Research article

Structural and functional left ventricular impairment in subjects with chronic spinal cord injury and no overt cardiovascular disease

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Context: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in subjects with long-term spinal cord injury (SCI). More specific recommendations for CVD prevention in this population are needed.

Methods: One hundred thirty male subjects (47 subjects with SCI and 83 able-bodied persons (ABPs), mean age 43.89 ± 1.9 and 45.44 ± 12.2 years; $P = 0.48$) underwent transthoracic echocardiography (TTE). The effects of age, weight, mean arterial pressure (MAP) and level of physical training on cardiac adaptations were evaluated through multiple regression analysis.

Results: In subjects with SCI, TTE revealed increased wall thickness ($P < 0.05$), lower *E* wave, *E/A* ratio and early diastolic myocardial relaxation velocity on Tissue Doppler Imaging (TDI) ($P < 0.05$) and higher systolic myocardial contraction velocity on TDI (0.10 ± 0.02 vs. 0.09 ± 0.02 m/seconds, $P = 0.002$) and peak systolic pressure to end-systolic volume ratio (3.62 ± 1.39 vs. 2.82 ± 0.90 , $P < 0.001$) compared with ABPs. Aortic diameters were larger in subjects with SCI than ABPs. Differences remained statistically significant even after adjustment for age, weight, MAP, and level of physical training. Weight and age were found to be independent variables that substantially affected left ventricular structure and function in subjects with SCI.

Conclusions: Subjects with post-traumatic chronic SCI and no overt cardiovascular risk factors, exhibit initial left ventricular remodeling (as assessed by TTE) compared with ABPs. Lifestyle modifications, including regular physical exercise and weight control, should be implemented in all subjects with SCI, even at a very early stage, in order to reduce cardiovascular risk and prevent the development of CVD.

Keywords: Spinal cord injury, Echocardiography, Left ventricular function, Overweight

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in subjects with chronic spinal cord injury (SCI).^{1,2}

This population usually exhibits a greater atherosclerotic burden than able-bodied persons (ABPs)³ because of a higher prevalence of cardiovascular risk factors and physical inactivity, resulting in increased body weight, low high-density lipoprotein cholesterol

(HDL), and hyperglycaemia.⁴ Subjects with SCI typically experience body composition changes with rapid loss of muscle mass, thinning of bone tissue and fat accumulation especially in the sub-lesional area, which significantly affect functional capacity, quality of life and the risk for developing comorbidities.⁵

The incidence of CVD, type 2 diabetes, obesity, and osteoporosis and the risk of target organ damage due to increased heart rate (HR) and blood pressure (BP) variability related to the autonomic nervous system dysfunction are higher in subjects with SCI than in ABPs of similar age and gender, with subsequent earlier onset of CVD and increased mortality.^{6–12}

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The aim of this study was to detect early cardiac involvement in subjects with SCI without known CVD by using a two-dimensional transthoracic color Doppler echocardiography (TTE) and to explore potential anthropometric and clinical correlates.

Methods

Study protocol

Forty-seven male subjects (mean age 43.9 ± 12.2 years) with chronic SCI were compared with 83 healthy male ABPs (mean age 45.4 ± 12.2 years). All subjects with SCI had a complete lesion below the C6 level, were manual wheelchair users for at least five years (mean time since injury 22.12 ± 14.5 years) and were on oxybutynin therapy for bladder control. Subjects with SCI were classified as "A" on the ASIA Impairment Scale¹³ and all injuries were traumatic in origin.

Subjects with SCI were on regular medical follow-up (every 12 months) in order to exclude CVD. ABPs were all volunteers without known CVD.

All subjects underwent voluntary screening for CVD, including a questionnaire about medical history, use of any drugs in the previous five years, cardiovascular risk factors, and lifestyle habits (alcohol intake, smoking, and physical training in the last four years). The questionnaire was completed with data from hospital charts and/or personal records if available. Exclusion criteria for both groups were known coronary artery, cardiac or pulmonary disease, and/or other chronic medical problems, including diabetes, dyslipidemia, and hypertension requiring medical therapy.

