), and peak exercise ($r = 0.62$, $p = 0.055$), in Group 2.
Conclusion: In this study, we demonstrated the feasibility and accuracy of EV cardiac output assessment in adults with CHD. We also demonstrated, for the first time, that EV cardiac output assessment was reproducible under different loading conditions, and that EV can be used for the assessment of cardiac output augmentation at peak exercise.

1. Introduction

Congenital heart disease (CHD) is a common and understudied cause of heart failure [1,2]. Abnormal filling pressures and cardiac output are the hallmarks of heart failure, and are responsible for heart failure-related symptoms and morbidities [3–6]. The assessment and longitudinal monitoring of hemodynamic indices such as cardiac output, is therefore important for prognostication and titration of therapy in patients with heart failure [7,8]. Cardiac catheterization is the gold standard for cardiac output assessment [9,10]. However, it is invasive, and hence not ideal for longitudinal monitoring. Doppler echocardiography provides noninvasive assessment of cardiac output using the continuity equation [11]. However Doppler stroke volume calculation is based on geometric assumptions about the anatomy of the left ventricular outflow tract; and these assumptions may not always be valid in CHD patients with complex anatomy [7,8]. There are very limited data about the feasibility and accuracy of Doppler-derived cardiac output assessment in the setting of complex CHD [7,8], and this may be one of the reasons why this technique is not routinely applied in clinical practice in the CHD population.

Electrical velocimetry (EV) is an impedance cardiography technique that provides continuous assessment of stroke volume and cardiac output by measuring the maximum rate of change of impedance to peak aortic blood acceleration [12]. Some studies have reported good correction between cardiac output assessment by

Abbreviations: CHD, congenital heart disease; VO_2, oxygen consumption; EV, electrical velocimetry.

* Corresponding author at: Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States.

E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

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EV and invasive hemodynamic assessment [12–16]. However, the feasibility and reproducibility of EV cardiac output assessment under different loading conditions have not been studied. The purpose of the current study was to determine the feasibility, reproducibility and accuracy of cardiac output assessment by EV in adults with CHD undergoing cardiac catheterization.

2. Methods

This is a cross-sectional study of adults (age >18 years) with CHD that had right and/or left cardiac catheterization with simultaneous invasive and noninvasive cardiac output assessment at Mayo Clinic Rochester, Minnesota from January 1, 2017 through March 31, 2019. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization. Of 61 patients that made the study inclusion criteria, Interventional procedures were performed in 32 (53%) patients. The interventions were device closure of atrial septal defect n = 19, transcatheter pulmonary valve replacement n = 8, dilation and stent implantation in pulmonary artery/Fontan conduit n = 4, and balloon dilation of coarctation n = 1). We divided the cohort into 2 groups: Group 1 (n = 54) comprised of patients that had hemodynamic assessment at rest alone, and Group 2 (n = 7) comprised of patients that had hemodynamic assessment both at rest and during exercise.

The primary study objective was to determine the correlation between invasive and noninvasive cardiac output assessment at rest in Group 1 patients. Among Group 1 patients that underwent cardiac output assessment pre- and post-intervention, we performed a subgroup analysis to determine the reproducibility of the EV technique by comparing the Fick and EV cardiac output correlations pre- and post-intervention. The secondary objective was to determine the correlation between invasive and noninvasive cardiac output assessment at rest and peak exercise in Group 2 patients. Invasive cardiac output assessment was based on the Fick's principle while the noninvasive cardiac output assessment was based on impedance cardiography using EV.

2.1. Electrical velocimetry

Impedance cardiography is a noninvasive technology measuring total electrical conductivity of the thorax and its changes in time, in order to provide a continuous assessment of stroke volume and cardiac output [12]. The details about this technique have been extensively described [12]. Impedance cardiography is based upon the assumption that the human thorax is a non-homogeneous electrical conductor, and therefore conforms to parallel conduction theory when exposed to a field of alternating current [17]. As a result, the orientation of the erythrocytes in the aorta changes quickly from random to alignment in the direction of blood flow upon opening of the aortic valve. The alignment of erythrocytes during early systole and the following increasingly random orientation produces a pulsatile change in electrical conductivity which is reflected in a decrease in thoracic electrical impedance during early systole and followed by increase in the later part of the cardiac cycle. EV is an impedance cardiography technique that measures peak aortic blood acceleration and mean aortic blood velocity based on changes in impedance, and then provides a continuous assessment of stroke volume and cardiac output based on these variables [12].

