Left ventricular mechanics in untrained and trained males with tetraplegia

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Abstract

Reduced left ventricular (LV) function is common in tetraplegia, yet it is unknown if intrinsic myocardial function is attenuated. This study examined the effect of SCI and exercise-training status on LV mechanics (intrinsic function) and LV systolic/diastolic function by comparing untrained (UT) and trained (TT) individuals with tetraplegia, and able-bodied (AB) individuals. Individuals with tetraplegia had a traumatic, chronic, motor-complete cervical spinal cord injury. Nine UT males (40±10 yrs), eight TT males (30±5 yrs) and nine AB males (37±9 yrs) participated in the study. LV indices were assessed using two-dimensional transthoracic echocardiography, with speckle-tracking analysis for the determination of LV mechanics. For systolic function, stroke volumes were lower in both UT (59±9 ml, \(P<0.001\)) and TT (63±9 ml, \(P<0.001\)) relative to AB (82±11 ml), while systolic mechanics were similar across groups. Diastolic function was only reduced in UT, including a lower ratio of early to late transmitral filling velocity (1.55±0.28) relative to TT (2.07±0.42, \(P<0.05\)) and AB (2.44±0.61, \(P<0.01\)) and longer isovolumetric relaxation times in UT (101±7 ms) relative to TT (88±11 ms, \(P<0.05\)) and AB (85±6 ms, \(P<0.01\)). Diastolic mechanics (apical circumferential strain rate) were significantly enhanced in TT (3.03±0.83 \(s^{-1}\)) compared to AB (1.85±0.65 \(s^{-1}\), \(P<0.05\)). There was a trend (\(p=0.062\)) for a between-group difference in apical radial diastolic strain rate (UT: -2.51±0.83 \(s^{-1}\); TT: -3.92±1.96 \(s^{-1}\); AB: -1.84±0.46 \(s^{-1}\)). In tetraplegia, attenuated LV systolic function is not attributed to intrinsic dysfunction, while exercise-training status appears to improve both global LV diastolic function and LV mechanics.

**Keywords:** echocardiography; exercise; spinal cord injury; strain rate.
Introduction

Cardiac adaptations following a spinal cord injury (SCI) have been well documented by echocardiography studies over the past few decades. While changes in both left ventricular (LV) structure and global LV systolic and diastolic function have been observed in individuals with tetraplegia and paraplegia,\(^1\)\(^-\)\(^12\) there appears to be a lesion level-dependent effect of SCI on cardiac function with the most severe changes occurring in individuals with tetraplegia. In particular, reductions in global LV systolic function including stroke volume (SV), cardiac output (\(\tilde{Q}\)) and ejection fraction (EF) have been documented in both untrained individuals with tetraplegia (UT) and trained individuals with tetraplegia (TT) relative to either individuals with paraplegia or able-bodied (AB) controls.\(^1\)\(^,\)\(^5\)\(^,\)\(^8\)\(^,\)\(^11\)\(^,\)\(^12\) Conversely, global LV diastolic function appears to be influence by exercise-training status whereby global LV diastolic dysfunction in present in UT while Paralympic athletes with tetraplegia (TT) have global LV diastolic values comparable to AB individuals.\(^11\)

While it has long been speculated that the differences in global function are attributed to reductions in loading, it still remains to be determined whether inherent dysfunction in the myocardium itself is a contributing factor. The assessment of LV mechanics has become increasingly more common in clinical investigations due to its capacity to quantify the magnitude and rate of LV deformation (strain and rotation) in systole and diastole.\(^13\) In AB patients with global LV systolic dysfunction, including lower SV, \(\tilde{Q}\) and EF, there is a concomitant reduction in systolic mechanics.\(^14\) Impairments in systolic mechanics have also been documented in AB populations with normal or preserved EF,\(^15\) highlighting the potential of LV mechanics to serve as early diagnostic markers of impending LV dysfunction. Additionally, AB individuals with global LV diastolic dysfunction also demonstrate attenuated LV diastolic
mechanics. We recently demonstrated that LV mechanics were not affected in TT when compared to Paralympic athletes with paraplegia. However, it remains to be determined how LV mechanics are affected in UT, in addition to how the values in UT and TT compare to a control sample of AB individuals. Therefore, the primary objective of this study was to examine the effect of SCI on both LV mechanics and indices of global LV systolic and diastolic function by comparing individuals with tetraplegia and AB individuals. The secondary objective was to examine the effect of chronic exercise-training on LV outcomes given evidence that exercise-training may improve diastolic function post-SCI. This was accomplished by including both a UT and TT (i.e., Paralympic Wheelchair Rugby athletes) group. We hypothesized that any impairment in global measures of LV systolic and diastolic function in the groups with tetraplegia would be attributed to reductions in indices of LV mechanics.
Materials and Methods

