Original Article

Carotid Artery Stiffness and Development of Hypertension in People with Paraplegia and No Overt Cardiovascular Disease: A 7-year Follow-up Study

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Abstract

Objectives: The aim of this study was to compare arterial stiffness between people with paraplegia and able-bodied persons (ABPs) and to assess cardiovascular markers that may be predictive of the development of arterial hypertension in people with spinal cord injury (SCI). **Setting:** This study was conducted at rehabilitation Hospital, Udine (Italy). **Methods:** Fifty-seven patients with SCI were prospectively enrolled and compared with 88 healthy ABPs. All patients underwent comprehensive transthoracic echocardiography, and one-point left common carotid artery (CCA) color-Doppler study for arterial stiffness. **Results:** Patients with SCI had significantly lower body mass index (BMI) and diastolic blood pressure (BP) compared with ABPs, and significantly higher carotid stiffness values (and lower arterial compliance) ($P < 0.05$) after adjustment for age, sex, BMI, physical activity, and heart rate. The SCI patients had lower values of the right ventricular function parameters (tricuspid annular plane systolic excursion and right Sm; $P < 0.0001$), increased wall thickness, and impaired diastolic function. At 7-year follow-up, 10.5% of SCI patients showed high BP; they were significantly heavier with a tendency toward increased abdominal obesity after adjustment for age and systolic BP. BMI was found to be an independent predictor of the development of hypertension. **Conclusions:** Patients with posttraumatic chronic SCI and no overt cardiovascular disease exhibit higher CCA stiffness along with the left and right ventricular involvement, compared with ABPs. People with paraplegia who develop arterial hypertension show increased CCA stiffness mediated by obesity. Lifestyle modifications and weight control should be promoted in all patients with SCI, even at a very early stage.

Keywords: Cardiac function, carotid artery stiffness, spinal cord injury

Introduction

Persons with spinal cord injury (SCI) still remain at high risk for premature death despite a substantial improvement in survival. This is mainly due to cardiovascular diseases (CVD)[1] as a result of sedentary lifestyle, body composition changes (decreased lean body mass and increased fat mass), higher rates of impaired glucose tolerance, insulin resistance and diabetes, low high-density lipoprotein cholesterol[2], deterioration of arterial function below the lesion level,[3] and sympathovagal imbalance. This translates into low heart rate, increased blood pressure (BP) variability, loss of diurnal fluctuation of BP, and disturbed reflex control. Any of these factors may account for the increased risk of CVD.[4] Arterial hypertension is one of the most common causes of CVD, with a prevalence ranging from 14% to 61% in SCI patients,[5-7] and the risk of developing high BP is time-related.[8] Bauman *et al*. reported an incidence of systolic BP (SBP) of 19% and 46% in paraplegic individuals with high- and low-thoracic lesions, respectively, and hypothesized that hypertension could be related to arterial stiffness.[9]

Arterial stiffness is an index of target organ damage and a strong independent predictor of cardiovascular morbidity and mortality.[10,11] An increase in arterial stiffness makes

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wave reflection from the peripheral arterial tree to occur earlier, resulting in increased left ventricular (LV) afterload, reduced diastolic coronary perfusion, and impaired diastolic relaxation. Increased arterial stiffness and systolic afterload are also responsible for LV remodeling and LV hypertrophy, which in turn are independent predictors of cardiovascular events.[12,13] Data from the Framingham study also underline the relationship between arterial stiffness and cardiovascular events regardless of BP control.[14] On the other hand, physical inactivity is a potent stimulus for vascular remodeling, whereas physical exercise lowers BP, arterial stiffness, and abdominal fat.[15,16] Since 2007, the European Society of Hypertension included the evaluation of pulse wave velocity (PWV) as a marker of organ damage in the management of hypertensive patients, which was confirmed in the more recent guidelines.[17]

The aims of this study are (i) to evaluate local arterial stiffness, as assessed by one-point local carotid stiffness, in chronic SCI subjects with no overt CVD compared with a group of healthy able-bodied persons (ABPs), and (ii) to determine if carotid stiffness plays a role in predicting the development of hypertension in paraplegic patients.