In this study, EV-derived cardiac output was measured with the Cardiotronic Hemodynamic Monitoring System (Osypka Medical, Berlin, Germany and San Diego, CA, USA). It involves placement of 4 pairs of standard electrocardiogram electrodes at the neck and the level of the diaphragm, and then using these electrodes to transmit high frequency (50 kHz) alternating current of a constant magnitude (2 mA, rms), thereby inducing a current field parallel to the axis of the spine [12,18]. By means of voltage-sensing electrodes placed within the current field, the quasi-static basal transthoracic impedance Z_0 (ohms) and the impedance change $\Delta Z(t)$ are calculated by Ohm's Law $(Z = U/I)$ from the demodulated basal transthoracic voltage U (volts) and cardiac-synchronous voltage change $\Delta U(t)$, respectively. By electronic differentiation of $\Delta Z(t)$, the first time-derivative is obtained $dZ(t)/dt$, from which its peak magnitude, $dZ(t)/dt_{min}$, and left ventricular ejection time (flow time) are measured and entered into the Bernstein–Osypka SV equation to compute EV-derived cardiac output [19].

2.2. Invasive cardiac output assessment at rest (Group 1)

All studies were performed on chronic medications in the fasted state and mild sedation using 7 Fr fluid-filled catheters. Catheter position was confirmed by appearance on fluoroscopy, characteristic pressure waveforms, and oximetry. Systemic arterial pressures and saturations were assessed at the time of left heart catheterization, or via femoral or radial arterial cannulation in patients that did not undergo concurrent left heart catheterization. In patients with intracardiac shunt, the superior vena cava saturation was used as the mixed venous oxygen (O_2) saturation while the pulmonary artery saturation was used as the mixed venous O_2 saturation in patients without intracardiac shunt. We used the pulmonary artery wedge saturation as the pulmonary venous O_2 saturation. Cardiac output was determined by the Fick technique using assumed O_2 consumption (VO_2) and directly measured O_2 contents in the pulmonary and systemic circulations (assumed VO_2/arteriovenous O_2 difference) [20]. Cardiac index was calculated by indexing the cardiac output to body surface area.

2.3. Invasive cardiac output assessment at rest and exercise (Group 2)

In Group 2 patients, we performed hemodynamic assessment with expired gas analysis (MedGraphics, St. Paul, MN) both at rest and during exercise. The cardiopulmonary exercise test protocol used at the Mayo Clinic cardiac catheterization laboratory has been described [21]. In brief, all patients underwent hemodynamic assessment and VO_2 measurement at rest, and this was followed by exercise testing using supine bike. The exercise protocol consisted of 2-miniute stages of 20 W increments until exhaustion (peak exercise). Maximum effort was defined as respiratory exchange ratio >1.1 [22]. In order to avoid motion artifact, EV-derived cardiac output was recorded within 30 s after cessation of exercise.

2.4. Statistical analysis

Data were presented as mean ± standard deviation or number (%). Linear regression was used to determine the correlation between invasive (Fick-derived) and noninvasive (EV-derived) cardiac output. In order to assess the reproducibility of the EV technique, we compared the slope of the Fick-EV cardiac correlations pre- and post-intervention. We calculated cardiac output augmentation at peak exercise among Group 2 patients by subtraction cardiac output at rest from cardiac output at peak exercise. We then compared exercise-induced cardiac output augmentation between Fick and EV techniques. A $p < 0.050$ was considered statistically significant. All statistical analyses were performed with JMP software (version 14.0; SAS Institute Inc, Cary NC).