Participants

Inclusion criteria for the UT and TT groups were traumatic, chronic (≥1 year post-injury), motor-complete cervical SCI. The neurological level and completeness of the SCI were confirmed using the International Standards for Neurological Classification of SCI.\(^\text{17}\) The UT and AB groups had to be engaged in ≤5 hr/wk of physical activity or exercise training while the TT group had to be engaged in ≥15 hr/wk of exercise training and have at least 3 years of competitive sports participation. Exclusion criteria included <18 years of age, any acute illness or history of cardiovascular disease that was confirmed with a verbal medical history, or any cognitive or language barrier that prevented them from following English instructions. All participants were free from overt disease and no participants reported comorbidities including hypertension, diabetes, and dyslipidemia. Two AB, five UT and three TT participants were taking regular medications, which are outlined in Table 1. All procedures conformed to the Declaration of Helsinki and were approved by the Research Ethics Boards at the University of British Columbia and Brunel University, and all participants provided written informed consent. Participants were instructed to abstain from food and drink for four hours, caffeine and alcohol for 12 hours, and exercise for 24 hours prior to testing. On the day of testing, individuals with tetraplegia were asked to void their bladders to reduce the influence of sympathetic reflex activation on blood pressure.

Hemodynamic measurements

Following five minutes of quiet rest, seated brachial artery blood pressures were measured in duplicate from the left brachial artery using an automated machine (Dinamap Pro 300 V2; GE
Healthcare, Milwaukee, USA). Participants then transferred to a supine position and following ten minutes of rest, supine brachial artery blood pressures were recorded in duplicate from the left brachial artery.

Cardiac assessment

Participants were positioned in the left lateral decubitus position. All cardiac images were collected using two-dimensional echocardiography (Vivid 7; GE Healthcare, Horten, Norway) and analyzed offline by a single blinded investigator using dedicated software (EchoPAC; GE Healthcare, Horten, Norway) according to the recommendations of the American Society for Echocardiography.13, 18, 19 All cardiac indices were determined from the average of three cardiac cycles.

LV dimensions including internal diameter, interventricular septal wall thickness and posterior wall thickness at end-diastole and end-systole were determined from parasternal long axis views. Relative wall thickness was calculated as [(2×end-diastolic posterior wall thickness)/end-diastolic LV internal diameter]. LV mass was calculated according to the formula by Devereux et al., and indexed to body surface area calculated using the Du Bois and Du Bois equation.18 Sphericity index was calculated as the ratio of LV maximum long-axis diameter by LV maximum short-axis diameter.20 LV end-diastolic and end-systolic volumes, SV and EF were determined from the apical four-chamber view using the modified single-plane Simpson’s method. \( \dot{Q} \) was calculated as the product of SV and heart rate. Pulsed-wave Doppler at the tips of the mitral valve leaflet was used to determine isovolumetric relaxation time, early (E) and late (A) transmitral filling velocities, and the resultant E/A ratio.
Indices of LV mechanics were derived from apical four-chamber and parasternal short axis images at the level of the mitral valve (basal), papillary muscle (mid), and apex (apical). Images were analyzed using 2D speckle-tracking software in accordance with current guidelines.\textsuperscript{13} To control for differences in heart rate, raw speckle-tracking traces were imported into customized post-processing software (2D Strain Analysis Tool, Stuttgart, Germany), which interpolates the data into 600 points in systole and 600 points in diastole using a standard cubic spline algorithm. Peak strain and strain rate in systole and diastole were determined for each parasternal short axis view (radial, circumferential) and the apical four-chamber view (longitudinal). Basal and apical peak rotation and rotation rate in systole and diastole were determined. Twist was determined as the maximum value obtained when subtracting the frame-by-frame basal rotation from the frame-by-frame apical rotation. Peak systolic twisting velocity and early diastolic untwisting velocity were derived in the same manner from frame-by-frame basal and apical rotation rate data. Peak torsion, a measure of twist normalized to LV chamber size, was calculated by dividing peak twist by the LV end-diastolic length. To determine whether LV mechanical function in SCI is potentially underpinned by altered subendocardial/subepicardial contribution to LV twist, the torsion-to-shortening ratio was calculated as previously described.\textsuperscript{21}