Methods

General characteristics

This is an extension of a previous study from our group, which was conducted in 47 male subjects with SCI and no overt CVD, prospectively enrolled during 2008 with the aim to detect early cardiac involvement using transthoracic echocardiography (TTE) and to explore potential anthropometric and clinical correlates.[18] The present study included a total of 57 subjects with chronic SCI (with 8 females among the 10 additional SCI patients) and without known CV disease, out of a group of 148 patients with spinal cord lesion consecutively enrolled and compared with 88 healthy ABPs. The SCI group was clinically evaluated after 7 years (2014) for the development of fixed hypertension. As in the previous study, all SCI patients were followed at the Department of Rehabilitation (Udine, Italy) and the echocardiographic and local carotid stiffness exams were performed at the outpatient office of the San Daniele Hospital (San Daniele, Udine) at baseline. All the subjects were asked to take part at the study. The study protocol has been described previously.[18] Briefly, all subjects with SCI had a complete lesion below the C8 level, were manual wheelchair users (mean time since injury 22.12 ± 14.5 years) and were on oxybutynin therapy for bladder control. They were classified as Grade A on the ASIA Impairment Scale,[19] and all injuries were traumatic in origin. People with SCI were on regular medical follow-up (every 12 months), and here, we report data at 7-year follow-up. ABPs were all volunteers without known CVD, they were considered only at baseline.

Screening for CVD included a questionnaire about medical history, time since injury, drug intake, cardiovascular risk factors, and lifestyle habits (alcohol intake, smoking, and physical training in the last 4 years). Exclusion criteria for both groups were known coronary artery or pulmonary disease, and/or other chronic medical conditions, including diabetes, dyslipidemia, and hypertension requiring medical therapy.

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 examination, and just before the carotid stiffness study. Phase V Korotkoff sounds were used to measure diastolic BP (DBP), except in patients with sounds tending to zero, in whom phase IV was taken. Arterial hypertension was defined by office SBP ≥140 mmHg and/or DBP ≥90 mmHg taken on three separate occasions over a 1-month period. Pulse pressure (PP = SBP − DBP) and mean arterial pressure (MAP = [DBP + (SBP + DBP)]/3) were calculated.

In subjects with SCI, weight and height were measured as previously described in detail.[18] Weight was measured using a portable, digital wheelchair, and height was derived from a length board. Length was determined using an elastic tape measure, measuring segmentally from heel to knee, knee to hip, and hip to head.[20]

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

In all subjects, TTE examinations were performed with a dedicated ultrasound machine (Aloka, ProSound Alpha 10, Tokyo, Japan) in accordance with the American Society of Echocardiography guidelines.[21] All studies were reviewed and analyzed off-line (COMPACS, Rev. 10.5.8, Medimatic, Genoa, Italy) by an independent observer blinded to the clinical characteristics of the study population. Measurements were made by the average of three to five cardiac cycles. 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. LV ejection fraction was calculated by Simpson's rule in the apical four-chamber view. 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).[22] 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.[23]

Stroke volume, cardiac output (CO), and cardiac index (CO normalized for BSA) were calculated.[24] Early (E) and late (A) transmitral flow velocities, E/A ratio, and E-wave deceleration time were measured. Tissue Doppler imaging (TDI) was derived from the four-chamber view at both the septal and lateral mitral annulus, and the mean was calculated. Systolic myocardial contraction velocity (Sm), early diastolic myocardial relaxation velocity (Em), and late diastolic relaxation during atrial contraction (Am) were measured, and E/Em ratio was

calculated.[25,26] TDI was derived also at the lateral corner of the tricuspid annulus. Evaluation of the right ventricle included tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation, inferior vena cava, pulmonary artery systolic pressure (PASP), and right atrial volume according to the American Society of Echocardiography recommendations.[27]

