ORIGINAL ARTICLE

Altered left ventricular diastolic function in subjects with spinal cord injury

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Study design: This is cross-sectional study.

Objectives: The aim of this study is to investigate the cardiac structure and function of subjects with spinal cord injury (SCI) and the impact of metabolic, hemodynamic and inflammatory factors on these parameters.

Setting: São Paulo, Brazil.

Methods: Sixty-five nondiabetic, nonhypertensive, sedentary, nonsmoker men (34 with SCI and 31 healthy subjects) were evaluated by medical history, anthropometry, laboratory tests, analysis of hemodynamic and inflammatory parameters and echocardiography.

Results: Subjects with SCI had lower systolic blood pressure and higher levels of C-reactive protein and tumor necrosis factor receptors than the healthy ones. Echocardiography data showed that the SCI group presented similar left ventricular (LV) structural and systolic parameters, but lower initial diastolic velocity (E_m) (9.2 ± 0.5 vs 12.3 ± 0.5 cm s⁻¹; $P < 0.001$) and higher peak early inflow velocity (E)/ E_m ratio (7.7 ± 0.5 vs 6.1 ± 0.3 ; $P = 0.009$) compared with the able-bodied group, even after adjustment for systolic blood pressure and C-reactive protein levels. Furthermore, injured subjects with $E/E_m > 8$ had lower peak spectral longitudinal contraction (S_m) (9.0 ± 0.7 vs 11.6 ± 0.4 cm s⁻¹; $P < 0.001$) and cardiac output (4.2 ± 0.2 vs 5.0 ± 0.2 l min⁻¹; $P = 0.029$), as well as higher relative wall thickness (0.38 ± 0.01 vs 0.35 ± 0.01 ; $P = 0.005$), than individuals with SCI with $E/E_m < 8$, but similar age, body mass index, blood pressure, injury level, metabolic parameters and inflammatory marker levels.

Conclusion: Subjects with SCI presented impaired LV diastolic function in comparison with able-bodied ones. Moreover, worse LV diastolic function was associated with a pattern of LV concentric remodeling and subclinical decreases in systolic function among injured subjects. Overall, these findings might contribute to explain the increased cardiovascular risk reported for individuals with SCI.

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Keywords: SCI; echocardiography; tissue Doppler; diastolic function

Introduction

Cardiovascular disease is frequently detected in subjects with spinal cord injury (SCI).^{1,2} Previous studies demonstrated that subjects with SCI exhibit higher atherosclerotic burden in comparison with able-bodied individuals.³ Interestingly, this process is not explained by traditional cardiovascular risk factors, indicating that alternative mechanisms might influence the development of early atherosclerosis in such individuals.³ On the other hand, patients with SCI are

exposed to higher circulating levels of inflammatory markers in comparison with able-bodied individuals,⁴ suggesting inflammatory mechanisms to be potential candidates to explain the increased cardiovascular risk in these subjects.

Left ventricular (LV) diastolic dysfunction is consistently associated with worse cardiovascular outcomes⁵ and has been independently related to increased circulatory inflammation markers in several diseases of the cardiovascular system.⁶ Similarly, the development of LV diastolic dysfunction has been reported in individuals subjected to prolonged physical inactivity,^{7,8} thereby suggesting that patients with SCI might be at a higher risk of developing abnormalities in LV function. The aim of this study was to investigate cardiac functional and structural parameters in SCI and able-bodied subjects and evaluate the impact of clinical, hemodynamic, metabolic and inflammatory variables in this regard.

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Materials and methods

A total of 65 nondiabetic, nonhypertensive, sedentary men (34 with SCI and 31 healthy subjects) were cross-sectionally evaluated. Subjects with SCI were enrolled from a university hospital outpatient clinic, whereas healthy subjects were recruited among the employees of the hospital. Further exclusion criteria for both groups included current or past smoking, known coronary artery, cardiac or pulmonary disease, cancer, regular medical therapy and clinical evidence of active infection. In all, 18 tetraplegic and 16 paraplegic individuals composed the SCI group. The average period elapsed after injury was 6.7 ± 0.8 years among all subjects with SCI. SCI level ranged from C4 to T12 and the American Spinal Injury Association (ASIA) Impairment Scale was defined as complete (ASIA A) for all patients with SCI, except for two paraplegics classified as incomplete (ASIA B).

