Cardiology

Cardiology , DOI: 10.1159/000533574
Received: March 21, 2023
Accepted: August 2, 2023
Published online: October 12, 2023

Feasibility Of Noninvasive Assessment of Cardiac Output During Exercise In Healthy Adults By A Novel Elaboration On Systolic Time Intervals

Kim C-H, Cierzan BS, Patel N, Borlaug BA, Johnson BD

ISSN: 0008-6312 (Print), eISSN: 1421-9751 (Online)
https://www.karger.com/CRD
Cardiology

Brief Report

Feasibility Of Noninvasive Assessment of Cardiac Output During Exercise In Healthy Adults By A Novel Elaboration On Systolic Time Intervals

Chul-Ho Kim, PhD, Bradley S. Cierzan, MS, Nisha Patel, BS, Barry A. Borlaug, MD, Bruce D Johnson, PhD

Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905

Short Title: Systolic time interval and cardiac output

Corresponding Author:
Bruce D. Johnson, Ph.D.

Professor of Medicine and Physiology
Department of Cardiovascular Disease
Mayo Clinic
200 First st. SW
Rochester, MN 55905
USA
507) 538-0325
Johnson.Bruce@mayo.edu

Number of Tables: 0
Number of Figures: 2
Word count: abstract (238), **main text** (1172)
Keywords: Systolic time interval, cardiac output, exercise, hemodynamic,

Abstract

BACKGROUND. Although assessment of cardiovascular hemodynamics during exercise can provide clinical insights, it is challenging to acquire it in clinical settings.

OBJECTIVES. Accordingly, this preliminary study was to determine whether a novel elaboration on Systolic Time Interval measures (eSTICO) method of quantifying Cardiac Output and Stroke Volume was comparable to those obtained using a validated soluble gas (OpCircCO) method or calculation based on oxygen consumption (VO_2CO) during exercise.

METHODS. For the present study, 14 healthy subjects (male: n=12, female: n= 2) performed incremental exercise on a recumbent cycle ergometer. At rest and during exercise, cardiac output (CO) was obtained via the eSTICO method while the OpenCircCO and VO_2CO measures were obtained at the last minute of each workload.

RESULTS. At peak, there was no difference between eSTICO and OpCircCO (12.39±3.06 vs. 13.96±2.47 L/min, $p>0.05$) while there was a slight difference between eSTICO and VO_2CO (12.39±3.06 vs. 14.28±2.55 L/min, $p<0.05$). When we performed correlation analysis with all subjects and all measures of CO at all WL, between eSTICO and OpenCircCO, there was a good relationship ($r=0.707$, $p<0.001$) with a Bland and Altman agreement analysis demonstrating a –1.6 difference (95% LoA: -6.3-3.5). Between eSTICO and VO_2CO, we observed an $r=0.865$ ($p<0.001$) and a Bland and Altman agreement analysis with a -1.2 difference (95% LoA: -4.8–2.4).

CONCLUSION. A novel exploitation of cardiac hemodynamics using systolic timing intervals may allow a relatively good assessment of cardiac output during exercise in healthy adults.

INTRODUCTION

Assessment of cardiovascular hemodynamics during exercise can provide unique clinical insight into disease pathophysiology. In addition, cardiac output (CO) kinetics during exercise is considered a useful parameter in diagnosis and defining prognosis. However, there are challenges in performing more invasive measures in many clinical settings due to logistical complications, patient risk and excessive cost. Accordingly, non-invasive measures including techniques that use inhalation of soluble gases, thoracic bioreactance, thoracic bioimpedance, ultrasound, and arterial waveforms have been used.

Systolic time interval has been used in clinical studies to determine left ventricular function performance [1, 2]. In addition, echocardiographic and electrocardiographic measures based on systolic time intervals have been applied to quantify CO and left ventricular function in clinical settings [3, 4]. A more novel approach for non-invasively assessing cardiac hemodynamics has been developed using signals from a combination of standard ECG and pulse oximetry. The combination and configuration enable direct measures of Pre-Ejection Period, Left Ventricular Ejection Period-Systolic Timing Intervals, Diastolic Filling Time, Central and Peripheral Pulse Transit Time, and Pulse Wave Velocity; with subsequent calculation of Stroke Volume and CO derived from a novel elaboration on Systolic Time Interval measures (eSTICO). However, this method has not been previously compared to other common non-invasive measures during moderate activity. Therefore, this study compared this eSTICO method to a soluble gas method developed and validated in our laboratory as well as to accepted equations for CO based on measures of VO_2 and work.

