



Modulation of left ventricular diastolic filling during exercise in persons with cervical motor incomplete spinal cord injury

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Abstract

Purpose To characterize left ventricular diastolic function during an exertional challenge in adults with incomplete cervical spinal cord injury (icSCI).

Methods In this cross-sectional study, a two-group convenience sample was used to compare left ventricular LV diastolic performance during a 5–10 W·min⁻¹ incremental arm ergometer exercise protocol, using bioimpedance cardiography. Subjects were eight males with cervical incomplete spinal cord injury (icSCI; C5-C7: age 39 ± 14 years) versus eight able-bodied males (CON: age 38 ± 13 years). Left ventricular (LV) diastolic indices included end-diastolic volume (EDV) and early diastolic filling ratio (EDFR). LV ejection time (LVET), inotropic index (dZ/dT^2) and stroke volume (SV) were compared between the groups at peak exercise, and maximum workload for the icSCI group (isomax).

Results EDV (at peak exercise: 131.4 ± 7.3 vs 188.78 ± 9.4, $p < 0.001$; at isomax: 131.4 ± 7.3 vs 169 ± 23, $p = 0.0009$) and EDFR (at peak exercise 73 ± 14% vs 119 ± 11%, $p = 0.006$; at isomax 94 ± 10; $p = 0.009$) were significantly reduced in icSCI compared to CON, respectively. Significant differences in LVET (icSCI: 273 ± 48 vs CON: 305 ± 68; $p = 0.1$) and dZ/dT^2 (icSCI: 0.64 ± 0.11 vs CON: 0.85 ± 0.31; $p = 0.1$) were not observed at isomax, despite a significant decrease in SV in the subjects with icSCI (77.1 ± 6.05 mL vs 105.8 ± 9.2 mL, $p < 0.00$)

Conclusion Left ventricular filling was impaired in the subjects with icSCI as evidenced at both peak exercise and isomax. It is likely that restrictions on the skeletal muscle pump mechanized the impairment but increased left ventricular wall stiffness could not be excluded as a mediator.

Keywords Diastolic function · Exercise · Spinal cord injury · Stroke volume · Cardiac preload · Cardiac filling ratio

Abbreviations

ASIA American spinal injury impairment scale
AET-CPET Arm ergometer cardiopulmonary exercise test

ANOVA Analysis of covariance
 dZ/dT^2 Cardiac inotropic index
EDFR Early diastolic filling ratio
EDV End diastolic volume
EF Ejection fraction
icSCI Incomplete spinal cord injury
IPAQ International physical activity questionnaire
isomax Peak workload obtained by icSCI
LVET Left ventricular ejection time
MAP Mean arterial pressure
MEP Maximal voluntary expiratory pressures
MIP Maximal voluntary inspiratory pressures
Qt Cardiac output
STR Systolic time ratio
SVR Systemic vascular resistance
SV Stroke volume
TSI Time of injury
 VO_{2max} Maximal oxygen uptake

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WR Work rate
ZCG Bioelectrical impedance cardiography

Introduction

Partial segmentation of the neuronal pathways that travel in the spinal cord alters cardiac dynamics that are subsumed by the somatic and autonomic nervous systems (Lujan and DiCarlo 2016; Weidner et al. 2017). In patients with incomplete cervical spinal cord injury (icSCI), the sympathetic nervous system (SNS) can be impaired, attenuating vasoconstriction in the arms, legs, and splanchnic area below the level of the lesion (Weidner et al. 2017). Additionally, muscle paralysis or partial paralysis, occurring as a result of interruption of the neuromotor pathways may limit muscle contraction capacity and thus the effectiveness of the muscle pump. Left ventricular filling dynamics is mediated by the voracity of the muscle pump and neural drive, which are primary determinants of cardiac venous return (VR) (Odom et al. 2016). Consequently, any deficit in muscle pumping capacity and sympathetic outflow could limit left ventricular filling.

Research has typically focused on the extrinsic regulation of cardiac dynamics (Figoni et al. 1991; West et al. 2013; Lujan and DiCarlo 2016; DeVeau et al. 2017). In individuals with spinal cord injury, impairment of ventricular systolic performance often emerges gradually over time (Kessler et al. 1987; Davis et al. 1990; Binkhorst et al. 1992; Hostettler et al. 2012; Hasnan et al. 2013). However, limited progress has been made in understanding the association between the pathophysiology of left ventricular systolic hypokinesia and left ventricular filling (LV) dynamics (Weidner et al. 2017).

Left ventricular stroke volume (LVSV) is regulated by a balance among myocardial contractility (i.e., inotropic state), afterload and cardiac preload (Richardson et al. 2000; Baan et al. 2012; Crisafulli et al. 2015). Diastolic filling is a dynamic process during which 60–80% of the VR enters the LV during the early passive filling phase (Little and Downes 1990; Sidebotham 2007; Klabunde 2011). Venous return is precisely equal to LVSV on a beat-to-beat basis due to impositions of the closed-loop cardiovascular system (Guyton et al. 1957; Permutt and Caldini 1978). Decreases in left ventricular diastolic function are often associated with increased risk of cardiovascular diseases (Garshick et al. 2005; Paulus et al. 2007).

Making the understanding of the influence of cardiac filling limitations on LV performance in SCI even more difficult, most of the research in this area of study has used animal models in which complete spinal transection is induced in the laboratory (Fragata and Areias 1996), centering primarily on instances of exaggerated system breakdown

(Malliani et al. 1972; Inskip et al. 2012; Crisafulli et al. 2015). The completeness of the lesion may introduce variability to the response, since patients with complete SCI present not only significant limitation of skeletal muscle control, but also a pattern of sympathetic “decentralization” (Wecht and Bauman 2013). In contrast, patients with partial spinal cord transection have partial de-efferentation of motor function and may have some preserved autonomic function (Currie et al. 2015). Although most clinical injuries are anatomically incomplete, little is known about the subtle underlying effects of a cervical spinal cord injury on ventricular filling and cardiac loading conditions, particularly when the injury only partially transects the spinal cord.

LV diastolic filling is a crucial component of the cardiovascular response to physical activity (Little and Downes 1990; Baan et al. 2012) and a determinant of overall cardiovascular health (Paulus et al. 2007) however, there is currently a dearth of studies characterizing the effects of incomplete SCI induced restrictions on diastolic function during exercise performance in individuals who have icSCI. Because the level and completeness of the lesion may influence the cardiovascular response and performance during exercise, it is important to understand the impairment related to partial de-efferentation of the spinal pathway. Therefore, the aim of this study was to characterize LV diastolic filling and volume during an exercise challenge in adults with incomplete cervical spinal cord (icSCI).

Methods

Study design and subject selection

A convenience sample of individuals with icSCI and able-bodied controls who did not have SCI was recruited for this cross-sectional study. The study was approved by the institutional review board at George Mason University (GMU Project # 1237293-1). Written informed consent was obtained from each participant, after detailed information about the study protocol and testing procedure, potential risks, and subject’s rights were discussed with each subject. Signing of the consent form signified enrollment in the study. All subjects were recruited from the greater Washington D.C. metropolitan area. Those with icSCI were recruited through advertisements in support groups, from SCI rehabilitation clinics and from community events. The control subjects were recruited through flyers posted in community spaces. The subjects included in this study were voluntarily recruited between June and November 2018. After inclusion, subjects completed incremental exercise test protocols to volitional exhaustion, after which data were compared between the groups.

Inclusion/exclusion criteria

Subjects with icSCI were eligible to participate in the study according to the following criteria: motor incomplete cervical spinal cord injury (icSCI: C5–C7), defined as having American Spinal Injury Impairment Scale (ASIA classification C–D) (Maynard et al. 1997) at least 8-months post-injury; and between the ages of 18–65 years old. Subjects were required to be able to arm crank safely with both hands on the arm crank ergometer at 50-RPM. Subjects also were required to answer no to all questions on the Physical Activity Readiness Questionnaire (PARQ+) (Warburton et al. 2018) and not be at high risk for a cardiac event as determined by the health history questionnaire and American College of Sports Medicine (ACSM) risk assessment model (Riebe et al. 2015).