Clinical data included information on the participants' ages and, when applicable, injury duration. Body mass index was calculated as body weight divided by height squared, and body surface area was evaluated by the Dubois formula. Blood pressure was measured using validated digital oscillometric device (Omron HEM-705CP, Omron Corp., Kyoto, Japan).

Blood samples were obtained on the morning after 12 h of fasting for analysis of glucose, lipid fractions and inflammatory markers. Inflammatory markers in sera (tumor necrosis factor (TNF) receptor-I, TNF receptor-II, interleukin-6, e-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and transforming growth factor- β) were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA). C-reactive protein in sera was measured by latex-enhanced immunonephelometric assays (Dade Behring, Newark, NJ, USA).

Echocardiography studies were performed by a skilled physician on each subject in the sitting position with a Vivid 3 Pro apparatus (General Electric, Milwaukee, WI, USA) equipped with a 2.5-MHz transducer, as previously described.⁹ Aortic root, LV and left atrial dimensions were assessed from 2D-guided M-mode tracings, according to the recommendations of the American Society of Echocardiography.¹⁰ Relative wall thickness was computed as twice the posterior wall thickness divided by LV end-diastolic diameter. LV peak wall stress was calculated by the formula: $0.86 \times (0.334 \times \text{systolic blood pressure} \times \text{LV end-diastolic diameter}) / (\text{posterior wall thickness} \times (1 + (\text{posterior wall thickness} / \text{LV end-diastolic diameter}))) - 2$.¹¹ Mitral inflow velocity was examined with pulsed Doppler from the four-chamber apical view and the following indices were evaluated: peak early inflow velocity (*E*), peak atrial inflow velocity (*A*) and peak early/atrial velocity ratio (*E/A*). Tissue Doppler imaging evaluated the septal and lateral ventricular walls as previously described.¹² Peak spectral longitudinal contraction (*Sm*), initial (*Em*) and final (*Am*) diastolic velocities for three consecutive beats were analyzed. Systolic volume was generated from Doppler interrogation of transaortic flow at the aortic annular level and aortic cross-sectional area. Cardiac output was calculated as systolic volume $\times$ cardiac frequency, while peripheral vascular resistance was obtained by the formula: mean blood pressure/cardiac output.

Intraobserver and interobserver LV mass variabilities were <6 and $<10\%$, respectively. Intraobserver *Sm* and *Em* variability were $<7\%$, whereas interobserver variabilities of these variables were $<11\%$.

Continuous parametric and nonparametric variables are presented as means $\pm$ s.e. and median (interquartile range), respectively. The Kolmogorov-Smirnov test was used to test for normal distribution of the variables. The χ^2 -test was used to compare categorical variables, while unpaired *t*-test and Mann-Whitney test compared parametric and nonparametric continuous variables, respectively. Pearson's or Spearman's methods were used to assess univariate correlations between studied variables and parameters of LV diastolic function. General linear model analyses were used to assess intergroup differences in echocardiographic parameters after adjustment for relevant covariates. A *P*-value of <0.05 was considered significant.

The study was approved by the Ethics Committee of our institution and informed consent was obtained from all participants. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Results

Clinical, hemodynamic and inflammatory features of SCI and healthy subjects are presented in Table 1. Mean age, body size, diastolic blood pressure, heart rate, cardiac output, peripheral vascular resistance, serum lipid fractions and glucose levels did not differ between the groups, whereas systolic blood pressure was significantly lower in individuals with SCI. Higher serum C-reactive protein, TNF-receptor I and TNF-receptor II levels were detected in subjects with SCI, whereas no differences in serum interleukin-6, e-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and transforming growth factor- β levels were found between the groups.

Echocardiographic parameters are shown in Table 2. Aortic root, left atrial and LV structural parameters, as well as LV peak wall stress, ejection fraction, *E/A* ratio and *Sm* measurements were comparable in both groups. Nonetheless, significantly reduced *Em* and higher *E/Em* ratio were found in men with SCI. In this regard, results of general linear model analysis revealed no important influence of systolic blood pressure and C-reactive protein levels on LV diastolic differences between SCI and able-bodied subjects (Table 2). Moreover, univariate correlation analyses showed no significant relationship between echocardiographic parameters and injury time or inflammatory markers among subjects with SCI, whereas no differences in echocardiographic parameters were detected between paraplegic and tetraplegic individuals (data not shown).