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Science software (IBM Corporation, Armonk, NY, USA) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA). Data were assessed for normality using Shapiro-Wilk tests and Q-Q plot analyses. Between group differences (UT, TT, AB) were assessed using one-way analyses of variance and Kruskal-Wallis tests for normally and non-normally distributed data, and Bonferroni and Dunn’s
post-hoc comparisons were performed when significant main effects were detected. To determine whether differences in global LV function following SCI were associated with underpinning mechanics, Pearson correlations were performed between global and mechanic indices using a pooled sample of UT and TT. Between-group differences in SCI-specific demographics were compared using an independent t-test. Data are presented as mean ± SD unless otherwise noted, with $P<0.05$ considered statistically significant.
Results

Participant characteristics are presented in Table 1. Individuals in the UT group were older and had a longer time post-injury compared to the TT group. Supine and seated heart rates were higher in UT compared to AB, while seated blood pressures were lower in both UT and TT relative to AB.

LV dimensions and global LV systolic and diastolic functional outcomes are presented in Table 2. Both UT and TT had smaller aortic diameters, end-diastolic LV internal dimensions, and end-diastolic volumes compared to AB. The relative wall thickness was larger in UT compared to AB, while LV mass index was larger in UT compared to TT. For global LV systolic function, the UT group had a lower EF than the AB group, while both groups with tetraplegia had lower SV relative to AB. Reduced LV diastolic function including higher A, lower E/A and longer isovolumetric relaxation time was present in UT compared to both TT and AB.

LV mechanic parameters are presented in Table 3. There were no statistically significant between-group differences in rotation, rotation rate, twist, twisting and untwisting velocities, torsion, torsion-to-shortening ratio, strain, and basal and apical strain rates. For LV systolic mechanics at the mid level, circumferential strain rate was higher in both UT and TT compared to AB, while radial strain rate was only lower in UT compared to TT (TT vs. AB, \( P=0.092 \)). For LV diastolic mechanics, apical circumferential strain rate was higher in the TT group compared to AB, while there was a trend for between-group differences in mid level circumferential strain rate (\( P=0.088 \)) and apical radial strain rate (\( P=0.062 \)). In the groups with tetraplegia, diastolic apical radial strain rate was related to E/A (Fig 1A), while there was a trending relationship between diastolic apical circumferential strain rate and isovolumetric relaxation time (Fig 1B). Confidence intervals for all echocardiography data are presented in a Supplementary Table.
Discussion

This is the first study to examine the effect of SCI and exercise-training status on LV mechanics. Compared to AB individuals, global LV systolic function was reduced while LV systolic mechanics were similar in individuals with tetraplegia, regardless of training status. In contrast, global LV diastolic function was similar in the TT and AB groups, but significantly lower in the UT group. This finding may be attributed to enhanced LV diastolic mechanics in exercise-trained individuals with tetraplegia.

Indices of global LV systolic function were reduced in the UT and TT groups relative to AB individuals. Reductions in SV in individuals with tetraplegia have consistently been demonstrated,\(^1, 8, 11, 12\) while EF has been reported as reduced\(^8\) or unchanged.\(^5, 11, 12\) It is important to note the average EFs observed in our samples with tetraplegia were not below a clinical threshold (i.e., \(≤54\%\)),\(^{18}\) and therefore should probably not be interpreted as systolic dysfunction. Instead, we propose that the reduction in SV can be attributed to the reduction in end-diastolic volume, as end-systolic volume was similar between groups. Reductions in preload and subsequently end-diastolic volume following SCI are attributed to decreased venous return.\(^5\) Mechanical effects including SCI-induced reductions in circulating blood volume\(^{22}\) and the loss of the skeletal and respiratory muscle pumps,\(^{23, 24}\) as well as sympathetic effects including reductions in vascular tone and an absence of vasoconstriction below the level of injury\(^{25, 26}\) are responsible for the reduction in venous return.