Carotid stiffness analysis

Local one-point arterial stiffness was evaluated at the level of the left common carotid artery (CCA), 1–2 cm before its bifurcation, with the patient's neck extended and slightly rotated, using a high-definition echo-tracking ultrasound system (Alpha 10, Aloka, Tokyo, Japan) as previously described.[28-30] Briefly, a wide-band multifrequency 5–13 MHz linear probe was used. Echo-tracking uses the raw radiofrequency signals that are based on the video signals with an accuracy of 0.01 mm. The optimal angle between the ultrasound beam and the vessel wall for diameter change measurements by echo-tracking is 90°. A different independent ultrasound beam was used to detect perpendicular blood flow [Figure 1, left panel]. The ultrasound beam steering angle can be changed from −30° to +30° with 5° angular increments. The echo-tracking gates were manually set at the boundaries.

Local CCA parameters [Figure 1, bottom] included β-stiffness (stiffness parameter), index of arterial stiffness independent of BP: $\beta = \ln(Ps/Pd)/([Ds - Dd]/Dd)$; Ep (pressure-strain elastic modulus), index of the mechanical properties of the arterial wall: $Ep = (Ps - Pd)/([Ds - Dd]/Dd)$; PWV (one-point PWV) derived from β-stiffness and providing information on arterial stiffness at a specific region of interest: $PWV\beta = \sqrt{(\beta Pd/2\rho)}$; arterial compliance (AC), index of blood vessel compliance describing the absolute change in diameter or area for a given pressure change: $AC = \pi (Ds \times Ds - Dd \times Dd)/[4\times (Ps - Pd)]$. Ps and Pd are systolic and diastolic brachial pressure (used as a surrogate of carotid SBP and DBP), Ds and Dd are carotid arterial systolic and diastolic diameter, and ρ is blood density (1050 kg/m^3).

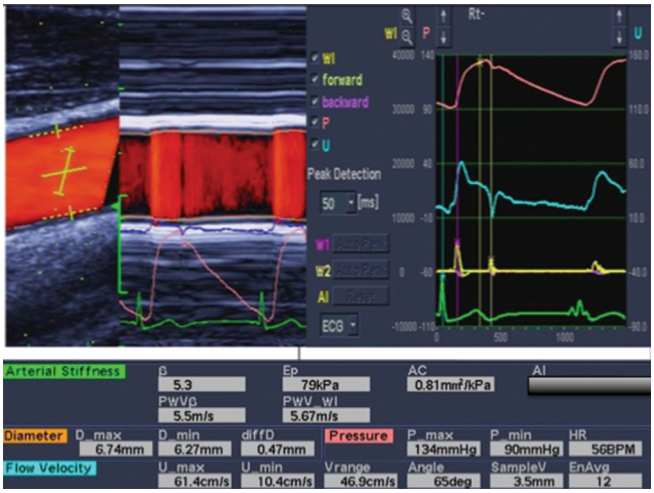

Figure 1: Top left panel: long-axis view of the common carotid artery and ultrasound beam configuration with independent beam steering function. The solid line shows the ultrasound beam direction for velocity measurements whereas the dotted line shows the ultrasound beam direction for measurements of diameter change. Top right panel: Pink P = Pressure wave; light blue U = Velocity; Green ECG. Bottom: Arterial stiffness parameters; Diameter: Diameter of the common carotid artery; Pressure: Brachial arterial pressure and heart rate

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables. Unpaired Student's *t*-test or nonparametric Kruskal–Wallis test was used to assess differences between groups as appropriate, and Chi-square test was applied for categorical variables. Differences between SCI and ABP groups were adjusted for age, sex, BMI, physical training (Model A), and model A + heart rate using ANOVA. Simple correlation test by Pearson's method was done to assess univariate relations, and multivariate logistic regression analysis was used to identify significant independent variables for the development of arterial hypertension, considered as dichotomous outcome. The variables were selected according to their clinical relevance and potential impact on the development of hypertension, and the selection was performed using an interactive stepwise backward elimination method with a level of probability of 0.01. The variables tested in the univariate analysis included clinical data (age, time since injury, BMI, mean BP) and parameters of carotid stiffness. Significant variables were entered in the multivariate logistic regression analysis.