Recent evidence has suggested that *E/Em* ratio values <8 might be a good marker of normal diastolic function.⁵ Therefore, enrolled subjects were evaluated according to this cutoff point. All able-bodied subjects presented *E/Em* <8 , whereas 13 individuals with SCI (38%) did not. The features of subjects with SCI were then investigated according to these echocardiographic criteria (Table 3). Noticeably,

Table 1 Clinical, hemodynamic and inflammatory features

Variable	SCI (n = 34)	Healthy subjects (n = 31)	P-value
Age (years)	31.9 ± 1.3	31.1 ± 1.3	NS
Time of injury (years)	6.7 ± 0.8	—	NS
Body mass index (kg m ⁻²)	23.6 ± 0.7	24.5 ± 0.7	NS
Systolic blood pressure (mm Hg)	108.5 ± 3.4	119.9 ± 1.9	0.009
Diastolic blood pressure (mm Hg)	71.1 ± 2.3	71.9 ± 1.9	NS
Heart rate (b.p.m.)	73.1 ± 2.1	71.2 ± 1.5	NS
Cardiac output (ml min ⁻¹)	4.7 ± 0.2	4.9 ± 0.2	NS
Peripheral vascular resistance (dynes × s × cm ⁻⁵)	1459 ± 56	1486 ± 68	NS
Glucose (mg per 100 ml)	81.6 ± 2.4	76.5 ± 3.0	NS
LDL-cholesterol (mg per 100 ml)	108.5 ± 6.6	99.8 ± 7.0	NS
HDL-cholesterol (mg per 100 ml)	42.2 ± 1.8	44.2 ± 2.0	NS
Triglycerides (mg per 100 ml)	110.2 ± 10.6	92.4 ± 9.2	NS
TNF-receptor I (ng ml ⁻¹)	1.81 ± 0.12	1.48 ± 0.13	0.043
TNF-receptor II (ng ml ⁻¹)	3.14 ± 0.05	2.93 ± 0.07	0.024
Interleukin-6 (ng ml ⁻¹)	7.3 ± 1.7	7.6 ± 2.9	NS
E-selectin (ng ml ⁻¹)	16.2 ± 2.5	10.7 ± 1.7	NS
ICAM-1 (ng ml ⁻¹)	91.1 ± 7.8	78.2 ± 9.6	NS
VCAM-1 (ng ml ⁻¹)	402 ± 35	438 ± 42	NS
C-reactive protein (ng ml ⁻¹)	2.22 (6.63)	0.55 (1.0)	0.001
TGF-β (ng ml ⁻¹)	30.3 ± 2.9	31.2 ± 5.1	NS

Abbreviations: b.p.m., beats per minute; HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; LDL, low-density lipoprotein; NS, nonsignificant; SCI, spinal cord injury; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1.

Table 2 Echocardiographic parameters

Variable	SCI (n = 34)	Control (n = 31)	P-value	P-value ^a
<i>Structural parameters</i>				
Aortic root diameter (mm)	31.1 ± 0.6	31.8 ± 0.5	NS	—
Left atrium diameter (mm)	30.6 ± 0.7	32.3 ± 0.7	NS	—
LV end-diastolic diameter (mm)	45.8 ± 0.8	46.0 ± 0.7	NS	—
Interventricular septum (mm)	8.7 ± 0.2	8.7 ± 0.2	NS	—
Posterior wall thickness (mm)	8.2 ± 0.1	8.5 ± 0.2	NS	—
Relative wall thickness (mm)	0.36 ± 0.01	0.37 ± 0.01	NS	—
LV mass index (g m ⁻²)	83.7 ± 2.5	85.9 ± 3.7	NS	—
<i>Functional parameters</i>				
LV peak wall stress, × 10 ³ dynes cm ⁻²	145.4 ± 4.9	156.3 ± 4.4	NS	—
Ejection fraction (%)	67.2 ± 0.9	69.0 ± 0.9	NS	—
Fractional shortening (%)	37.3 ± 0.7	38.7 ± 0.7	NS	—
E/A ratio	1.46 ± 0.07	1.54 ± 0.04	NS	—
Sm (cm s ⁻¹)	10.6 ± 0.4	10.1 ± 0.3	NS	—
Em (cm s ⁻¹)	9.2 ± 0.5	12.3 ± 0.5	<0.001	<0.001
Am (cm s ⁻¹)	9.0 ± 0.5	8.0 ± 0.3	NS	—
E/Em ratio	7.7 ± 0.5	6.1 ± 0.3	0.008	0.009

Abbreviations: Am, final diastolic velocity; E/A ratio, peak early/atrial inflow velocity ratio; Em, initial diastolic velocity; LV, left ventricular; NS, nonsignificant; SCI, spinal cord injury; Sm, peak spectral longitudinal contraction.