Exclusion criteria for the icSCI group included complete neurological spinal cord injury (ASIA: A/B), significant exercise-limiting orthopedic impairment or surgery secondary to the injury, such as orthopedic complications, spasms or contractures that prevent safe arm cranking. Further exclusion criteria included a history of coronary heart disease or cardiac dysfunction such as pulmonary hypertension or heart failure, history of HIV infection or antiretroviral therapy, any medication that would limit or enhance cardiovascular function or exercise performance, severe renal disease, mitochondrial dysfunction of any etiology, and severe psychiatric conditions.

Subjects in the control group (CON) were required to be “physically inactive” defined according to an International Physical Activity Questionnaire (IPAQ) score of < 600 metabolic equivalent task (MET) min/week (Serón et al. 2010) and to have no history of SCI or neurological impairment. CON was matched within 5 years of age, ± 5 kg of body weight and ± 5 cm of height relative to the subjects with icSCI.

Exclusion criteria for the control group were identical to that of the icSCI group: history of coronary heart disease or cardiac dysfunction such as pulmonary hypertension or heart failure, history of HIV infection or antiretroviral therapy, any medication that would limit or enhance cardiovascular function or exercise performance, severe renal disease, mitochondrial dysfunction of any etiology, severe psychiatric conditions and musculoskeletal conditions of the upper extremities.

Off-study and dismissal criteria were the same for those with icSCI and CON. The criteria included any exacerbation of disease status that required hospitalization before the testing day, onset of any of the study exclusion criteria and significant alteration or poor signal quality of the bioimpedance cardiography (ZCG) during the test.

Study protocol and procedure

A single visit to the Functional Performance Laboratory, Department of Rehabilitation Science at George Mason University was required. After inclusion, consent and enrollment, all subjects in both icSCI and control groups completed an incremental arm-ergometer exercise test to volitional exhaustion. LV diastolic and systolic function measurements were obtained at rest and during exercise by bioimpedance cardiography (ZCG; PhysioFlow PF-05TM, Manatec Biomedical, Paris, France). Volitional exhaustion was determined as the subject’s inability to maintain the required 50-RPM cranking rate despite strong encouragement.

Anthropometric and cardiovascular measurements

Resting blood pressure and heart rate were taken in a seated position. The height of all patients with icSCI was measured in the supine position using a flexible measuring tape, positioned from the top of the skull to the base of the heels (ankles) (Bradtmiller 2000). Body mass was measured with a weighing scale (Detecto 6500 Portable Bariatric Wheelchair Scale) and determined by subtracting the weight of the wheelchair from weight (wheelchair plus subject). In the non-disabled group, height (cm) was measured using a digital scale. The individual’s body mass index (BMI) was calculated in kilograms per square meter (kg/m^2).

Physical Activity Questionnaires

Physical activity in icSCI was assessed using the Leisure-time physical activity questionnaire for people with SCI (LTPA-SCI) (Ginis et al. 2012) to help quantify the workload to be used during the exercise test for icSCI. Interviewer-administered questionnaires were used to gather information on the types, frequency and duration of activities performed over a particular period of time to quantify the current level of PA into categories of low, moderate and vigorous physical level. Able-bodied controls were classified as being physically inactive according to an International Physical Activity Questionnaire (IPAQ) score of < 600 metabolic equivalent task (MET) min/week (Serón et al. 2010).

Pulmonary function and respiratory muscle strength tests

Spirometry maneuvers were performed in accordance with the standards established by Miller et al. (2005) All the tests were performed while the subject was in the seated position, breathing room air through a breathing tube held in the mouth, with the nose being occluded by a nose-clip. Testing included forced vital capacity (FVC), forced

expiratory volume in 1 s (FEV_1), and maximum voluntary ventilation (MVV) over 12 s (Ultima Cardio₂; Medical Graphics Corporation, St. Paul, MN, USA). The strength of the respiratory muscles was assessed using a Respiratory Pressure Meter (Micromedical Ltd, Rochester, Kent, UK) to measure maximal voluntary inspiratory (MIP) and expiratory (MEP) pressures at the mouth (European and Society 2002) and was performed according to recommendations from ATS/ERS (European and Society 2002).

Left ventricular (LV) performance assessment

A bioimpedance cardiography system (ZCG, PhysioFlow PF-05TM, Manatec Biomedical, Paris, France) system (ZCG) was used to measure left ventricular diastolic and systolic performance at rest and during exercise (Allen et al. 1990). Patients were connected to the equipment using silver/silver chloride electrodes (Ag/AgCl, Skin-tact FS-50) and ECG electrodes placed on the subjects' neck and thorax. The system was digitally interfaced and calibrated according to manufacturer guidelines (Charloux et al. 2000; Richard et al. 2001; Tordi et al. 2004). Subjects were asked to remain motionless as a resting blood pressure was taken in the seated position, followed by recording of 30 consecutive heartbeat cycles using the PhysioFlow system to conclude the calibration process. Two electrodes were placed on the left side of the neck above the supraclavicular fossa, adjacent to each other. Two other electrodes were placed on the back, one at the same level as the level of xiphisternum. The last two electrodes (ECG₁, ECG₂) were used to capture the ECG signal and were placed in the V₁ and V₅ locations, over the fourth intercostal space on the right side of the sternum, and over the fifth intercostal space at the midaxillary line on left.

Preload, which is related to the sarcomere length and tension at the end of diastole, could not be measured directly and noninvasively in the intact heart, but instead were estimated by noninvasive ZCG measurements. ZCG-derived indices of diastolic function, LV end-diastolic volume (EDV) and early diastolic filling ratio (EDFR), were the primary diastolic function variables measured in this study. Other indices obtained from the ZCG waveform were left ventricular ejection time (LVET), LV stroke volume, cardiac inotropy dZ/dT^2 and systemic vascular resistance. The time-dependent change in impedance in the thorax is the approximate inverse of the pulse tracing obtained from Doppler ultrasound analyses. From the ZCG signal, EDFR was measured as the quotient of the relative amplitude of the velocity of the early diastolic filling wave (O wave) and the velocity of the systolic wave (S), expressed as a percentage ($O_{wave}/S_{wave} \times 100$).

Arm ergometer cardiopulmonary exercise test (AET-CPET) procedure

All individuals performed a graded exercise protocol on an arm-crank ergometer (Monark Rehab Trainer 881). Gas exchange was measured during exercise using a Medgraphics Ultima Cardio2 (Medical Graphics Corporation, St. Paul, MN). The gas analyzers used were calibrated prior to each test for air flow and volume, as well as oxygen and carbon dioxide concentration of expired air, and corrected for temperature, barometric pressure and humidity (Edvardsen et al. 2013).

Subjects with icSCI performed the tests in their wheelchairs, with their hands secured to the handles of the arm ergometer using hand flexion gloves or wraps. Subjects in the control group sat in a chair that was adjusted for the height of the ergometer. The midpoint of the ergometer was set at shoulder level and the distance from the ergometer was set at a slight flexion in the elbow when the arms were extended. The test began with 10 min of seated rest during while baseline left ventricular and breath-by-breath gas exchange data were simultaneously measured. This was followed by an incremental arm ergometer exercise protocol (Fig. 1) where a 3-min warm-up at 0 W was followed by a stepwise increase in resistance of 5 or 10 W·min⁻¹ until volitional exhaustion. All individuals in the control group performed a 10 W·min⁻¹ CPET to volitional exhaustion defined as the inability to sustain the 50 rpm cranking despite verbal correction and strong encouragement from the testing staff. The work rate increment for those with icSCI was 5 W·min⁻¹ based on their self-reported classification of physical activity (Lasko-McCarthy and Davis 1991) using the Leisure-time physical activity questionnaire for people with SCI (LTPA-SCI) (Ginis et al. 2012). The 10 W min⁻¹ and 5 W min⁻¹ work rates were selected to allow all subjects to achieve peak exertion within a test duration of 8–12 min (Fig. 1). During the test, subjects in both groups were instructed to maintain a cadence of 50–60 revolutions per minute (RPM), as indicated on the arm cycle ergometer

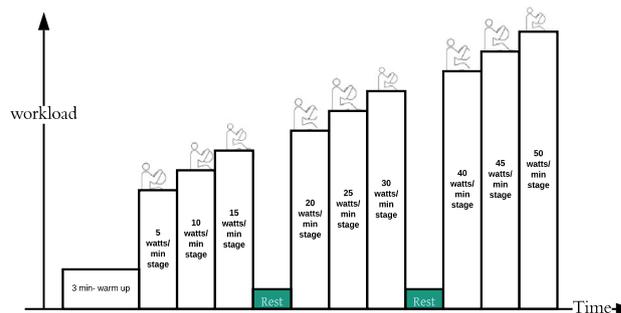


Fig. 1 Schematic illustration of the incremental arm exercise test (AET) 1 min stages

digital display. The CPET was discontinued when the participants had a drop in the cycling cadence that could not be returned and sustained within the designated cadence of 50–60 rpm, or attained a condition of volitional exhaustion defined as the patients expressed desire to stop cranking due to extreme fatigue despite strong encouragement from the testing staff (Maher and Cowan 2016). Additional symptomatic endpoints for stopping the tests were those recommended by the American College of Sports Medicine, according to the guidelines for early test termination (American College of Sports Medicine 2018). The exercise protocol was interspersed with a 1-min non-exercise period after every 3-min of arm cycling, for automated measurement of brachial arterial blood pressure, using an automated arm cuff (Omron, HEM-907, Omron Healthcare, UK).