3. Results

A total of 61 patients met the study inclusion criteria, and EV-cardiac output assessment was feasible in 100% of the patients. The mean age at the time of cardiac catheterization was 47 ± 14 years, and 32 (53%) were males. Table 1 shows the baseline clinical characteristics of the cohort. The most common diagnoses were atrial septal defect and Fontan physiology. Among the 18 patients with Fontan physiology, 9 had tricuspid atresia, 6 had double inlet left ventricle, 2 had pulmonary atresia with intact ventricular septum and 1 had complete atrioventricular canal defect. Right heart catheterization was performed in all 61 patients, while concomitant left heart catheterization was performed in 38 (62%) patients. Interventional procedures were performed in 32 (53%) cases (device closure of atrial septal defect n = 19, transcatheter pulmonary valve replacement n = 8, dilation and stent implantation in pulmonary artery/Fontan conduit n = 4, and balloon dilation of coarctation n = 1).

The mean Fick-derived cardiac output and cardiac index was 5.9 ± 1.2 l/min and 2.8 ± 0.7 l/min/m^2 respectively in Group 1 patients, Table 2. The mean EV-derived cardiac output and cardiac index measured was 5.7 ± 0.9 l/min and 2.7 ± 0.5 l/min/m^2 respectively. There was a good correlation between Fick-derived and EV-derived cardiac index (r = 0.89, R^2 = 0.79, p < 0.001) and there was excellent agreement between cardiac index assessment by both methods (bias −0.4 l/min/m^2, 95% limits of agreement −0.6 to + 0.5), Fig. 1. Of the 32 patients that underwent intervention, simultaneous Fick and EV cardiac output assessments were performed in 26 patients pre- and post-intervention. Among these 26 patients, the correlations between Fick and EV cardiac output pre- and post-intervention were (r = 0.90, R^2 = 0.81, p < 0.001) and (r = 0.88, R^2 = 0.77, p < 0.001). There was no difference in the strength of correlation of Fick and EV cardiac output pre- and post-intervention (p-interaction 0.244) indicating good reproducibility of the technique, Supplementary Fig. 1 (see Table 3).

Seven patients with history of Fontan palliation (Group 2) underwent rest and exercise cardiac catheterization with expiratory gas analysis and direct VO_2 measurement. Table 2 shows invasive hemodynamic indices at rest and peak exercise. The Fick-derived cardiac index at rest and peak exercise was 2.2 ± 0.3 l/min/m^2 and 3.9 ± 0.7 l/min/m^2 respectively. The EV-derived cardiac index at rest and peak exercise was 2.1 ± 0.2 l/min/m^2 and 4.1 ± 0.9 l/min/m^2 respectively. There was a modest correlation between Fick-derived and EV-derived cardiac index at rest (r = 0.68, R^2 = 046, p = 0.032), and peak exercise (r = 0.62, R^2 = 0.38, p = 0.055), Supplementary Fig. 2 A and B. There was good agreement between cardiac index assessment at rest (bias −0.1 l/min/m^2, 95% limits of agreement −0.3 to + 0.2), and peak exercise (bias −0.3 l/min/m^2, 95% limits of agreement −0.6 to + 0.), Supplementary Fig. 2C and D. There was no difference in cardiac output augmentation as measured by Fick compared to EV (1.5 ± 0.0.5 vs 1.6 ± 0.3 l/min/m^2, p = 0.568), Supplementary Fig. 3.

Table 1
Baseline Characteristics (n = 61).

Age, years	47 ± 14
Male	32 (53%)
Body mass index, kg/m^2	31 ± 5
Body surface area, m^2	1.9 ± 0.4
Congenital Heart Disease diagnosis	
Atrial septal defect	22 (36%)
Tetralogy of Fallot	12 (20%)
Fontan physiology	18 (30%)
Coarctation of aorta	5 (8%)
Ebstein anomaly	2 (3%)
Partial atrioventricular canal defect	2 (3%)
Laboratory tests	
Hemoglobin, g/dl	13.8 ± 1.5
Creatinine, mg/dl	1.0 ± 0.3
NT-proBNP, pg/ml	176 (93–299)
Medications	
Loop diuretics	6 (10%)
Beta blockers	14 (22%)
RAAS antagonist	16 (24%)

RAAS: renin angiotensin aldosterone system.
NT-proBNP: N-terminal pro b-type natriuretic peptide.