METHODS

Subjects and experimental procedure

This study was reviewed and approved by Mayo Clinic Institution of Review Board (IRB). To achieve the goal of the study, 14 healthy subjects (male: n=12 and female: n=2; age=35±12 years; Ht=177.3±7.8cm; Wt=81.1±13.2kg; BMI=25.8±3.9kg/m^2) were recruited. Subjects who had a history of cardiovascular diseases and/or pulmonary disorders and orthopedic limitations were excluded from the study. After completion of informed consent, they performed 5 stages (0, 40, 80, 120 and 160 watts) of incremental exercise on a recumbent cycle ergometer (Lode Corival, Groningen, Netherlands). Workloads (watt) were increased every 5 minutes. During the experimental procedure, CO measures and oxygen consumption (VO_2) were obtained at the last minute of each workload at rest and each stage of exercise for analysis.

Systolic time interval-based CO measure

Systolic Time Intervals (STI) were first investigated by Weissler et al., and colleagues in 1968 and it has been shown to express a credible characterization of cardiovascular function [4]. We tested a noninvasive system developed by Cardiac Profiles, Inc, Franklin TN. The FloWave® introduces novel elaborations on STI derived from measures of arterial tone that may address the absence of afterload-related limitations of the original methods. The device uses algorithms to derive cardiac output and related variables from signals produced from a single lead ECG and 2 standard pulse oximeters—one placed on an ear and one on a finger (Fig. 1a). Signals are captured to a handheld device that continuously transmits both raw physiologic signals and computed cardiac parameters via Bluetooth to a standard android tablet for display, storage and analytics (Fig. 1b). For this study, we used a standard GE/Marquette soft tip finger pulse oximeter and Masimo E1 ear pulse oximeter. A single ECG electrode was attached to the upper right clavicle with two electrodes on the lower left chest. Pre Ejection Period (PEP) was calculated using the QRS of the ECG as the Time Stamp and the arrival time of the pulse wave at each of the two Photoplethysmography (PPG) sensors to first calculate wave velocity and then PEP. Patient demographics were used to estimate the distance from the PPG sensors to the aorta along the arterial Tree.

Comparison Methods for Cardiac Output

Open circuit CO measure (OpCircCO). Cardiac output was measured via the utilization of an open circuit acetylene wash-in method developed in our laboratory and validated with direct Fick. This method takes advantage of the solubility of acetylene in the pulmonary circulation and has been tested under resting and vigorous exercise conditions with good agreeability [5].

Oxygen consumption-based CO (VO_2CO). Cardiac output was also estimated based on the well-established relationship between oxygen uptake and workload. According to the Fick equation, the changes in CO are relatively constant with the change in oxygen uptake or work during exercise unless there are more pathological conditions (e.g., pulmonary limitations, cardiac dysfunction) but can also be altered somewhat by gender, body habitus or age [5, 6]. Oxygen consumption-based CO (VO_2CO) was calculated using equations based on gender and age in healthy adults [7].

Statistical analysis

To compare VO_2, heart rate (HR), stroke volume (SV) and CO at rest and peak between eSTICO and OpenCircCO and between eSTICO and VO_2CO, a paired sample t-test was conducted and the values are illustrated as mean±SD. In addition, to observe relationships between the various methods of quantifying CO, between eSTICO and OpenCircCO and between eSTICO and VO_2CO, CO at rest and various levels of exercise were obtained. Afterward, correlation analysis and Bland-Altman agreement analysis were performed with all subjects and all measures of CO at all workloads. Analysis was performed using SPSS (version 25) and statistical significance was established as a nominal alpha of 0.05

RESULTS

Out of 14 subjects, 3 subjects stopped exercise at the end of 80W, 1 stopped at the end of 120W and 9 completed all exercise stages. At the highest individual workloads, subjects reached a VO_2 of 1.96±0.48 L/min and a heart rate (HR) of 140±22 bpm. For eSTICO and OpCircCO, there were no significant differences in CO (5.53±1.30 vs. 6.11±1.32 L/min, $p>0.05$) and stroke volume (SV) (69.87±18.37 vs. 79.79±20.36 ml/beat, $p>0.05$) at rest. There were also no differences in CO (12.39±3.06 vs. 13.96±2.47 L/min, $p>0.05$) and SV (87.97±18.12 vs. 99.51±19.90 ml/beat, $p>0.05$) at peak exercise. For eSTICO and VO_2CO, there were no significant differences in CO (5.53±1.30 vs. 5.31±0.58 L/min, $p>0.05$) and SV (69.87±18.37 vs. 69.11±11.32 ml/beat, $p>0.05$) at rest. However, eSTICO and VO_2CO showed slight differences in CO (12.39±3.06 vs. 14.28±2.55 L/min, $p<0.05$) and SV (87.97±18.12 vs. 102.85±17.18 ml/beat, $p<0.05$) at peak exercise.