Data from the pulmonary gas exchange analysis system and bioelectrical impedance cardiography were collected continuously throughout the test.

Data analysis

Data processing

Data were smoothed to remove excess noise using a simple rolling numbers bin average. Data values were calculated as the average of all data points within a consecutive 5-s interval, in which the average included all of the data points that were in last four seconds of the previous bin plus all of the data points occurring in the next second in the sequence. The variables of interest were analyzed using this method during the 10-min seated rest and at 25%, 50%, 75%, 100% of peak VO_2 and isomax. Peak values for breath-by-breath measures of the gas exchange variables and beat-to-beat measures of cardiac function were obtained using the average of 20-s intervals immediately before individuals reached volitional exhaustion (Hostettler et al. 2012; Deboeck et al. 2014). The variables of interest were compared between the groups at the stated percentages of peak VO_2 and at the peak workload obtained by icSCI (isomax).

Statistics

The Shapiro–Wilks test indicated that the data were normally distributed. Baseline data were analyzed using an independent T test to compare group means. Two-way analyses of variance (ANOVA) and, where appropriate covariance [ANCOVA, controlling for the effects of Heart rate (HR) and cardiac contractility (dZ/dT^2)] were used to determine between- and within-group differences at the percentages of peak VO_2 and at peak exercise. Heart rate (HR) and cardiac contractility, were included as covariates in the ANCOVA

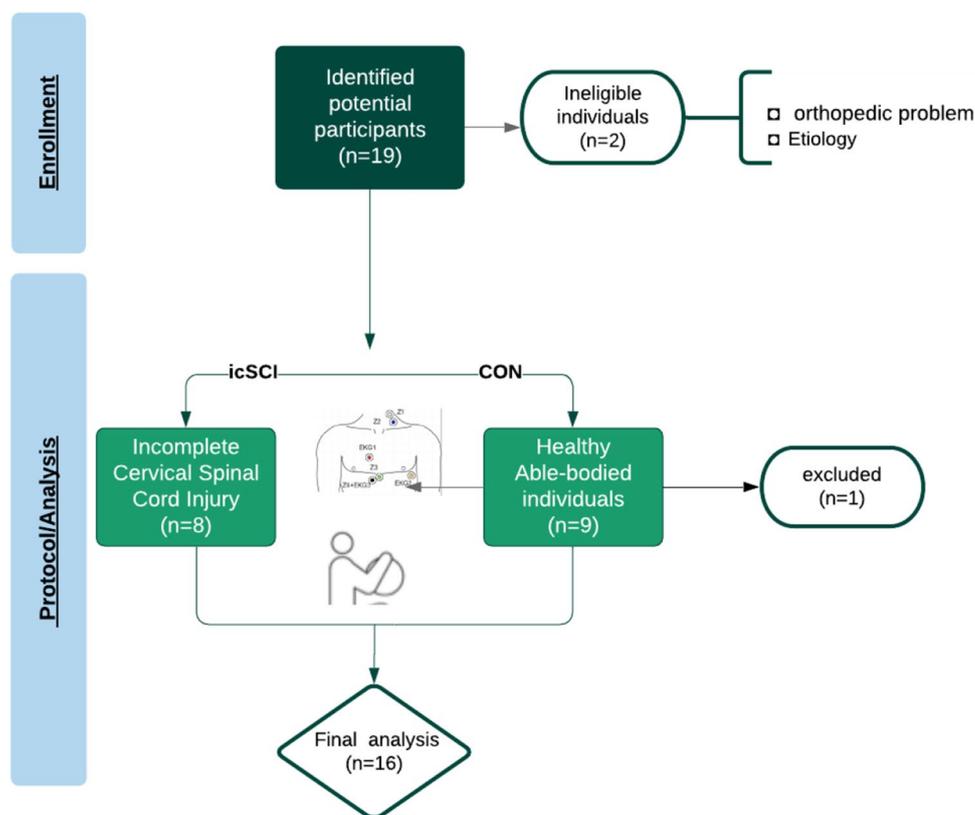
model due to their potential influence on diastolic function (Cheng et al. 1990; Harrison et al. 1991; Lavine 2005). Tukey's post hoc tests were performed if a significant F ratio was observed. Data were compared between the groups at isomax by separate one-way analyses, again using ANOVA and ANCOVA. Statistical significance was accepted at $p < 0.05$. All data processing was conducted with the Stata version 16 statistical program. Data are reported as means \pm 1 standard deviation unit.

Results

A total of 17 males voluntarily participated in the study (Fig. 2). One participant was excluded from the analyses due to poor ZCG signal quality. The remaining 16 subjects comprised the icSCI ($n=8$) and CON ($n=8$) groups (Table 1). Subjects with icSCI had cervical lesions between the C5 and C6 vertebrae and were 9 ± 5 years past their injury. All of the tests ended as a result of inability to sustain the designated cranking cadence or volitional exhaustion. There were no adverse events associated with the study.

Resting cardiac output (Qt) was 33% higher for the controls than for those with icSCI, which was concurrent with a higher systolic, diastolic and mean arterial pressure (Table 2). However, significant group differences in resting systemic vascular resistance (SVR) were not observed. Resting left ventricular chronotropic (HR) and inotropic (dZ/dT^2) conditions were not significantly different between the icSCI and control groups, nor were resting ejection fraction and resting left ventricular diastolic function. Pulmonary MIP was significantly lower ($p=0.020$) in icSCI (69.0 ± 17.8 mmHg) than in CON (89.7 ± 15.4 mmHg), as was MEP (59.6 ± 16.4 mmHg vs. 83.4 ± 14.8 mmHg, $p=0.008$) despite the lack of group difference in MVV (icSCI 126.6 ± 39.8 vs. CON 152.7 ± 27.4 , $p=0.14$).

At the peak exercise, the RER (icSCI 1.15 ± 0.05 vs non-icSCI 1.22 ± 0.08) RPE (icSCI 9 ± 0.7 vs non-icSCI 9 ± 0.8) were not significantly different between the groups. Peak workload (controls 60 ± 5 W vs icSCI 29 ± 10 W, $p=0.001$) and peak VO_2 (controls 19.15 ± 3.38 mL/kg/min vs. icSCI 11.15 ± 4.03 mL/kg/min, $p=0.008$) were significantly higher in the controls than in icSCI, even though a significant group difference in exercise duration was not observed (CON 11 ± 3 min vs. icSCI 8 ± 2 min). In icSCI, EDVR increased significantly above rest and plateaued by approximately 50% peak VO_2 , whereas in CON, EDVR continued to rise until volitional exhaustion, becoming significantly higher than icSCI by 75% peak VO_2 . EDV increased between rest and peak exercise in both groups, but EDV was significantly higher in CON than icSCI by 25% peak VO_2 . In subjects with icSCI, the within-group increase in EDV over rest was not observed until peak VO_2 had been attained (Fig. 3). Peak

Fig. 2 Consort diagram of the study flow**Table 1** Physical characteristics for all enrolled subjects

Variables	icSCI (<i>n</i> = 8)	CON (<i>n</i> = 8)
Age (years)	39 ± 14	38 ± 13
Weight (kg)	75.1 ± 10.6	76 ± 8.3
Height (cm)	181.6 ± 4.9	176 ± 4.8
BMI (kg cm ⁻²)	22.7 ± 2.5	24.5 ± 1.6
Gender, <i>n</i> (male/female)	8/0	8/0
ASIA classification (%)		
C	7 (87.5%)	–
D	1 (21.5%)	–
Etiology		
Falls	3 (37.5%)	–
Car accident	5 (62.5%)	–

ASIA American spinal injury association impairment scale, BMI body mass index, SCIM spinal cord injury independence measure, cm centimeters, kg weight in kilograms

cardiac output and stroke volume (SV) were significantly reduced in those with icSCI compared to CON (Table 3), whereas the peak ejection fraction was not significantly different (56 ± 12 for icSCI vs 59 ± 7 for CON, $p = 0.5$).