Despite reductions in global LV systolic function, most indices of LV mechanics in systole were similar between UT, TT and AB. This was a surprising observation given both twist/torsion and strain are known to be correlated with SV and EF in non-SCI populations.\(^{27, 28}\) Additionally, head-down bed rest, which mirrors the typical reductions in LV dimensions and
global LV systolic function observed following SCI, have also documented reductions in strain and systolic strain rates. That both groups with tetraplegia exhibited ‘normal’ values for systolic mechanics in the face of reduced global systolic function suggests that there may be a mechanical compensation post-SCI to at least partially support systolic function. This “maintenance” of systolic mechanics in our groups with tetraplegia may be secondary to neuronal and/or non-neuronal adaptations. While we cannot rule out possible neuronal mechanisms in our study, we believe they are unlikely to explain maintained systolic mechanics in our sample of individuals with tetraplegia since seated blood pressure was substantially lower in the groups with tetraplegia, implying a loss of descending sympathetic control. This is supported by evidence of attenuated maximum heart rates in both untrained and trained individuals with tetraplegia. Instead, we believe the chronically reduced blood pressure in our groups with tetraplegia acted to reduce afterload and create a mechanically conducive environment for the preservation of systolic mechanics. Evidence in support of this postulate is found in an AB study, whereby nitroglycerin administration increased both longitudinal and circumferential strain rates. Preservation of systolic mechanics may also be attributed to structural adaptations. LV shape, measured using the sphericity index, is related to LV twist. Similar to previous studies, we did observe a reduction in end-diastolic LV internal diameter in the groups with tetraplegia. However, despite these reductions, sphericity index was similar across groups. Thus despite reductions in its dimensions, LV shape is preserved following SCI, which in turn may aid in the maintenance of LV mechanics.

Contrary to the systolic function observations, indices of global LV diastolic function were only reduced in the UT group. The maintenance of diastolic function in athletes with tetraplegia has been previously demonstrated. We reported no difference in diastolic indices
between Paralympic athletes with tetraplegia and paraplegia,\textsuperscript{12} as well as no difference in transmitral filling velocities and tissue Doppler velocities between Paralympic athletes with tetraplegia and AB individuals.\textsuperscript{8} More recently, de Rossi and colleagues\textsuperscript{11} observed a higher ratio of early transmitral filling velocity to early myocardial tissue velocity (E/E’) in sedentary individuals with tetraplegia compared to athletes with tetraplegia. Normal diastolic function is indicated by an E/E’ ratio <8.\textsuperscript{34} Athletes in this study were below this cutoff (6.3±0.4) while the sedentary group was above (8.8±0.8), suggesting exercise following SCI can prevent diastolic dysfunction. Presently no studies have identified the mechanisms responsible for the maintenance of diastolic function in athletes with tetraplegia. We observed significantly faster apical circumferential strain rates in diastole in TT relative to AB. Additionally, circumferential strain rate at the papillary muscle and apical radial strain rate during diastole were also trending with higher values in the groups with tetraplegia. Collectively these observations suggest diastolic mechanics may be enhanced in athletes with tetraplegia, which facilitates LV filling and subsequently attenuates the reduction in function, which is observed in the UT group. This is supported by the relationships between apical strain rate and E/A and isovolumetric relaxation time. These relationships have been previously reported in AB individuals, where E/A was related to radial, longitudinal and circumferential strain rates in diastole.\textsuperscript{35} In terms of the temporal sequence of diastole, untwisting coincides with relaxation and precedes diastolic suction and subsequent filling.\textsuperscript{36} Thus a faster diastolic strain rate would shorten isovolumetric relaxation time and lengthen the filling phase leading to an increase in E/A.