Table 2
Fick-derived Cardiac Output Assessment (Group 1, n = 54).

Mixed venous saturation, %	65 ± 6
Pulmonary arterial saturation, %	74 ± 8
Pulmonary venous saturation, %	96 ± 3
Systemic artery saturation, %	95 ± 3
AV O_2 difference, %	31 ± 4
Hemoglobin, g/dl	13.8 ± 1.1
Body surface area, m^2	2.1 ± 0.4
Cardiac output, l/min	5.9 ± 1.2
Cardiac index, l/min/m^2	2.8 ± 0.7

AVO_2: arteriovenous oxygen saturation.

4. Discussion

In this study, we demonstrated the EV cardiac output assessment was feasible in all patients, and that there was a good correlation between cardiac output assessment by Fick and EV in adults with different types of CHD diagnoses. Among the subset of patients that underwent cardiac output assessment pre- and post-intervention, there was no difference in the Fick-EV cardiac output correlations pre- and post-intervention. The current study demonstrated the feasibility, reproducibility and accuracy of EV cardiac output assessment, and therefore supports the use of this technique for noninvasive cardiac output assessment in the CHD population. We also observed modest correlations for tests performed at rest and during exercise in single ventricle patients, though based on a very small sample size. This has important clinical applications with regards to exercise testing in patients with complex anatomy since Doppler echocardiogram may not be feasible in such settings.

In a prospective study of 32 pediatric patients that underwent cardiac catheterization, Norozi et al. [12] reported an excellent correlation (r = 0.96) between Fick and EV-derived cardiac assessment. In another study, Suttner et al. [13] compared EV-derived cardiac output and thermodilution after elective cardiac surgery in 74 adults, and reported a good correlation (r = 0.83) between both techniques. In a prospective study of 30 patients with aortic stenosis, all patients underwent transthoracic echocardiography, cardiac catheterization and EV [14]. Aortic valve area was calculated using 3 methods: continuous wave Doppler velocity and stroke volume derived from the continuity equation; continuous wave Doppler velocity and EV-derived stroke volume; and invasively with Gorlin method as the gold standard. Aortic valve area calculated using EV-derived stroke volume had a better correlation with valve area by Gorlin (r = 0.91) compared to valve area by continuity equation (r = 0.76). This suggests that, in comparison to the continuity equation, the EV-derived stroke volume had a better correlation with invasively measured stroke volume. All these prior studies demonstrated the accuracy of EV cardiac output assessment in comparison to the gold standard of invasive hemodynamic assessment. The current study agrees with results of these prior studies, and also provides two novel insights about EV cardiac output assessment. First, we tested the reproducibility of this tech-

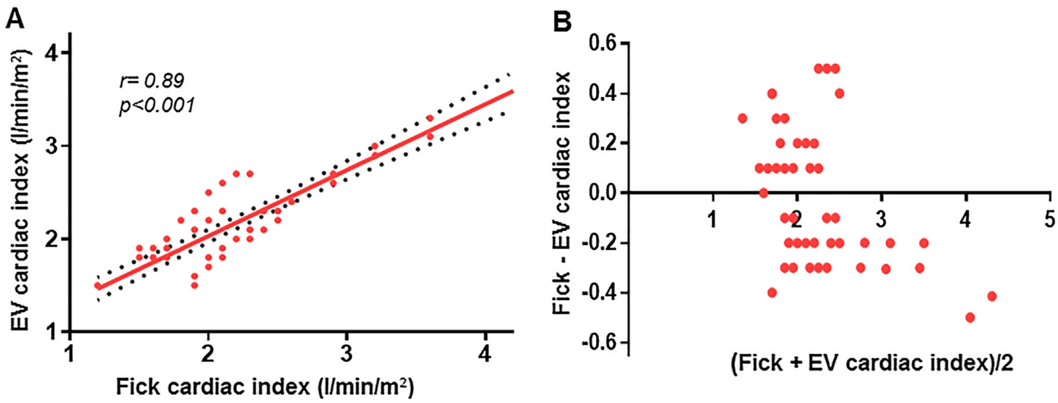

Fig. 1. Linear regression (A) and Bland-Altman plot (B) of Fick-derived cardiac index and Electrical velocimetry (EV)-derived cardiac index.