Maximal workload in icSCI was approximately 50% of the workload in CON (isomax). Therefore, variables of interest were compared between groups at a workload identical to the maximal workload achieved by icSCI. Both EDVR

and EDV in icSCI were significantly lower at in icSCI at peak exercise than in CON at isomax (Fig. 4). Additionally, LV ejection time was not significantly different after controlling for the inotropic and chronotropic condition in both icSCI (273 ± 48 ms) and CON (305 ± 68 ms). Work rate correlated significantly with EDV ($r = 0.84$, $p \leq 0.0001$) and EDVR ($r = 0.80$, $p = 0.0003$) provide evidence of a substantial correlation of mechanical muscle pump impairment on cardiac filling.

Table 4 shows the cardiovascular responses to incremental arm-crank in icSCI at maximal workload and in able-bodied controls at identical workload. Diastolic and systolic blood pressures were decreased in icSCI compared to CON values at isomax but a significant difference in systemic vascular resistance was not apparent. However, there were no significant group differences in dZ/dT^2 , HR or systemic vascular resistance (SVR) at identical workload. A significantly lower value for cardiac output and stroke volume was observed in those with icSCI compared to the controls at isomax (Fig. 5).

Discussion

The subjects with icSCI in this study had reduced LV end-diastolic volume and diastolic filling ratio compared to able-bodied controls, even after adjusting for the effects

Table 2 Seated baseline cardiac indices

Variables	icSCI (n=8)	CON (n=8)	p value
HR (bpm)	71 ± 11	74 ± 6	0.62
SV (mL)	58 ± 9	74 ± 8	0.004
Qt (L/min)	4 ± 1	6 ± 1	0.005
EF %	53 ± 13	56 ± 11	0.59
SVR (dyn. s/cm ⁵)	1283.6 ± 224.7	1203.4 ± 271.2	0.53
dZ/dT2, no unit	0.4 ± 0.1	0.4 ± 0.1	0.5
EDFR (%)	52.8 ± 6.3	49.2 ± 3.7	0.18
EDV (mL)	114.4 ± 21.7	134.2 ± 16	0.06
STR (%)	0.5 ± 0.2	0.4 ± 0.2	0.44
LVET (ms)	359 ± 35	389 ± 34	0.12
Systolic blood pressure (mmHg)	89 ± 5	115 ± 11	<0.001
Diastolic blood pressure (mmHg)	61 ± 4	73 ± 6	0.002
Mean arteria pressure (mmHg)	70 ± 4	87 ± 7	<0.001
FEV ₁ /FVC, % pred	77 ± 7	81 ± 7.3	>0.05
MVV	126.6 ± 39.8	152.7 ± 27.4	>0.05
FVC (L)	4.4 ± 1	4.8 ± 1	>0.05
FEV1(L)	3.2 ± 0.7	3.9 ± 0.9	>0.05

Data presented as mean ± standard deviation

HR heart rate, SV stroke volume, Qt cardiac output, EF left ventricular ejection fraction, SVR systemic vascular resistance, dZ/dT2 cardiac inotropic index, EDFR early diastolic filling, EDV end diastolic volume, STR Systolic time ratio, LVET left ventricular ejection time, %pred %predicted, FVC forced vital capacity, FEV1 forced expiratory volume in 1 s, MVV maximal voluntary ventilation

of inotropic, chronotropic conditions. The reduction in the cardiac volumetric condition and early diastolic filling was concomitant with decreases in cardiac stroke volume and cardiac output. These findings were in agreement with other studies (Phillips et al. 1998; Jacobs and Nash 2004). Those with icSCI in the current study had incomplete spinal cord lesions with intact triceps function and were able to arm-crank. However, it did not appear that this exercise was sufficient for eliciting a volume loading condition in subjects with icSC.

In the current study diastolic and systolic function were measured by ZCG. The ZCG is entirely noninvasive and its application and validity during exercise testing have been established (Charloux et al. 2000; Richard et al. 2001; Tordi et al. 2004). Many studies in the broader literature have suggested that the ZCG device can be used to provide acceptable noninvasive evaluations of cardiac output (Qt), at rest and during exercise, comparing the measures to those obtained by the direct Fick equation (Charloux et al. 2000), indocyanine-green dye dilution (Robach et al. 2008), or CO₂ rebreathing methods (Siebenmann et al. 2015; Spiering et al. 1998; Tordi et al. 2004). Further, bioelectrical impedance measures in the thorax provide tracings that are the approximate inverse of the pulse tracing obtained from Doppler ultrasound analyses (Leão et al. 2017; Patterson 1989). The ZCG has gained favor as it offers the advantages of being completely noninvasive, relatively inexpensive, and is easy to use, while providing continuous information and adequate

evaluation of cardiac function during maximal exercise (Charloux et al. 2000; Richard et al. 2001). Moreover, ZCG has been widely applied in patients with SCI, and information regarding Qt and its determinants have been reported at rest, during exercise and up to VO_{2max} (Godinez 2018; Hoekstra et al. 2012; Lee et al. 2017; Machač et al. 2016; Milia et al. 2014). Since the determinants of Qt are based on the ZCG waveform, this technique provides a suitable measurement that can be used in the expansion of our current knowledge base regarding the diastolic filling response to severe and peak arm-crank exercise in individuals with icSCI.

Several studies have been reported characterizing diastolic filling at rest in patients with cervical complete spinal cord injury at rest (de Groot et al. 2006; Matos-Souza et al. 2009). More recent reports convey diastolic impairments after SCI (Matos-Souza et al. 2009; De Rossi et al. 2014; Driussi et al. 2014; Schreiber et al. 2017). Current literature suggested the higher the level of the lesion, the more likely to present with impaired diastolic function, especially during exercise. Diastolic performance at rest in patients with complete SCI (C4 to T12) had lower initial diastolic velocity (Em) and higher early diastolic flow-to-myocardial tissue velocities compared with healthy controls, even after adjustment for systolic blood pressure (Matos-Souza et al. 2009). Another recent study showed that individuals with complete midthoracic spinal cord injury above T6, presented with lower E_m and higher peak early inflow velocity/initial