The dataset had <1% of missing data for general characteristics, hemodynamics, echocardiographic, and carotid parameters. A significant proportion of laboratory data was missing and could not be replaced with plausible estimated values; therefore, they were excluded from the analysis.

The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using SYSTAT v. 12.0 (Systat Software Inc., Chicago, IL, USA).

Results

The general characteristics of the study population are reported in Table 1 and the data represent the baseline characteristics. Subjects with SCI were lighter, with lower DBP compared with ABPs. People with paraplegia had smaller left atrial volume, lower E/A ratio, CO/BSA and Sm, and higher relative wall thickness [Table 2]. Right ventricular parameters also differed between groups: tissue Doppler-derived TAPSE and Sm, as well as right ventricular volume, were significantly lower in patients with SCI than in ABPs whereas tricuspid regurgitation and PASP were significantly higher [Table 2]. Parameters of local carotid stiffness were higher and compliance lower in subjects with SCI [Figure 2]. All differences were statistically significant also after adjustment for age, sex, BMI, physical activity (Model A), and model A + heart rate.

At 7-year follow-up, 6 subjects with SCI (10.5%) developed hypertension, and drug therapy was started. At baseline, subjects with SCI who developed hypertension were

Table 1: General characteristics of spinal cord injury subjects and able-bodied persons at baseline

Variables	Subjects with SCI (n=57)	ABPs (n=88)	P	P	
				Model A	Model A + HR
Age (years)	42.8±12.8	45±13.3	0.3	-	-
Gender (male/female)	49/8	77/11	0.8	-	-
Weight (kg)	71.1±11.4	76.8±12.1	0.005	-	-
BMI (kg/m^2)	23.6±3.4	25.2±3.5	0.006	-	-
Waist (cm)	89.6±13.3	91.1±10.9	0.6	-	-
Physical activity (yes/no)	19/37	34/54	0.0001	-	-
Smoker (yes/no)	13/42	18/70	0.6	-	-
SBP (mmHg)	124.3±18.9	128.4±16.3	0.2	0.6	0.6
DBP (mmHg)	73.3±11.9	79.4±11.4	0.003	0.011	0.018
HR (bpm)	67.8±14	68.2±13.3	0.8	0.6	-

Model A=Age, sex, BMI physical activity. SCI=Spinal cord injury, ABPs=Able-bodied persons, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate

Table 2: Echocardiographic characteristics of spinal cord injury subjects and able-bodied persons at baseline

Variables	Subjects with SCI (n=57)	ABPs (n=88)	P	P	
				Model A	Model A + HR
Left atrium (mm)	33.6±5.1	35.7±5.5		0.3	0.3
Left atrial volume (ml)	40.9±16	51.3±18.8	0.001	0.005	0.007
Left atrial volume/BSA (ml/m^2)	21.99±9.7	26.7±9.1	0.005	0.013	0.014
LVM/BSA (g/m^2)	104.7±26.9	104.7±24.2	0.9	0.3	0.3
RWT	35.8±7.9	33.3±4.8	0.02	0.007	0.006
EF (%)	61.2±2	61.7±5.7	0.6	0.9	0.9
CO/BSA	2152±713	2616±802	0.001	0.001	0.002
Sm (m/s)	0.09±0.02	0.1±0.02	0.02	0.03	0.03
E wave (m/s)	0.60±0.13	0.67±0.17	0.005	0.005	0.006
A wave (m/s)	0.51±0.16	0.48±0.15	0.2	0.06	0.052
E/A	1.26±0.39	1.49±0.53	0.003	0.0001	0.0001
E/Em	6.29±1.69	6.42±1.9	0.7	0.2	0.19
TAPSE (mm)	21.8±4.1	25.7±5.0	0.0001	0.0001	0.0001
Right atrial volume (ml)	27.5±10.4	41.57±16.7	0.0001	0.0001	0.0001
TR (m/s)	1.7±0.7	1.3±0.9	0.005	0.02	0.01
PASP (mmHg)	16.8±6.96	14.1±8.8	0.052	0.12	0.14
Right Sm (m/s)	0.11±0.02	0.13±0.02	0.0001	0.0001	0.0001