All study participants were divided into three groups on the basis of the self-reported level of physical training: not performing regular physical activity (group 0), exercising one to three hours per week (group 1) and more than three hours per week (group 2).¹⁴ All subjects who performed regular physical activity (groups 1 and 2) had been practicing aerobic exercise (hand-cycling in subjects with SCI and running or cycling in ABPs).

BP measurements were taken twice on the right arm in the supine position in a quiet room, using a mercury sphygmomanometer, before and at the end of the TTE exam. Phase V Korotkoff sounds were considered as diastolic blood pressure (DBP), except in subjects with sounds tending to zero, in whom phase IV was taken. Pulse pressure (PP = SBP – DBP, where SBP = systolic blood pressure) and mean arterial pressure (MAP = [DBP + (SBP + DBP)]/3) were calculated.

In subjects with SCI, weight was measured with the participant wearing light clothing, to the nearest 0.1 kg using a portable, digital wheelchair scale (Health O Meter 2450KL, Brooklyn, NY, USA). The

wheelchair weight was subtracted from the weight of the participant sitting in the wheelchair. Subjects with SCI were then transferred to a length board (National Lifesaving Society item EQ-10, Edmonton, AB, Canada) positioned on a bed. The subject's legs were straightened, the head positioned in the Frankfurt plane, and feet placed in dorsal flexion. Length was determined using an elastic tape measure, measuring segmentally from heel to knee, knee to hip and hip to head.¹⁵

In ABPs, height and body weight were measured using a stadiometer and balance platform scale, respectively. The scale was calibrated prior to each data collection session. Participants were weighed in pants and shirt, and height was taken with shoes removed.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

The study was approved by the institution ethics committee and informed consent was obtained from all participants.

Echocardiographic measurements

TTE examinations were performed with commercially available equipment in all subjects (Aloka, ProSound Alpha 10, Tokyo, Japan) in accordance with the American Society of Echocardiography guidelines.¹⁶ Specific views included parasternal long- and short-axis views, apical four, two, and three-chamber views, and subcostal views including respiratory motion of the inferior vena cava. Pulsed and continuous wave Doppler interrogation was performed on all four cardiac valves. All studies were reviewed and analyzed off line by an independent observer blinded to the clinical characteristics of the study population. Specific measurements were made by the average of three-to-five cardiac cycles.

M- and B-mode measurements

Standard M-mode measurements of the left ventricle were taken at end diastole and end systole from the parasternal short-axis view at papillary muscle level. Left ventricular (LV) ejection fraction was calculated by Simpson's rule in the apical four-chamber view.¹⁶ LV mass index was calculated with the Devereux formula and indexed to body surface area ($BSA = 0.20247 \times \text{height}^{0.725} \times \text{weight}^{0.425}$, DuBois formula).¹⁷ Relative wall thickness was calculated as $(IVSd + PWTd)/LVIDd$ where IVSd is interventricular septal thickness in diastole, PWTd is posterior wall thickness in diastole, and LVIDd is LV internal diameter in diastole.¹⁸

Aortic measurements

Two-dimensional measurements of the aortic root were made at end-diastole in parasternal long-axis views at

four levels: aortic annulus (defined echocardiographically as the hinge points of the aortic cusps); sinuses of Valsalva; supraaortic ridge; and proximal ascending aorta. Measurements were made perpendicular to the long axis of the aorta using the leading edge technique in views showing the largest aortic diameters^{19,20} and the diameters were indexed to BSA.

Left ventricular systolic function

Stroke volume (SV) was calculated by multiplying LV outflow tract area by the outflow tract time velocity integral. Cardiac output (CO) was calculated by multiplying SV by HR and cardiac index (CO normalized for BSA).²¹ The peak systolic pressure to end-systolic volume ratio (PSP/ESV) was used as an index of LV systolic performance corrected for afterload. End-systolic pressure was approximated as 0.9 times brachial SBP.²²