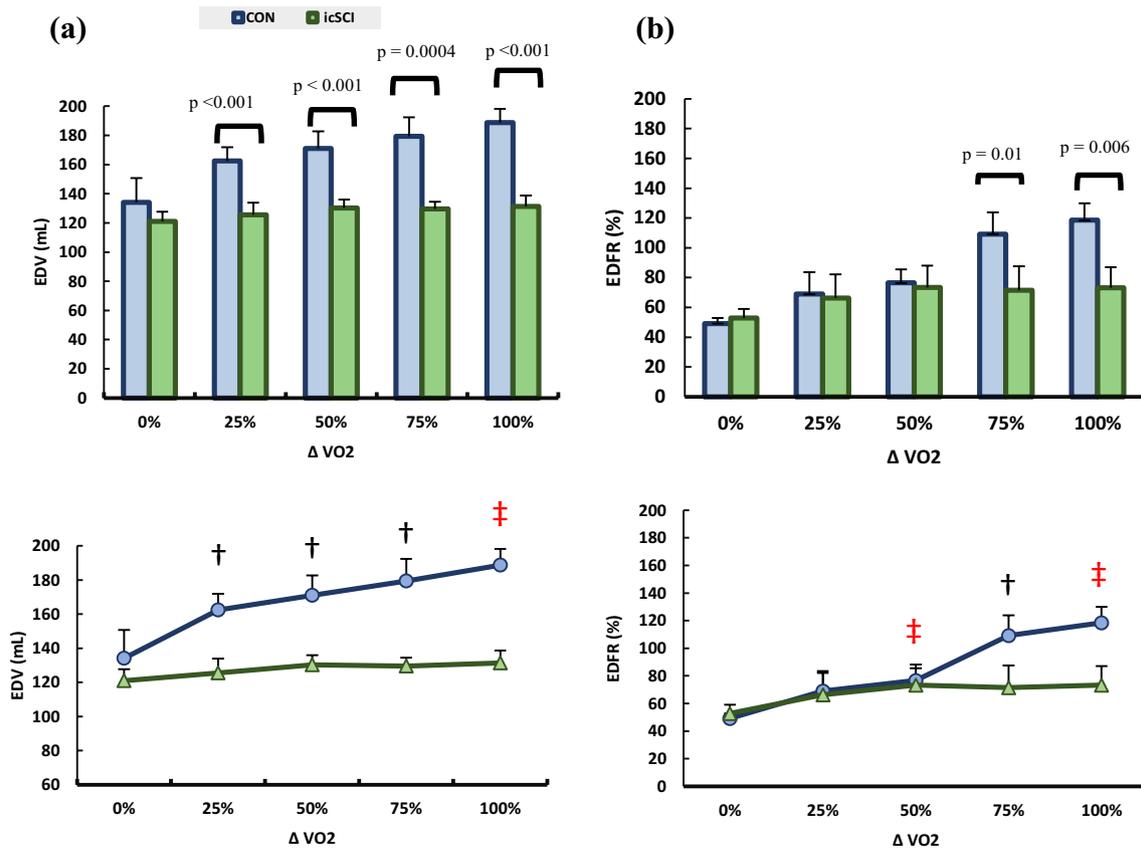


Fig. 3 Illustration of left ventricular diastolic response to exercise. *EDV* end diastolic volume, *EDVR* left ventricular early diastolic filling ratio. Bars represent group mean values and error bars represent standard deviations. **a** Representation of the physiological responses between icSCI and CON. *p* value for comparison obtained from

ANCOVA using “*dZ/dT²* and HR” as covariates. **b** Representation of the response pattern within the group. †Signifies statistically significant difference from baseline in both groups, *p* < 0.05. ‡Signifies a statistically significant difference from baseline in CON group only, *p* < 0.05

Table 3 Peak central hemodynamic responses to incremental arm-crank in both groups

Variables	icSCI (n = 8)	CON (n = 8)	<i>p</i> value
HR (bpm)	111 ± 15	159 ± 12	<0.001
SV (mL)	77 ± 6	109 ± 7	<0.001 [†]
Qt (L/min)	8 ± 3	17 ± 2	<0.001 [†]
SVR (dyn s/cm ⁵)	757 ± 224	491 ± 85	0.007
<i>dZ/dT²</i> (Ohm/s ²)	0.6 ± 0.1	0.9 ± 0.2	0.0002
MAP (mmHg)	77 ± 6	105 ± 12	<0.001

Data presented mean ± standard deviation

The level of significance was set at *p* < 0.05

[†]This variable was statistically significantly different in the ANCOVA model using “cardiac inotropic index (*dZ/dT²*) and heart rate (HR) as covariate

diastolic velocities ratio (*E/E_m*), which is a marker of low LV diastolic function (Schreiber et al. 2017). Reduction in the LV early diastolic function has been shown to be related to the implication of impairment in the sympathetic activity.

Findings from this study might have clinical implications, suggesting the likelihood of incomplete SCI to show a similar pattern of impairment. Given that SCI individuals with rostral injury, in particular above T6, usually exhibited declined sympathetic activities (Phillips et al. 1998).

Conversely, preserved left ventricular diastolic performance has been observed in those with complete SCI at rest (Eysmann et al. 1995; de Groot et al. 2006; Matos-Souza et al. 2009). De Groot et al. (2006) investigated LV diastolic function in a smaller sample of tetraplegics using conventional echocardiography and tissue Doppler imaging during relaxation and found no LV diastolic function abnormality. Nevertheless, this hypothesis needs to be elucidated during dynamic challenged exercise. It is unclear how the ventricular filling manifested when the heart is exposed to perturbation, such as exercise, which can be used to unmask any impairment in the left ventricular filling dynamics that otherwise may not appear during resting conditions. Variability in the findings of available reports might be attributed to lack of specification of the level of

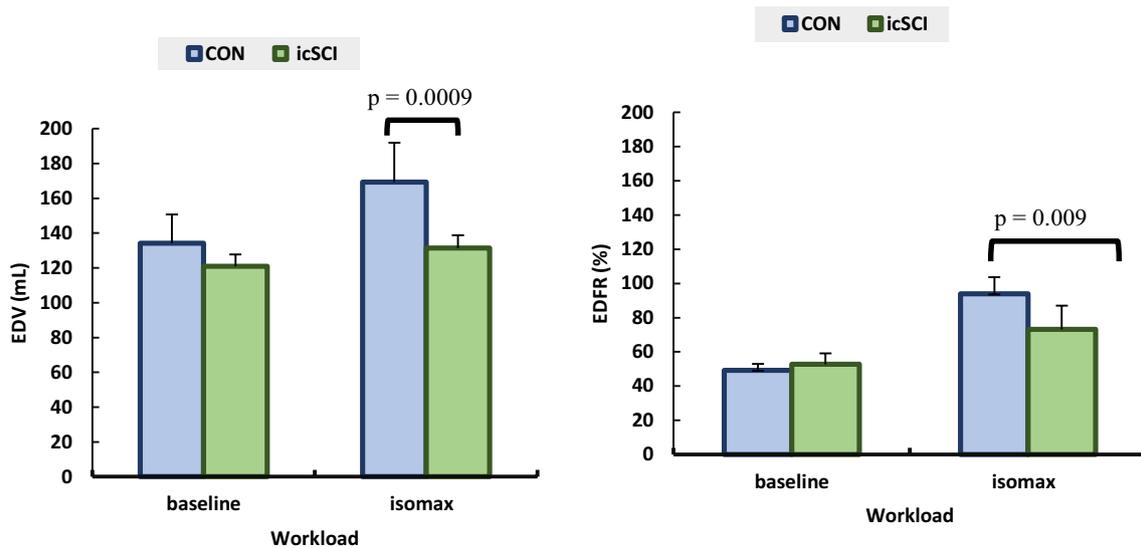


Fig. 4 Illustration of left ventricular end diastolic volume and early diastolic filling ratio response to exercise at isomax. Bars represent group mean values and error bars represent standard deviations. *p* value for comparison obtained from ANCOVA using “dZ/dT² and HR” as covariates

Table 4 Cardiovascular responses to incremental arm-crank in icSCI at maximal workload and in able-bodied controls at identical workload

Variables	icSCI (n=8)	CON (n=8)	<i>p</i> value
Cardiac parameters			
HR (bpm)	111 ± 15	112 ± 6	0.8
dZ/dT ² (Ohm/s ²)	0.64 ± 0.1	0.85 ± 0.3	0.10
SVR (dyn s/cm ⁵)	757 ± 223	758 ± 195	0.9
Systolic blood pressure (mmHg)	99 ± 10	133 ± 11	<0.001
Diastolic blood pressure (mmHg)	66 ± 6	80 ± 13	0.02
Mean arterial pressure (mmHg)	77 ± 6	97 ± 11	0.0006
EF%	56 ± 12	57.7 ± 17.1	0.8
LVET (ms)	273 ± 48	305 ± 68	0.1 [†]
V _E (L/min)	31.9 ± 3.4	23.1 ± 5.5	0.001
<i>f</i> (breath/min)	27.98 ± 7.4	19.87 ± 6.9	0.04
V _T (L)	1.03 ± 0.3	1.2 ± 0.3	0.8

Data presented mean ± standard deviation. *p* values derived from independent sample *t* tests

HR heart rate, dZ/dT² cardiac inotropic index, SVR systemic vascular resistance, EF left ventricular ejection fraction, LVET left ventricular ejection time, V_E minute ventilation, *f* breathing frequency, V_T tidal volume

[†]*p* value was obtained from the ANCOVA model using (dZ/dT²) and (HR) as covariate. The level of significance was set at *p* < 0.05

lesion, sample sizes, the techniques that have been used, and posture variability during the testing, which may account for much of discrepancy. The fact that in this study, the impairment of diastolic volume and filling was manifested during

physical perturbation not at rest suggested the interplay of many mechanisms.