Model A=Age, sex, BMI, physical activity. SCI=Spinal cord injury, ABPs=Able-bodied persons, HR=Heart rate, BSA=Body surface area, LVM=Left ventricular mass, RWT=Relative wall thickness, EF=Ejection fraction, CO=Cardiac output, Sm=Systolic myocardial contraction velocity, Em=Early diastolic myocardial relaxation velocity, TAPSE=Tricuspid annular plane systolic excursion, TR=Tricuspid regurgitation, PASP=Pulmonary artery systolic pressure, BMI=Body mass index

significantly heavier with greater local carotid stiffness as determined by Ep and PWV, but all parameters of carotid stiffness did not remain significant after adjustment for age, SBP and BMI [Table 3]. Subjects with SCI also showed diastolic dysfunction (larger left atrial volume/BSA, higher A wave and lower E/A ratio) but statistical significance was lost after adjustment for confounders. Among echocardiographic parameters, CO/BSA remained significantly higher [Table 4]. In the simple correlation analysis, the relationship between potential predictors of development of hypertension were age versus arterial stiffness (Ep: R = 0.49, P = 0.05; PWV: R = 0.58, P = 0.03) and BMI versus arterial stiffness (β-stiffness: R = 0.35, P = 0.008; Ep: R = 0.36, P = 0.006; AC: R = -0.41, P = 0.002; PWV: r = 0.36, P = 0.007). Baseline BP correlated only with AC in a negative fashion (either mean BP or SBP; r = −0.29, P = 0.028). No relation was found between time since injury and age, arterial stiffness, BMI, and BP. At multiple logistic regression analysis (dependent variables were age, time since injury, BMI, mean BP), BMI was found to concur with the development of hypertension (odds ratio 1.42; 95% confidence interval 1.05–1.90; P = 0.022).

Discussion

In the present longitudinal study, patients with SCI with no overt CVD exhibited not only LV impairment, as previously reported,[18] but also right ventricular involvement, including reduced right ventricular contractility, and

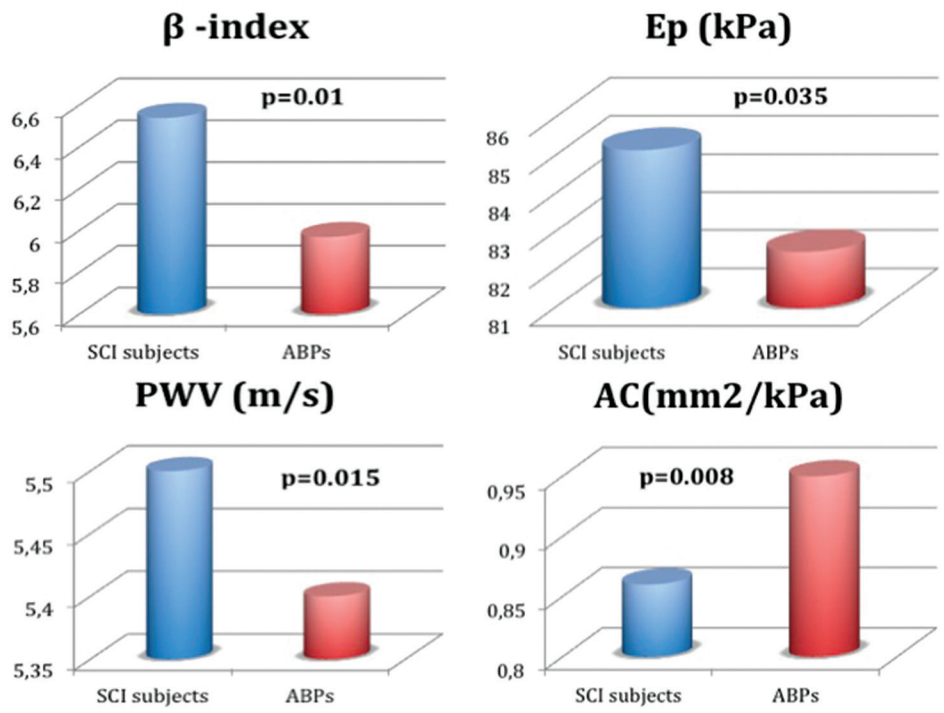

Figure 2: Parameters of carotid stiffness (β-index, elastic modulus, one-point pulse wave velocity) and arterial compliance in people with paraplegia versus able-bodied persons after adjustment for age, sex, body mass index, physical activity, and heart rate