Color-Doppler analysis

Early (*E*) and late (*A*) transmitral flow velocities, *E/A* ratio, and *E* wave deceleration time were measured. Tissue Doppler imaging was carried out in the four-chamber view at both the septal and the lateral mitral annulus, and the mean between the two values was calculated. Systolic myocardial contraction velocity (*Sm*), early diastolic myocardial relaxation velocity (*Em*), and late diastolic myocardial relaxation velocity during atrial contraction (*Am*) were measured and the *E/Em* ratio was calculated.^{23,24}

Statistical analysis

Data are expressed as mean $\pm$ standard deviation for continuous variables. Unpaired Student's *t* test was used to assess group differences, and χ^2 test was applied for categorical. Differences between SCI and ABP groups were adjusted for age, MAP, weight, and level of physical training. Multivariate linear regression

analysis was performed to identify significant independent determinants of cardiac adaptations and their individual association with clinical relevant variables. The variables entered into the analysis were age, MAP, weight, and level of physical training, selected according to their clinical relevance as shown by literature. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using SYSTAT v. 12.0.

Results

No differences were found in LV structure and function between subjects with SCI with the lesion between C5 and T6 and subjects with SCI with the lesion between T7 and L2, hence they were considered as a homogeneous group.

Subjects with SCI and ABPs were similar in age, height, smoking habits (21% vs. 18%), level of physical training, HR, SBP, and MAP. Weight, BMI and DBP were significantly lower in subjects with SCI (Table 1).

Subjects with SCI practicing regular physical exercise had lower BMI (group 0: 25.12 ± 3.15 m/kg², group 1: 23.13 ± 2.56 m/kg², group 2: 22.06 ± 2.81 m/kg², $P = 0.012$). Smokers were equally distributed in all groups.

Subjects with SCI showed early signs of LV remodeling compared with ABPs (Table 2). Aortic diameters were significantly different between the two groups (Table 2).

Although LV contractility parameters were higher in subjects with SCI, LV hemodynamic parameters were lower (Fig. 1) and the diastolic function was worse than ABPs (Table 3). Differences between the two groups remained statistically significant also after adjustment for age, MAP, weight, and level of physical training.

Table 1 Demographic and clinical characteristics

	SCI subjects, <i>n</i> = 47 Mean $\pm$ SD	ABPs, <i>n</i> = 83 Mean $\pm$ SD	<i>P</i>
Age (years)	43.9 $\pm$ 11.9	45.4 $\pm$ 12.2	0.48
Weight (kg)	71.9 $\pm$ 11.0	79.2 $\pm$ 10.9	<0.001
Height (cm)	175.6 $\pm$ 9.2	176.2 $\pm$ 5.8	0.6
BMI(kg/m ²)	23.3 $\pm$ 3.1	25.5 $\pm$ 3.3	<0.001
Smoking	10 (21%)	15 (18%)	0.4
Level of physical training 0/1/2*	15/12/20	28/28/27	0.6
SBP (mmHg)	125.9 $\pm$ 19.8	128.4 $\pm$ 15.9	0.44
DBP (mmHg)	74.3 $\pm$ 11.4	79.3 $\pm$ 9.7	0.01
HR (bpm)	68.0 $\pm$ 13.2	67.0 $\pm$ 13.4	0.66
MAP (mmHg)	91.4 $\pm$ 13.3	95.6 $\pm$ 10.9	0.056
PP (mmHg)	51.6 $\pm$ 14.4	49.1 $\pm$ 11.0	0.25

ABP, able-bodied person; SCI, spinal cord injury; BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SD, standard deviation.

*0 = no regular physical training; 1 = one to three hours of physical training; 2 = more than three hours of physical training per week.