^aadjusted for C-reactive protein and systolic blood pressure by general linear model analysis.

individuals with SCI with $E/Em > 8$ had lower Em, Sm, cardiac output, aortic root size and LV diastolic diameter, as well as higher relative wall thickness in comparison with those with $E/Em < 8$. Conversely, no further differences in clinical, hemodynamic, metabolic, inflammatory and echocardiographic parameters were detected between the subgroups.

Discussion

Cardiovascular disease is commonly seen in persons with SCI and recent evidence has demonstrated that individuals with

SCI display increased subclinical atherosclerosis in comparison with the able-bodied ones.^{1,3} In this report, the analysis of cardiac structure and function in a sample of young, nonhypertensive, nondiabetic nonsmoker individuals revealed that (1) subjects with SCI exhibited an impaired LV diastolic function in comparison with the able-bodied ones; (2) diastolic dissimilarities between SCI and healthy subjects persisted after adjusting for hemodynamic and inflammatory parameters; (3) worse LV diastolic function was paralleled by a pattern of LV concentric remodeling among subjects with SCI. Overall, these data suggest that subjects with SCI exhibit alterations in LV diastolic function independently of

Table 3 Clinical features of SCI patients according to *E/Em* ratio

Variable	<i>E/Em</i> < 8 (n = 21)	<i>E/Em</i> > 8 (n = 13)	P-value
Age (years)	31.6 ± 1.6	32.6 ± 2.2	NS
Body mass index (kg m ⁻²)	23.8 ± 0.9	23.4 ± 1.2	NS
Time of injury (years)	7.3 ± 1.1	5.7 ± 1.1	NS
Paraplegic/tetraplegic (n)	10/11	5/8	NS
Systolic blood pressure (mm Hg)	108.7 ± 3.9	108.2 ± 6.6	NS
Diastolic blood pressure (mm Hg)	71.0 ± 2.0	71.4 ± 3.9	NS
Cardiac output (ml min ⁻¹)	5.0 ± 0.2	4.2 ± 0.2	0.029
Aortic root diameter (mm)	32.0 ± 0.6	29.6 ± 1.1	0.039
Left ventricular end-diastolic diameter (mm)	46.8 ± 0.7	44.2 ± 0.9	0.031
Interventricular septum thickness (mm)	8.4 ± 0.2	9.1 ± 0.3	NS
Posterior wall thickness (mm)	8.1 ± 0.1	8.5 ± 0.2	NS
Relative wall thickness (mm)	0.35 ± 0.01	0.38 ± 0.01	0.005
LV mass index (g m ⁻²)	83.6 ± 3.1	83.8 ± 4.3	NS
<i>E/A</i> ratio	1.44 ± 0.05	1.50 ± 0.15	NS
<i>Sm</i> (cm s ⁻¹)	11.6 ± 0.4	9.0 ± 0.7	< 0.001
<i>Em</i> (cm s ⁻¹)	10.8 ± 0.4	6.8 ± 0.4	< 0.001

Abbreviations: *E/A* ratio, peak early/atrial inflow velocity ratio; *Em*, initial diastolic velocity; LV, left ventricular; NS, nonsignificant; SCI, spinal cord injury; *Sm*, peak spectral longitudinal contraction.

traditional cardiovascular risk factors. In addition, given that diastolic dysfunction is associated with worse cardiovascular outcomes,⁵ it is possible that altered LV function might contribute to explain the increased cardiovascular risk reported for patients with SCI.²