The interplay between the mechanical and metabolic effects of muscle contraction and diastolic filling during exercise has been documented (González-Alonso et al. 2008). For example, it has been shown that a single muscle contraction is capable of inducing an intramuscular pressure that effectively translocates more than 40% of the intra-muscular blood volume to the central venous pool (Stewart et al. 2004). Furthermore, it has been reported that the increase in filling volume during the first minute of exercise can be attributed to the regulation of the central venous pressure by the muscle pump (Notarius and Magder 1996). In the current study, LV filling in the non-disabled subjects was malleable to changes in workloads, despite the elicitation of exercise-induced tachycardia whereas neither EDV nor EDVR changed with exercise in the subjects with icSCI. The factors contributing to this response appeared to be independent of peak HR.

The concurrent reductions in peak EDV and EDVR in the subjects with icSCI at peak exercise were in accordance with previous studies that highlighted the association between the cardiac preloading condition and the diastolic filling rate (Borlaug et al. 2007; Pathé et al. 1990; Assa et al. 2013). In hemodialysis models, a significant reduction in transmitral flow velocities has been observed following a reduction in cardiac preloading (Assa et al. 2013). Additionally, an experimental study has demonstrated a significant increase in transmitral diastolic inflow velocities in healthy individuals after increasing preload via rapid saline infusion and a high salt diet (Mak et al. 2013). Increases in venous return tend to elevate left

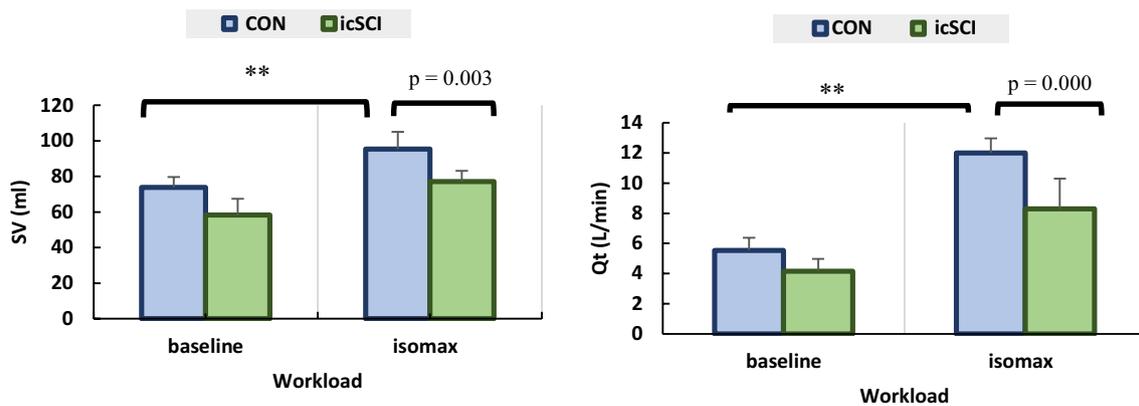


Fig. 5 Comparison of the cardiac output and stroke volume response to exercise. Bars represent group mean values and error bars represent standard deviations. **Signifies a statistically significant difference

($p < 0.05$) between the groups in the change from baseline to isomax. Abbreviation: Q_t cardiac output; SV stroke volume

ventricular filling, through higher diastolic filling velocities (Firstenberg et al. 2001; Assa et al. 2013).

Lower initial diastolic velocity and higher peak early inflow velocity/initial diastolic velocities ratio have been reported at rest in subjects with complete midthoracic SCI above T6 compared to non-SCI controls (Schreiber et al. 2017). This finding may suggest that LV diastolic function was declined in the individuals with SCI. The reduction in the LV early diastolic function was thought to be the result of impaired sympathetic activity. Of concern was that the level of SCI was below the level of cardiac sympathetic innervation, thus preserving the sympathetic outflow above the level of lesion (Schreiber et al. 2017). Thus, it is possible that other mechanisms might have been involved in the impairment of LV filling and cardiac preloading in those with icSCI. One such factor could have been an abnormal inotropic condition resulting from partial cardiac sympathetic deafferentation. Myocardial contractility is associated with diastolic velocities, as assessed by tissue Doppler cardiography (Zhang et al. 2002). Nevertheless, in the current study, a notable group difference in myocardial contractility was not observed at matched workloads. On the other hand, the compliance of the ventricle is known to influence cardiac volume loading. Conversely, it has been reported, in patients with complete spinal cord (Matos-Souza et al. 2011) and systemic arterial hypertension (Borges et al. 2006) that diastolic abnormalities could have occurred without major changes in the ventricular structure. In the subjects icSCI in the current study, a reduction EDVR at peak exercise was observed compared to controls, in concurrence with a lower peak work rate. However, the reduction was also apparent at the isomax intensity, thus making it impossible to rule out alterations in LV stiffness and compliance as mediators or contributors to the impaired LV filling overall.

Diminished blood volume has been reported in individuals with SCI secondary to partial loss of motor function below the level of injury (Houtman et al. 2000). Lord et al. (2018) found that a decrease of 25% in total blood volume resulted in 21% reduction in left ventricular end-diastolic volume and a 34% reduction in stroke volume (Lord et al. 2018). Additionally, a significant reduction in transmitral flow velocities, using Tissue Doppler echocardiography, has been reported after reduced preload during a dialysis session (Assa et al. 2013). The most direct evidence can be derived from models of hemodialysis (Assa et al. 2013). The data suggested that LV strain via hypovolemia independently influenced the LV filling. Furthermore, hypovolemia with lower cardiac preload has been shown to reduce cardiac distensibility and impede left ventricular diastolic function (Dorfman et al. 2008; Assa et al. 2013).

The potent physical properties of the cardiac structure may contribute to the volumetric measures and ventricular filling at a given filling pressure. A recent meta-analysis indicated that following traumatic complete spinal cord injury, a lesion-dependent impairment in the motor function and autonomic regulation along with activity limitation conspires to create cardiomyocyte atrophy (Squaire et al. 2018) and remodeling in left ventricular (LV) (Kessler et al. 1986; Eysmann et al. 1995; de Groot et al. 2006). Additionally, patients with quadriplegia have a tendency to decrease cardiac mass with aging due to reduction in the cardiac load and lack of increased afterload due to vasomotor impairment (Eysmann et al. 1995). This latter assumption may prove to apply in subjects with cervical incomplete lesions (tetraplegics), as they exhibit accentuated physical inactivity coupled with blood pooling and loss of vasomotor tone, which contributes to explaining the reported findings in this study.

Alternating intrathoracic pressure resulting from breathing mechanics and the pattern of breathing is known to

influence cardiac function by creating a respiratory muscle pump (Klabunde 2011). The respiratory pump influences venous return through augmentation of the changes in atrial pressure during the cardiac cycle (Harms et al. 1998). Impairment of ventilatory mechanics and substantial decrements in respiratory muscle strength could adversely affect ventricular filling and reduce cardiac stroke volume and particularly during exercise and physical activity.

The present study provides evidence of impaired cardiac filling, further limiting SV which may mediated my multifactorial mechanisms in icSCI. Altered LV compliance may also have played a role in the impairment. A lack of group differences in the cardiac afterload condition and the cardiac chronotropic and inotropic condition suggests that restrictions on overall cardiac output, in patients with icSCI, may be mediated by impaired LV diastolic performance, including both filling dynamics and the preloading volume.

Clinical implication

The findings of this study have both physiological and practical implications. It appears that, in people with icSCI, impaired diastolic filling, likely resulting from partial deafferentation and diminished muscle pump capacity, may contribute to overall limitations on cardiac function and oxygen delivery. The presence of increases in left ventricular stiffness, myocardial thickness and elasticity in the subjects with icSCI could be neither confirmed nor ruled out by the methods used in this study thus leaving the contribution of altered LV compliance and cardiac energetics open for consideration.