Table 3
Fick-derived Cardiac Output Assessment (Group 2, n = 7).

	Rest	Peak	p
Mixed venous saturation, %	59 ± 3	51 ± 4	0.024
Pulmonary venous saturation, %	93 ± 2	91 ± 2	0.287
Systemic artery saturation, %	92 ± 2	91 ± 2	0.291
AV O_2 difference, %	34 ± 3	40 ± 4	0.026
Hemoglobin, g/dl	14.1 ± 0.8	14.1 ± 0.8	–
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	–
Cardiac output, l/min	4.5 ± 0.5	7.6 ± 0.9	0.010
Cardiac index, l/min/m^2	2.2 ± 0.3	3.9 ± 0.7	0.012

AVO_2: arteriovenous oxygen saturation.

nique by demonstrating similar Fick and EV cardiac output correlation coefficients under 2 different loading conditions (pre- and post-intervention) in the same cohort. Additionally we reported, for the first time, a modest correlation between Fick and EV cardiac output at peak exercise.

4.1. Clinical applications and future directions

Cardiac output assessment in patients with CHD can be challenging especially in the patients with complex anatomy [7,8]. A few studies have reported the use of Doppler echocardiography for cardiac output assessment in patients with Fontan palliation, but the feasibility and accuracy of Doppler cardiac output assessment is just modest at best [7,8]. Based on the results of the current study showing feasibility, reproducibility and accuracy of EV for cardiac output assessment, we speculate that EV may provide an alternative method for noninvasive cardiac output assessment in patients with complex CHD, while avoiding the technical challenges of obtaining 2-dimensional and Doppler indices required for Doppler cardiac output assessment in this population. The next potential application for EV is cardiac output assessment during exercise. While peak VO_2 analysis, spirometry and heart rate response during exercise can provide important diagnostic and prognostic data, incorporating cardiac output assessment during exercise will potentially improve the robustness of the exercise hemodynamic assessment. However it is important to highlight that only a very small number of patients underwent exercise testing, and this small sample size diminishes the confidence in the results. However unlike any other prior study on this subject, we demonstrated the reproducibility and accuracy of EV for cardiac output assessment under 3 different physiologic conditions (pre-intervention, post-intervention, post-exercise). The consistent correlations observed under the different loading conditions are reassuring about a robustness of EV for cardiac output assessment.

4.2. Limitations

The current study was limited by small sample size. Notwithstanding, the data showed accuracy and reproducibility of EV-derived cardiac output in comparison to the gold standard of Fick cardiac output. We were unable to obtained EV cardiac output assessment exactly at peak exercise (but within the first minute post exercise) because of motion artifact. However, the *temporal offset* in the timing of peak exercise cardiac output by Fick vs EV did not make a significant difference in the results as shown in the correlation analysis. The problem of motion artifact may limit the use of EV for the measurement of cardiac output increments at different stages of exercise testing.

4.3. Conclusions

In this study, we demonstrated the feasibility and accuracy of EV cardiac output assessment in adults with CHD. We also demonstrated for the first time that EV cardiac output assessment was reproducible under different loading conditions, and that EV can be used for the assessment of cardiac output augmentation at peak exercise. Our results support the use of EV for cardiac output assessment in patients with complex CHD since it is not limited by anatomic complexity and geometric assumptions. EV can also be incorporated in cardiopulmonary exercise testing to determine peak exercise cardiac output (in early recovery). Further studies are required to validate our findings, and to determine if EV-derived cardiac output indices improves risk stratification and prognostication in CHD patients.

CRediT authorship contribution statement

Alexander C. Egbe: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Muhammad Wajih Ullah:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Arslan Afzal:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Keerthana Banala:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Rahul Vojjini:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Maria Najam:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Karim Osman:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Sahith Thotamgari:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing. **Donald J. Hagler:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, original draft, Writing - review & editing.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100464.

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