Table 3: Differences in general characteristics and carotid stiffness at baseline between subjects with spinal cord injury, with and without future development of hypertension (Kruskal–Wallis test)

Variables	Subjects with SCI without HT (n=51)	Subjects with SCI who developed HT (n=6)	*P*	*P*	
				Adjusted for age, SBP	Adjusted for age, SBP, BMI*
Age (years)	42.3±12.7	47.2±7.9	0.3	-	-
BSA (m^2)	1.8±0.18	1.98±0.1	0.05	0.08	-
BMI (kg/m^2)	23.2±3.2	26.9±3.5	0.03	0.017	-
Waist (cm)	88.3±12.8	101.4±13.3	0.039	0.06	-
SBP (mmHg)	123.1±12.5	129.6±16.2	0.4	-	-
DBP (mmHg)	72.8±10.5	74.18±14.4	0.8	-	-
HR (bpm)	67.4±14.4	71.3±10.3	0.4	-	-
Pulse pressure (mmHg)	50.3±13.6	55.7±15.2	0.4	-	-
Mean BP (mmHg)	89.6±12.7	92.5±18.9	0.7	-	-
Physical activity (no/yes)	17/33	2/4	0.5	-	-
Smoker (no/yes)	40/11	4/2	0.5	-	-
β index*	6.19±2.56	9.86±7.7	0.1	0.019	0.098
Ep (kPa)*	80.4±34.2	127.7±76.4	0.04	0.016	0.079
AC (mm^2/kPa)*	0.87±0.34	0.73±0.29	0.6	0.5	0.75
PWV (m/s)*	5.4±1.1	6.5±1.4	0.04	0.041	0.71

*Data adjusted for BMI. SCI=Spinal cord injury, HT=Hypertension, BSA=Body surface area, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, BP=Blood pressure, β index=Stiffness parameter, Ep=Pressure-strain elastic modulus, AC=Arterial compliance, PWV=Pulse wave velocity

increased local carotid stiffness compared with ABPs, with higher values in those who developed arterial hypertension during follow-up. In the present study, 10.5% of SCI patients developed hypertension and body weight, expressed as BMI, was the main determinant of arterial stiffness and high BP.

In the available literature, the prevalence of hypertension among SCI subjects is variable, ranging from 14% to 61%, probably depending on the different definitions of elevated BP. In a multicenter cross-sectional study, Bauman *et al*. reported a prevalence of hypertension of 21.5%, defined as two or more high BP readings during the doctor visits.[9] Among 344

Table 4: Baseline echocardiographic characteristics of patients with spinal cord injury with and without future development of hypertension

Variables	Subjectss with SCI without HT ($n=51$)	Subjectss with SCI Who developed HT ($n=6$)	*P*	*P*	
				Adjusted for age, SBP	Adjusted for age, SBP, BMI
Left atrium (mm)	33.6±5.1	35.7±5.5	0.2	0.3	0.4
Left atrial volume (ml)	40.6±16.7	43.8±18.0	0.7	0.6	0.7
Left atrial volume/BSA (ml/m^2)	21.9±9.9	22.2±8.4	0.001	0.9	0.8
LVM/BSA (g/m^2)	103.8±26.9	110.9±21.0	0.5	0.7	0.7
RWT	35.6±8.1	37.1±4.8	0.4	0.9	0.9
EF (%)	61.2±2	61.7±5.5	0.5	0.6	0.3
CO/BSA	2053±653	2931±739	0.01	0.004	0.003
Sm (m/s)	0.10±0.02	0.10±0.02	0.9	0.9	0.6
E wave (m/s)	0.60±0.11	0.62±0.2	0.6	0.7	0.7
A wave (m/s)	0.50±0.16	0.63±0.16	0.05	0.1	0.1
E/A	1.29±0.39	0.97±0.17	0.048	0.1	0.3
E/Em	6.13±1.48	7.58±2.7	0.7	0.09	0.2
TAPSE (mm)	21.8±3.8	22.3±6.7	0.9	0.9	0.8
Right atrial volume (ml)	27.5±10.4	25.6±6.7	0.5	0.7	0.7
TR (m/s)	1.7±0.7	2±0.4	0.1	0.4	0.2
PASP (mmHg)	16.4±6.9	20.6±6.3	0.2	0.3	0.1
Right Sm (m/s)	0.28±0.11	0.26±0.07	0.8	0.7	0.7