Table 2 Cardiac and aortic dimensions

	SCI subjects, <i>n</i> = 47	ABPs, <i>n</i> = 83	<i>P</i>	<i>P</i> Adjusted for age, weight, MAP, level of physical training
	Mean ± SD	Mean ± SD		
LVIDd (mm)	48.9 ± 5.0	52.7 ± 4.4	<0.001	0.002
LVIDs (mm)	31.5 ± 4.2	32.7 ± 5.2	0.16	0.46
IVSd (mm)	9.9 ± 1.7	8.6 ± 1.3	<0.001	<0.001
PWTd (mm)	8.8 ± 1.6	8.7 ± 1.3	0.8	0.05
RWT	36.3 ± 8	33.3 ± 5.2	<0.001	0.001
LVMI gr/m ²	108.3 ± 26.2	106.7 ± 24.2	0.74	0.07
Aortic annulus (mm)	21.9 ± 2.7	21.1 ± 2.4	0.8	0.023
Aortic annulus/BSA (mm/m ²)	11.7 ± 1.4	11.1 ± 1.3	0.007	0.059
Valsalva sinuses (mm)	31.3 ± 3.9	32.0 ± 4.0	0.34	0.56
Valsalva sinuses/BSA (mm/m ²)	16.9 ± 2.2	16.5 ± 2.2	0.35	0.44
Supraaortic ridge (mm)	27.0 ± 2.7	26.3 ± 3.9	0.27	0.002
Supraaortic ridge/BSA (mm/m ²)	14.5 ± 1.6	13.5 ± 2.0	0.002	0.002
Proximal ascending aorta (mm)	29.1 ± 3.8	28.4 ± 5.3	0.5	0.007
Proximal ascending aorta/BSA (mm/m ²)	15.6 ± 2.0	14.5 ± 2.6	0.012	0.011

ABP, able-bodied person; SCI, spinal cord injury; MAP, mean arterial pressure; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVSd, interventricular septal thickness in diastole; PWTd, posterior wall thickness in systole; RWT, relative wall thickness; LVMI, left ventricular mass index; BSA, body surface area; SD, standard deviation.

Figure 1 Left ventricle hemodynamic parameters. ABP, able-bodied person; SCI, spinal cord injury; EF, ejection fraction; SV: stroke volume; CO, cardiac output; CI, cardiac index; Sm, systolic myocardial contraction velocity on Tissue Doppler Imaging; PSP/ESV, peak systolic pressure/end systolic volume ratio; n.s., not significant; *P, °P adjusted for age, weight, mean arterial pressure, level of physical training.

Multivariate linear regression analysis

On multivariate linear regression analysis, weight and age were found to be independent variables that substantially affected LV structure and function in the subjects with SCI. Aortic diameters correlated with weight and level of physical training (Table 4). In ABPs, age was the main determinant of diastolic dysfunction and aortic dimensions.

Discussion

SCI has an annual incidence of 15–52.5 cases per million population, affecting mainly males of 15–35 years of age. Medical advances in the management of patients with acute post-traumatic SCI have resulted in substantial improvement in life expectancy.²⁵ However,

CVD remains one of the leading causes of morbidity and mortality in this population accounting for 40.5% of deaths.^{8,26,27}

This study is the largest to date demonstrating differences in LV structure and function between subjects with post-traumatic SCI and apparently healthy ABPs, as identified by changes in anthropometric and clinical parameters.

Subjects with SCI had lower body weight than ABPs. Although BMI is not considered a sensitive marker of obesity in subjects with SCI,²⁸ we used specific BMI cut-off points (recommended: <22 kg/m²; overweight: ≥22 to <25 kg/m²; obese: ≥25 kg/m²)²⁹ according to which measures identified the SCI group as overweight. It is well known that weight loss *per se* improves insulin

Table 3 Left ventricular diastolic function parameters

	SCI subjects, <i>n</i> = 47	ABPs, <i>n</i> = 83	<i>P</i>	<i>P</i> Adjusted for age, weight MAP, level of physical training
	Mean ± SD	Mean ± SD		
<i>E</i> (m/second)	0.60 ± 0.13	0.66 ± 0.17	0.03	0.04
<i>A</i> (m/second)	0.51 ± 0.16	0.48 ± 0.16	0.21	0.16
<i>E/A</i>	1.24 ± 0.37	1.49 ± 0.52	0.002	<0.001
Deceleration time (ms)	271.9 ± 81.6	256.5 ± 85.0	0.34	0.27
<i>Em</i> (m/second)	0.09 ± 0.02	0.10 ± 0.02	0.04	<0.001
<i>Am</i> (m/second)	0.10 ± 0.02	0.11 ± 0.02	0.11	0.6