Between eSTICO and OpenCircCO, there was a good relationship ($r=0.707$, 95% CI: 0.552-0.815, $p<0.001$, Fig. 2a) with a Bland and Altman agreement analysis demonstrating a –1.6 difference (95% LoA: -6.8-3.5, Fig. 2b). Between eSTICO and VO_2CO, there was a strong relationship ($r=0.865$, 95% CI: 0.784-0.917, $p<0.001$, Fig. 2c) and a Bland and Altman agreement analysis with a -1.2 difference (95% LoA: -4.8–2.4, Fig. 2d).

DISCUSSION

The present preliminary study tested a noninvasive technology to quantify stroke volume and cardiac output at rest and during exercise using a novel combination of standard ECG and pulse oximetry sensors and derivation of systolic time intervals. We found in general that previously validated noninvasive measures based on respiratory gas exchange agreed well with the timing-based measures.

Measurements of CO have always been a challenge in terms of accuracy and safety in clinical and laboratory settings. In addition, there are complexities, limitations and inaccuracies with both invasive and noninvasive techniques, often limiting the practicality of performing many techniques. Thus, there is still the need for a simple, yet robust method to estimate CO in a variety of settings. In addition, most methods give a general or averaged value rather than a beat-by-beat quantification of

CO. In the present study, we tested a method that takes advantage of typical sensors often used in a cardiopulmonary exercise or stress laboratory to derive systolic time intervals that allow quantification of CO at rest and during exercise.

CONCLUSION

Although this was a preliminary study and limited to healthy individuals, the initial assessment suggests this is a useful method and may allow it to integrate well with ambulatory monitoring technology or with typical Cardiopulmonary Exercise Testing (CPET) for additive information regarding cardiac health.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by Mayo Clinic Institution of Review Board (IRB), approval number 19-011882/ date March 5, 2020.

Consent to participate statement: written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The present study was supported by Mayo Clinic Circulatory Failure Research Program.

Author Contributions

CHK: conceptualization, methodology, data collection, data analysis, writing initial draft, visualization. **BSC**: methodology, data collection, data analysis, writing reviewing and editing. **NP**: methodology, data collection, writing, reviewing and editing. **BAB**: conceptualization, methodology, data analysis, reviewing and editing. **BDJ** supervising, conceptualization, methodology, data analysis, reviewing and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants. Any further enquiries can be directed to the corresponding author.

References

1. Salvi P, Baldi C, Scalise F, Grillo A, Salvi L, Tan I, De Censi L, Sorropago A, Moretti F, Sorropago G, Gao L. Comparison between invasive and noninvasive methods to estimate subendocardial oxygen supply and demand imbalance. J Am Heart Assoc. 2021 Sep 7;10(17):e021207. DOI: 10.1161/JAHA.121.021207.

2. Pahlevan NM, Matthews RV. Cardiac triangle mapping: a new systems approach for noninvasive evaluation of left ventricular end diastolic pressure. Fluids. 2019 Jan 22;4(1):16. DOI:10.3390/fluids4010016

3. Reant P, Dijos M, Donal E, Mignot A, Ritter P, Bordachar P, Dos Santos P, Leclercq C, Roudaut R, Habib G, Lafitte S. Systolic time intervals as simple echocardiographic parameters of left ventricular systolic performance: correlation with ejection fraction and longitudinal two-dimensional strain. Eur J Echocardiogr. 2010; 11: 834-844. DOI: 10.1093/ejechocard/jeq084

4. Weissler A, Harris W, Schoenfeld C. Systolic Time Intervals in Heart Failure in Man. Circulation. 1968;37:149–159. DOI: 10.1161/01.cir.37.2.149

5. Johnson B, Beck K, Proctor D, Miller J, Dietz N, Joyner M. Cardiac output during exercise by the open circuit acetylene washin method: comparison with direct Fick. J Appl Physiol 2000; 88: 1650-1658. DOI: 10.1152/jappl.2000.88.5.1650

6. Beck KC, Randolph LN, Bailey KR, Wood CM, Snyder EM, Johnson BD. Relationship between cardiac output and oxygen consumption during upright cycle exercise in healthy humans. J Appl Physiol 2006; 101: 1474-1480. DOI: 10.1152/japplphysiol.00224.2006

7. Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR, Joyner MJ. Influence of age and gender on cardiac output-V̇ o 2 relationships during submaximal cycle ergometry. J Appl Physiol 1998; 84: 599-605. DOI: 10.1152/jappl.1998.84.2.599

Figure Legends

Fig. 1. a) Algorithm to derive cardiac output (CO) and related variables from signals produced from a single lead ECG and 2 standard pulse oximeters. **b)** Display of continuous signals from a single lead ECG and 2 standard pulse oximeters.

Fig. 2. Relationships and Bland-Altman agreement amongst eSTICO, OpCircCO and VO_2CO. a) relationship between eSTICO and OpCircCO, **b)** Bland-Altman agreement between eSTICO and OpCircCO, **c)** relationship between eSTICO and VO_2CO and **d)** Bland-Altman agreement between eSTICO and VO_2CO.