Limitations

The design used in this study required the use of a convenience sample due to the lack of a large database from which subjects could be randomly selected for inclusion. The sample size was determined by conjecture since preliminary data were not available for calculation of a necessary and sufficient sample size. While the size of this sample was sufficient for observing significant group differences in the main outcome variables, it was insufficient for assurance of representation with respect to the icSCI population at large. Moreover, heterogeneity of responses was also minimized by the inclusion of subjects within a narrow range of incomplete cervical lesions, all of which were above the cardiac sympathetic exit of the spinal cord. Women (by recruitment convenience) and participants with complete spinal cord injury (by design) were not included in this study creating a degree of gender bias. Thus, indications of this study

must be delimited to the current sample and can be applied broadly only as a basis for plausibility.

Blood pressure cannot be measured noninvasively during arm-ergometer CPET and was thus was measured immediately during the interspaced non-exercise period, rather than during actual exercise due to the impracticality of obtaining these measurements noninvasively during arm ergometer exercise. As a result, the systemic vascular resistance computations reflected the rate of decrease in blood pressure during immediate recovery, which is generally dependent on the pressure obtained during the preceding exercise bout. Variability in this response could have been introduced by the extent of incompleteness and location of the spinal cord lesion.

Although ZCG measures accurately index EDV and EDVR, the current study relied upon the generally accepted assumption that in the context of an anatomically intact cardiovascular system and even in the context of stable edema, venous return is equal to LVSV on a beat-to-beat basis due to impositions of closed-loop cardiovascular system. The assumption also applies to those with SCI in general and since abnormalities that would acutely affect plasma volume were not identified in the current population, we must conclude that the closed system principle is in operation.

Conclusions

This study provides evidence of impaired diastolic function in response to increases in exercise workload in individuals who have icSCI. While left ventricular filling is affected by a complex interplay of determinants, the diastolic function limitation appeared to be affected by muscle pump restriction and therefore venous return. Decreased ventricular wall compliance could also have contributed to the impairment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Allen MT, Fahrenberg J, Kelsey RM et al (1990) Methodological guidelines for impedance cardiography. *Psychophysiology* 27:1–23
- American College of Sports Medicine (2018) ACSM's guidelines for exercise testing and prescription, 10th edn. Wolters Kluwer, Philadelphia
- Assa S, Hummel YM, Voors AA et al (2013) Changes in left ventricular diastolic function during hemodialysis sessions. *Am J Kidney Dis* 62:549–556
- Baan J, Arntzenius AC, Yellin EL (2012) *Cardiac dynamics*. Springer, New York
- Binkhorst RA, Oeseburg B, Hopman MT (1992) Cardiovascular responses in paraplegic subjects during arm exercise. *Eur J Appl Physiol* 65:73–78
- Borges MCC, Colombo RC, Gonçalves JGF et al (2006) Longitudinal mitral annulus velocities are reduced in hypertensive subjects with or without left ventricle hypertrophy. *Hypertension* 47:854–860
- Borlaug BA, Melenovsky V, Redfield MM et al (2007) Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. *J Am Coll Cardiol* 50:1570–1577
- Bradtmiller B (2000) Anthropometry for persons with disabilities: needs in the twenty-first century. In: *Proceedings of the RESNA 2000 annual conference*. ERIC, pp 543–548
- Charloux A, Lonsdorfer-Wolf E, Richard R et al (2000) A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the “direct” Fick method. *Eur J Appl Physiol* 82:313–320
- Cheng CP, Freeman GL, Santamore WP et al (1990) Effect of loading conditions, contractile state, and heart rate on early diastolic left ventricular filling in conscious dogs. *Circ Res* 66:814–823
- Crisafulli A, Marongiu E, Ogoh S (2015) Cardiovascular reflexes activity and their interaction during exercise. *Biomed Res Int*. <https://doi.org/10.1155/2015/394183>
- Currie KD, West CR, Hubli M et al (2015) Peak heart rates and sympathetic function in tetraplegic nonathletes and athletes. *Med Sci Sports Exerc* 47:1259–1264. <https://doi.org/10.1249/MSS.0000000000000514>
- Davis GM, Servedio FJ, Glaser RM et al (1990) Cardiovascular responses to arm cranking and FNS-induced leg exercise in paraplegics. *J Appl Physiol* 69:671–677
- de Groot PC, van Dijk A, Dijk E, Hopman MT (2006) Preserved cardiac function after chronic spinal cord injury. *Arch Phys Med Rehabil* 87:1195–1200. <https://doi.org/10.1016/j.apmr.2006.05.023>
- De Rossi G, Matos-Souza JR, Costa E et al (2014) Physical activity and improved diastolic function in spinal cord-injured subjects. *Med Sci Sports Exerc* 46:887–892
- Deboeck G, Taboada D, Hagan G et al (2014) Maximal cardiac output determines 6 minutes walking distance in pulmonary hypertension (research article). *PLoS ONE* 9:e92324. <https://doi.org/10.1371/journal.pone.0092324>
- DeVeau KM, Harman KA, Squair JW et al (2017) A comparison of passive hindlimb cycling and active upper-limb exercise provides new insights into systolic dysfunction after spinal cord injury. *Am J Physiol Heart Circ Physiol* 313:H861–H870
- Dorfman TA, Rosen BD, Perhonen MA et al (2008) Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting. *J Appl Physiol* 104:1037–1044
- Driussi C, Ius A, Bizzarini E et al (2014) Structural and functional left ventricular impairment in subjects with chronic spinal cord injury and no overt cardiovascular disease. *J Spinal Cord Med* 37:85–92
- Edvardsen E, Hansen BH, Holme IM et al (2013) Reference values for cardiorespiratory response and fitness on the treadmill in a 20-to 85-year-old population. *Chest* 144:241–248
- European RS, Society AT (2002) ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 166:518
- Eysmann SB, Douglas PS, Katz SE et al (1995) Left ventricular mass and diastolic filling patterns in quadriplegia and implications for effects of normal aging on the heart. *Am J Cardiol* 75:201–203
- Figoni SF, Glaser RM, Rodgers MM et al (1991) Acute hemodynamic responses of spinal cord injured individuals to functional neuromuscular stimulation-induced knee extension exercise. *J Rehabil Res Dev* 28:9–18
- Firstenberg MS, Greenberg NL, Main ML et al (2001) Determinants of diastolic myocardial tissue Doppler velocities: influences of relaxation and preload. *J Appl Physiol* 90:299–307
- Fragata J, Areias JC (1996) Effects of gradual volume loading on left ventricular diastolic function in dogs: implications for the optimisation of cardiac output. *Heart* 75:352–357. <https://doi.org/10.1136/hrt.75.4.352>
- Garshick E, Kelley A, Cohen SA et al (2005) A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 43:408
- Ginis KAM, Phang SH, Latimer AE, Arbour-Nicitopoulos KP (2012) Reliability and validity tests of the leisure time physical activity questionnaire for people with spinal cord injury. *Arch Phys Med Rehabil* 93:677–682
- Godinez J (2018) Hemodynamic and cardiorespiratory responses to various arm cycling regimens in men with spinal cord injury
- González-Alonso J, Mortensen SP, Jeppesen TD et al (2008) Haemodynamic responses to exercise, ATP infusion and thigh compression in humans: insight into the role of muscle mechanisms on cardiovascular function. *J Physiol* 586:2405–2417
- Guyton AC, Lindsey AW, Abernathy B, Richardson T (1957) Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol Leg Content* 189:609–615
- Harms CA, Wetter TJ, McClaran SR et al (1998) Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol* 85:609–618
- Harrison MR, Clifton GD, Penneil AT, DeMaria AN (1991) Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol* 67:622–627
- Hasnan N, Ektas N, Tanhoffer AIP et al (2013) Exercise responses during functional electrical stimulation cycling in individuals with spinal cord injury. *Med Sci Sports Exerc* 45:1131–1138. <https://doi.org/10.1249/MSS.0b013e3182805d5a>
- Hoekstra F, Martinsen ØG, Verdaasdonk RM et al (2012) The initial systolic time interval in patients with spinal cord injury measured with impedance cardiography. *J Phys Conf Ser* 407:5. <https://doi.org/10.1088/1742-6596/407/1/012025>
- Hostettler S, Leuthold L, Brechbühl J et al (2012) Maximal cardiac output during arm exercise in the sitting position after cervical spinal cord injury. *J Rehabil Med* 44:131–136
- Houtman S, Oeseburg B, Hopman MT (2000) Blood volume and hemoglobin after spinal cord injury. *Am J Phys Med Rehabil* 79:260–265. <https://doi.org/10.1097/00002060-200005000-00008>
- Inskip JA, Ramer LM, Ramer MS et al (2012) Spectral analyses of cardiovascular control in rodents with spinal cord injury. *J Neurotrauma* 29:1638–1649
- Jacobs PL, Nash MS (2004) Exercise recommendations for individuals with spinal cord injury. *Sports Med* 34:727
- Kessler KM, Pina I, Green B et al (1986) Cardiovascular findings in quadriplegic and paraplegic patients and in normal subjects. *Am J Cardiol* 58:525–530
- Kessler KM, Pina I, Green B et al (1987) Cardiovascular findings in quadriplegic and paraplegic patients and in normal subjects. *Surv Anesthesiol* 31:257
- Klabunde R (2011) *Cardiovascular physiology concepts*. Lippincott Williams & Wilkins, Philadelphia