There are a variety of etiologies for LV systolic and diastolic dysfunctions, with the most common including myocardial ischemia (from coronary heart disease), hypertension and diabetes.\textsuperscript{37} None of our participants reported overt cardiovascular disease or comorbidities, and
blood pressures in our groups with tetraplegia were lower than the AB individuals. Additionally, the observation of normal or enhanced LV mechanics in those with tetraplegia suggests the intrinsic function of the myocardium was not impaired. Therefore, the observed differences in LV dimensions and global LV function between our groups with tetraplegia and AB individuals are likely attributed to decreased physical activity levels due to lower limb paralysis, and/or reduced filling due to venous pooling. Bed-rest studies in AB individuals, which both reduce physical activity levels and chronically unload the heart, demonstrate LV atrophy and reductions in global LV systolic and diastolic function.\textsuperscript{29, 31} Supine exercise training during bed-rest, on the other hand, has been shown to mitigate some of these adaptations.\textsuperscript{38, 39} Our cross-sectional comparison of UT and TT suggest regular exercise training post-SCI is associated with the maintenance of global LV diastolic function, an observation likely attributed to a significant increase in some LV diastolic mechanical parameters. In AB individuals with and without diastolic dysfunctions, exercise training is associated with favorable improvements in indices of global LV function and diastolic LV mechanics.\textsuperscript{40, 41} In individuals with SCI, exercise-training studies examining cardiac outcomes are limited to lower-limb interventions\textsuperscript{42, 43} or hybrid training (active arm with lower limb functional electrical stimulation)\textsuperscript{44} where positive cardiac adaptations have been reported, likely due to the facilitation of venous return by activation of the muscle pump. Given the cross-sectional nature of our study, it is unknown whether exercise-training post-SCI prevented the reduction in diastolic function observed in UT or helped recover it normative levels. To address this issue, future research should consider examining the capacity of both upper limb, lower limb and hybrid exercise training on modulating LV dimensions, global function and mechanics in individuals with SCI.
In AB populations, dysfunctions in both global LV function and LV mechanics are associated with an increased risk of developing cardiovascular disease.\(^4\) Furthermore, impairments in both measures of global LV systolic and diastolic function and LV mechanics derived from echocardiography are used in the diagnosis of heart failure.\(^5\) It is well established that cardiovascular disease is the leading cause of mortality in individuals with SCI,\(^6\) occurring at earlier ages than their AB peers.\(^7\) However similar to the AB population,\(^8\) coronary heart disease and cerebrovascular disease are the most prevalent forms of cardiovascular disease in individuals with SCI. In particular, individuals with tetraplegia are estimated to experience a five-fold increase in risk of cerebrovascular disease, while individuals with paraplegia are at an increased risk of coronary heart disease.\(^9,10\) While LV dysfunction may contribute to the pathology of coronary heart and cerebrovascular diseases, it does not appear to be the primary mechanism. Thus it remains to be determined whether the LV adaptations observed following tetraplegia occur as a compensatory mechanism to maintain function, or are indicative of latent cardiovascular disease. While the extent to which global LV systolic and diastolic function were reduced in our samples with tetraplegia would not meet a clinically relevant AB threshold, it is important to note that our samples were relatively young. Thus, further reduction in these outcomes over time is plausible, potentially increasing the risk for future cardiac related health problems.

**Limitations**

For this project, only a relatively low number of high-performance athletes with tetraplegia volunteered to participate. One consequence was that individuals in the TT group were significantly younger than those in the UT group. The primary differences between these
groups were in the indices of diastolic function. While global LV diastolic function decreases with age, diastolic dysfunction is typically observed later in life (>60 years). Additionally, Eysmann et al. observed no significant difference in the E/A ratio between young (<50 years) and old (≥50 years) individuals with tetraplegia. Individuals in our TT group also had a shorter time post-injury. In humans, the time course of cardiac adaptations following a SCI is presently unknown. Bed rest studies, which mimic the cardiac adaptations observed with SCI have documented changes in diastolic function within 5 weeks. Additionally, a previous study in sedentary individuals with tetraplegia who were a similar age and had a similar time post-injury as our TT group demonstrated reduced diastolic function. Therefore we do not believe differences in age or time-post injury explain the observed differences between the UT and TT groups.

Conclusion

In conclusion, our novel investigation into LV mechanics in individuals with tetraplegia provides two important contributions to the literature. First, similar LV systolic mechanics in the face of reduced global LV systolic function suggests that reductions observed in individuals with tetraplegia may be caused by reductions in loading rather than intrinsic changes in LV muscle function. Second, extensive exercise training in SCI is associated with enhanced LV diastolic mechanics, likely contributing to the preservation of global LV diastolic function.
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Author Disclosure Statement

No competing financial interests exist.
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