Previous studies in the literature aimed to evaluate LV diastolic function in subjects with SCI. Eysmann *et al.*,¹³ for instance, reported similar diastolic parameters in 17 subjects with SCI and in 17 able-bodied individuals, who were evaluated by conventional echocardiography. Conversely, de Groot *et al.*¹⁴ studied a smaller sample (seven tetraplegics and seven able-bodied subjects) and found no differences in LV diastolic function, as assessed by conventional echocardiography and tissue Doppler imaging. In this report, the assessment of a larger sample (34 SCI and 31 control individuals) revealed that injured subjects exhibited a similar *E/A* ratio, but lower *Em* and higher *E/Em* ratio than the able-bodied ones. These findings might have some clinical implications. First, tissue Doppler imaging may be more sensitive than conventional echocardiography for detection of abnormalities in LV diastolic function in individuals with SCI. Second, our data showing lower *Em* and higher *E/Em* in subjects with SCI corroborate previous reports demonstrating impaired LV compliance in individuals subjected to prolonged bed rest and space flight,^{7,8} thus indicating that physical inactivity may be associated with diastolic dysfunction. Nevertheless, this latter assumption is challenged by the lack of influence of injury level on LV diastolic function, as shown herein. Subjects with cervical lesions (tetraplegics) usually exhibit more accentuated physical inactivity than paraplegics. Therefore, the absence of worse diastolic function in tetraplegics argues against the notion that the extent of physical inactivity is a major determinant of LV functional alterations following SCI.

Clinical data have indicated that an *E/Em* ratio < 8 might be a good echocardiographic marker of normal LV diastolic function.⁵ In this report, the analysis of subjects with SCI split by this cutoff value revealed that patients with *E/Em* > 8

displayed lower cardiac output, LV end-diastolic diameter and aortic root diameter, compared with injured subjects with *E/Em* < 8, indicating that altered LV function is coupled with signs of lower volemic status. In addition, injured subjects with *E/Em* > 8 exhibited higher LV relative wall thickness but similar LV mass index, which resembles a pattern of concentric remodeling.¹⁵ On the other hand, worse LV diastolic function was not paralleled by variation in potential confounders, such as age, time of injury, blood pressure levels, metabolic parameters and inflammatory mediators. Thus, it is possible that alternative mechanisms might be involved in the physiopathogenesis of LV diastolic dysfunction in injured subjects. One potential candidate could be the abnormal activation of the renin–angiotensin–aldosterone system. Subjects with SCI may exhibit decreased cardiac output as a consequence of impaired vasomotor reflexes, reduced sympathetic outflow and decreased venous return, secondary to the lack of muscle contraction in the extremities.^{16,17} In such individuals, maintenance of blood pressure levels is thought to be dependent on the activation of the hormonal regulatory system, such as the renin–angiotensin–aldosterone axis.¹⁷ In turn, chronic upregulation of this system would potentially stimulate LV remodeling and diastolic dysfunction.¹⁸ Nevertheless, further studies are necessary to confirm this hypothesis.

The present data demonstrated that there are close correlations between longitudinal mitral annulus systolic and diastolic velocities in subjects with SCI. In this regard, individuals with *E/Em* > 8 exhibited lower *Sm* than those with *E/Em* < 8, reflecting unsuspected reductions of contractile activities in parallel with altered LV diastolic function. Accordingly, it has been previously shown that LV contractile activity, as assessed by tissue Doppler imaging, correlates with relaxation,¹⁹ supporting the notion that early myocardial LV relaxation is closely coupled to the previous systolic phase of the cardiac cycle. On the other hand, our data revealed that abnormalities in diastolic and systolic activities in patients with SCI were independent of LV hypertrophy or abnormal

increases in relative wall thickness.¹¹ These findings corroborate the data showing reductions in contractile and relaxing performances in hypertensive adults with mild or no increases in LV mass²⁰ and are compatible with the hypothesis that alterations in tissue Doppler indices may be apparent without major LV structural changes.

In summary, this study showed that subjects with SCI exhibited lower Em and higher E/Em ratio in comparison with the able-bodied ones, indicating that SCI is associated with worse LV diastolic function. These findings were independent of blood pressure levels, injury time, metabolic parameters and systemic inflammatory markers. In addition, the most accentuated alterations in LV diastolic function were paralleled by a pattern of LV concentric remodeling and subclinical decreases on systolic function among injured subjects. In the light of these novel data, further longitudinal studies are necessary to determine whether altered diastolic function contributes to increase the cardiovascular risk in individuals with SCI.

Conflict of interest

The authors declare no conflict of interest.

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