- Lasko-McCarthy P, Davis JA (1991) Protocol dependency of VO₂max during arm cycle ergometry in males with quadriplegia. *Med Sci Sports Exerc* 23:1097–1101
- Lavine SJ (2005) Effect of heart rate and preload on index of myocardial performance in the normal and abnormal left ventricle. *J Am Soc Echocardiogr* 18:133–141
- Leão RN, Silva PM, Branco L et al (2017) Systolic time ratio measured by impedance cardiography accurately screens left ventricular diastolic dysfunction in patients with arterial hypertension. *Clin Hypertens* 23:28
- Lee YH, Lee JH, Kim SH et al (2017) Hemodynamic adaptations to regular exercise in people with spinal cord injury. *Ann Rehabil Med* 41:25–33. <https://doi.org/10.5535/arm.2017.41.1.25>
- Little WC, Downes TR (1990) Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 32:273–290. [https://doi.org/10.1016/0033-0620\(90\)90017-V](https://doi.org/10.1016/0033-0620(90)90017-V)
- Lord R, MacLeod D, George K et al (2018) Reduced left ventricular filling following blood volume extraction does not result in compensatory augmentation of cardiac mechanics. *Exp Physiol* 103:495–501
- Lujan HL, DiCarlo SE (2016) Alterations in cardiac electrophysiology after spinal cord injury and implications for exercise. *The physiology of exercise in spinal cord injury*. Springer, New York, pp 77–103
- Machač S, Radvanský J, Kolář P, Kříž J (2016) Cardiovascular response to peak voluntary exercise in males with cervical spinal cord injury. *J Spinal Cord Med* 39:412–420
- Maher JL, Cowan RE (2016) Comparison of 1-versus 3-minute stage duration during arm ergometry in individuals with spinal cord injury. *Arch Phys Med Rehabil* 97:1895–1900
- Mak GS, Sawaya H, Khan AM et al (2013) Effects of subacute dietary salt intake and acute volume expansion on diastolic function in young normotensive individuals. *Eur Heart J Cardiovasc Imaging* 14:1092–1098
- Malliani A, Peterson DF, Bishop VS, Brown AM (1972) Spinal sympathetic cardiocardiac reflexes. *Circ Res* 30:158–166
- Matos-Souza JR, Pithon KR, Ozahata TM et al (2009) Altered left ventricular diastolic function in spinal cord injury subjects. *Am Heart Assoc*
- Matos-Souza JR, Pithon KR, Oliveira RTD et al (2011) Altered left ventricular diastolic function in subjects with spinal cord injury. *Spinal Cord* 49:65
- Maynard FM, Bracken MB, Creasey G et al (1997) International standards for neurological and functional classification of spinal cord injury. *Spinal Cord* 35:266–274
- Medicine AC of S (1991) Guidelines for exercise testing and prescription. Williams & Wilkins, Philadelphia
- Milia R, Roberto S, Marongiu E et al (2014) Improvement in hemodynamic responses to metaboreflex activation after one year of training in spinal cord injured humans. *Biomed Res Int* 2014:893468
- Notarius CF, Magder S (1996) Central venous pressure during exercise: role of muscle pump. *Can J Physiol Pharmacol* 74:647–651
- Odom EC, Fang J, Zack M et al (2016) Associations between cardiovascular health and health-related quality of life, behavioral risk factor surveillance system, 2013. *Prev Chronic Dis* 13:E99. <https://doi.org/10.5888/pcd13.160073>
- Pathé M, Laurenceau JL, Baron B et al (1990) Influence of preload changes on the filling function of the left heart ventricle studied by Doppler echocardiography. *Arch Mal Coeur Vaiss* 83:2061–2066
- Patterson RP (1989) Fundamentals of impedance cardiography. *IEEE Eng Med Biol Mag* 8:35–38
- Paulus WJ, Tschöpe C, Sanderson JE et al (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 28:2539–2550
- Permutt S, Caldini P (1978) Regulation of cardiac output by the circuit: venous return. *Cardiovasc Syst Dyn*:465–479
- Phillips WT, Kiratli BJ, Sarkarati M et al (1998) Effect of spinal cord injury on the heart and cardiovascular fitness. *Curr Probl Cardiol* 23:641–716
- Richard R, Lonsdorfer-Wolf E, Charloux A et al (2001) Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. *Eur J Appl Physiol* 85:202–207
- Richardson RS, Harms CA, Grassi B, Hepple RT (2000) Skeletal muscle: master or slave of the cardiovascular system? *Med Sci Sports Exerc* 32:89
- Riebe D, Franklin BA, Thompson PD et al (2015) Updating ACSM's recommendations for exercise preparticipation health screening. <https://doi.org/10.7916/D8M908BH>
- Robach P, Calbet JA, Thomsen JJ et al (2008) The ergogenic effect of recombinant human erythropoietin on VO₂max depends on the severity of arterial hypoxemia. *PLoS ONE* 3:e2996
- Schreiber R, Paim LR, de Rossi G et al (2017) Reduced Sympathetic Stimulus and Angiotensin 1–7 Are Related to Diastolic Dysfunction in Spinal Cord-Injured Subjects. *J Neurotrauma* 34:2323–2328
- Serón P, Muñoz S, Lanás F (2010) Levels of physical activity in an urban population from Temuco, Chile. *Rev Med Chil* 138:1232–1239. /S0034–98872010001100004
- Sidebotham D (2007) Cardiothoracic critical care. Elsevier Health Sciences, Amsterdam
- Siebenmann C, Rasmussen P, Sørensen H et al (2015) Cardiac output during exercise: a comparison of four methods. *Scand J Med Sci Sports* 25:e20–e27
- Squair JW, DeVeau KM, Harman KA et al (2018) Spinal Cord Injury Causes Systolic Dysfunction and Cardiomyocyte Atrophy. *J Neurotrauma* 35:424–434. <https://doi.org/10.1089/neu.2017.4984>
- Spiering W, Van Es PN, De Leeuw PW (1998) Comparison of impedance cardiography and dye dilution method for measuring cardiac output. *Heart* 79:437–441
- Stewart J, Medow MS, Montgomery L, Mcleod K (2004) Decreased skeletal muscle pump activity in patients with postural tachycardia syndrome and low peripheral blood flow. *Am J Physiol Heart Circ Physiol* 286:H1216–H1222. <https://doi.org/10.1152/ajpheart.00738.2003>
- Tordi N, Mourot L, Matusheski B, Hughson RL (2004) Measurements of cardiac output during constant exercises: comparison of two non-invasive techniques. *Int J Sports Med* 25:145–149
- Warburton DE, Jamnik V, Bredin SS et al (2018) The 2019 physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePAR-med-X+). *Health Fit J Can* 11:80–83
- Wecht JM, Bauman WA (2013) Decentralized cardiovascular autonomic control and cognitive deficits in persons with spinal cord injury. *J Spinal Cord Med* 36:74–81. <https://doi.org/10.1179/2045772312Y.0000000056>
- Weidner N, Rupp R, Tansey KE (2017) Neurological Aspects of Spinal Cord Injury. Springer, New York
- West C, Bellantoni A, Krassioukov A (2013) Cardiovascular function in individuals with incomplete spinal cord injury: a systematic review. *Top Spinal Cord Inj Rehabil* 19:267–278
- Zhang Y, Mei W, Pik-Yuk HO et al (2002) Left ventricular long-axis changes in early diastole and systole: impact of systolic function on diastole. *Clin Sci* 102:515–522