ABP, able-bodied person; SCI, spinal cord injury; MAP, mean arterial pressure; *E*, early transmitral flow velocity; *A*, late transmitral flow velocity; *Em*, early diastolic myocardial relaxation velocity; *Am*, late diastolic myocardial relaxation velocity during atrial contraction; SD, standard deviation.

sensitivity, BP, and metabolic profile as well as physical activity.³⁰ In this population part of the mortality causes are heart diseases as a consequence of the development of cardiovascular risk factors^{8,26,31–33}; introducing modifications of lifestyle habits, including physical training and weight loss^{34–36} may treat and prevent risk factors such as overweight.

An increase in wall thickness was documented in subjects with SCI compared with ABPs, also after adjustment for the level of physical training. This may reflect different causes, some of which might be the type of activities of daily living of subjects with SCI. Subjects with SCI perform a combination of isotonic and isometric exercises employing only the upper part of the body (e.g. manual wheelchair propulsion, weight-relief lifting and transfer tasks),^{37–41} related to physical strain⁴² and similar to that performed by able-body athletes participating in rowing, canoeing, and swimming, in whom increased LV wall thickness has been reported.^{43,44} In addition, SCI has also been found to be associated with altered BP and HR variability due to the unbalance sympatho-vagal interaction⁴⁵ which both may contribute to LV remodeling. In a group of individuals with high or low paraplegia compared with those with tetraplegia and non-SCI controls, Rosado-Rivera *et al.*⁴⁶ showed that elevated 24-hour HR was a marker of autonomic dysfunction. In addition, Schmid *et al.*⁴⁷ documented elevated resting catecholamine concentrations in paraplegics compared to controls. These findings, also reported in hypertensive population,^{48–50} may play a role in the tendency of LV remodeling. Further overweight has been shown to be associated with LV hypertrophy and target organ damage.⁵¹

In our study population, CO and cardiac index were significantly lower in subjects with SCI than in ABPs. Conversely, *Sm*, a relatively pre-load independent index of LV contractility,⁵² and PSP/ESV ratio were

significantly higher in subjects with SCI than ABPs. SCI individuals usually exhibit absence of peripheral vasoconstriction and muscle pump action of the lower extremities, as well as reduced pre-load and decreased capacity to increase HR during exercise.⁵³ Increased contractility at rest may reflect a compensatory up-regulation of LV function.⁵⁴ An abnormal activation of the renin–angiotensin–aldosterone system may also play a role in the development of LV dysfunction and remodeling.^{55–57}

Subjects with SCI had worse LV diastolic function than ABPs, likely caused by multiple contributing factors such as physical inactivity,^{58,59} body composition,⁶⁰ impaired glucose metabolism, reduced HDL cholesterol⁶¹ and sympatho-vagal imbalance.⁶² In our subjects with SCI, diastolic function is influenced by age, and body weight (previously described as a risk factor for the development of diastolic dysfunction).⁶³ Aortic dimensions were significantly larger in subjects with SCI than ABPs, likely because of increased blood flow to upper body parts. These findings are consistent with previous data demonstrating that vessel diameters are directly correlated with muscles work.¹⁹

In a small group of tetraplegic subjects (seven subjects, time since injury 17 years), de Groot *et al.*⁶⁴ found no significant differences in systolic and diastolic function compared with ABPs, though LV dimensions were significantly smaller in subjects with SCI than controls. In a group of 34 subjects with SCI (time since injury 6.7 years), Matos-Souza *et al.*⁶⁵ reported LV diastolic function impairment (lower *Em*, and higher *E/Em* ratio) compared with ABPs. Worse LV diastolic function (*E/Em* > 8) was associated with a pattern of LV concentric remodeling (high relative wall thickness) and subclinical decreases in systolic function (lower *Sm* and CO) among injured subjects. These dissimilarities with other studies may be attributable to differences in

Table 4 Multivariate linear regression analysis

Dependent variable	Independent variable	SCI subjects		ABPs	
		Standardized coefficient	P	Standardized coefficient	P
LVIDd (mm)	Age	−0.225	0.145	−0.114	0.295
	Weight	0.437	0.005	0.433	<0.0001
	MAP	−0.004	0.978	0.114	0.298
	Level of physical training	0.255	0.090	0.426	<0.0001
IVSd (mm)	Age	0.509	<0.0001	0.141	0.246
	Weight	0.044	0.739	0.161	0.204
	MAP	0.012	0.925	0.098	0.420
	Level of physical training	0.310	0.020	0.213	0.067
PWTd (mm)	Age	0.271	0.072	−0.020	0.858
	Weight	0.285	0.054	0.347	0.005
	MAP	0.206	0.160	0.211	0.067
	Level of physical training	0.151	0.294	0.209	0.057
RWT (mm)	Age	0.343	0.031	0.068	0.585
	Weight	0.035	0.816	0.095	0.465
	MAP	0.163	0.287	0.124	0.319
	Level of physical training	0.011	0.943	−0.034	0.776
E wave (m/second)	Age	−0.132	0.416	−0.221	0.076
	Weight	−0.201	0.209	−0.009	0.947
	MAP	0.095	0.552	0.128	0.301
	Level of physical training	0.104	0.504	0.073	0.533
A wave (m/second)	Age	0.461	0.002	0.390	0.001
	Weight	0.176	0.208	−0.087	0.444
	MAP	0.017	0.903	0.195	0.075
	Level of physical training	0.146	0.290	−0.170	0.103
E/A (m/second)	Age	−0.473	0.001	−0.328	0.003
	Weight	−0.323	0.017	0.107	0.340
	MAP	0.054	0.683	−0.212	0.051
	Level of physical training	0.016	0.902	0.285	0.006
Em wave (m/second)	Age	−0.533	<0.0001	−0.417	<0.0001
	Weight	−0.232	0.044	−0.163	0.126
	MAP	−0.278	0.017	−0.220	0.033
	Level of physical training	−0.036	0.744	−0.142	0.143
Supraaortic ridge (mm)	Age	0.180	0.213	0.424	<0.0001
	Weight	0.419	0.004	0.182	0.078
	MAP	0.173	0.223	0.246	0.014
	Level of physical training	0.283	0.046	0.155	0.099
Proximal ascending aorta (mm)	Age	0.226	0.090	0.321	0.004
	Weight	0.384	0.005	0.226	0.049
	MAP	0.343	0.010	0.177	0.113
	Level of physical training	0.353	0.008	0.237	0.26

ABP, able-bodied person; SCI, spinal cord injury; MAP, mean arterial pressure; LVIDd, left ventricular internal diameter in diastole; IVSd, interventricular septal thickness in diastole; PWTd, posterior wall thickness in diastole; RWT, relative wall thickness; E, early transmitral flow velocity; A, late transmitral flow velocity; Em, early diastolic myocardial relaxation velocity.

the study sample: we studied a population in which 68% of subjects with SCI used to perform mild-to-moderate physical exercise and had much longer mean time since injury.

On multivariate linear regression analysis, in subjects with SCI age and weight were independently correlated

with cardiac adaptations, and the increase in weight was proportional to the increase in LV wall thickness and diastolic impairment. MAP was found to correlate independently and negatively only with Em and to correlate positively with the ascending aorta diameter in both groups.

Study limitations

Several limitations should be considered when interpreting the findings of the study. First, 24-hour BP and electrocardiogram monitoring was not performed, and the variability of BP and HR in the study population cannot be quantified. Second, all the study participants did not undergo an exercise stress test for evaluation of cardiovascular fitness, and level of physical training was self-reported.

Third, no measurements of catecholamine, insulin, C-reactive protein, and cytokines levels were taken and no follow-up data are available.

Conclusions

These unique results support the concept that subjects with post-traumatic chronic SCI and no overt cardiovascular risk factors exhibit early signs of LV remodeling (as assessed by TTE) compared with ABPs. Life style modifications, including regular physical activity and weight control, should be implemented in all subjects with SCI, even at a very early stage, in order to reduce cardiovascular risk and prevent the development of CVD.

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