SCI=Spinal cord injury, HT=Hypertension, SBP=Systolic blood pressure, BMI=Body mass index, BSA=Body surface area, LVM=Left ventricular mass, RWT=Relative wall thickness, EF=Ejection fraction, CO=Cardiac output, Sm=Systolic myocardial contraction velocity, Em=Early diastolic myocardial relaxation velocity, TAPSE=Tricuspid annular plane systolic excursion, TR=Tricuspid regurgitation, PASP=Pulmonary artery systolic pressure

subjects with SCI evaluated by Hitzig *et al*., self-reported determination of hypertension was approximately 17% after 8 years of follow-up.[8] In a retrospective study conducted by Zhu *et al*. on 277 SCI subjects, almost 50% were diagnosed as hypertensive over a 5-year study period.[7] SBP was related to age, and the likelihood of developing high BP was double in obese SCI subjects than in those with low-normal weight.[7] The incidence of hypertension in patients with SCI is higher than in the general population. Data from the Framingham study showed that hypertension incidence increased with age both in men (3.3% at ages 30–39 to 6.2% at ages 70–79) and women (1.5% at ages 30–39 to 8.6% at ages 70–79).[31] Pereira *et al*. reported an incidence of high BP of 47.3 per 1000 person-years after a median follow-up of 3.8 years.[32]

In our study, body weight was found to be the key determinant of the development of high BP; this modifiable variable can act, either directly or indirectly, through arterial stiffness. Increased aortic PWV is considered the "gold standard" measure of regional arterial stiffness[33] and is an independent risk factor for both fatal and nonfatal cardiovascular events. The well-known cardiovascular risk factors such as obesity, diabetes mellitus, hypercholesterolemia, hypertension, and low physical activity, which are particularly common in patients with SCI, are all determinants of high PWV, along with autonomic disorders that may contribute to cardiovascular dysregulation. There are several reports describing the increase in aortic PWV in people with SCI. Miyatani *et al*.[34] compared a small group of male SCI patients with ABP controls and found that aortic PWV was higher in the former. In a subsequent study involving 87 patients with chronic SCI, the same authors reported that aortic PWV was even higher among paraplegic compared with tetraplegic individuals.[35] In the former paper,[34] people with SCI had higher BP than ABPs whereas in the latter study,[35] there was a higher proportion of paraplegic versus tetraplegic SCI patients with treated hypertension, diabetes, or lipidemia. The possible mechanisms accounting for increased aortic stiffness in people with SCI include an increase in collagen content in the arterial wall and long-term sympathectomy. Another explanation can be related to endothelial dysfunction resulting from reduced regional blood flow with decreased production of nitric oxide, which is a mediator of vasodilation.[36] In the present study, arterial stiffness was measured by means of one-point carotid stiffness, and subjects with SCI had higher values of local arterial stiffness than ABPs, also after adjustment for confounders. Although local arterial stiffness is believed by some to be influenced by no cardiovascular risk factors other than age,[37] more recently an association between carotid stiffness (also measured by echo-tracking),[38] target organ involvement,[39,40] and cardiovascular events has been reported in different pathophysiological scenarios, including healthy people.[41-43] Moreover, our group showed a direct correlation between one-point carotid PWV and carotid–femoral PWV, identifying a cutoff of 6.65 m/s instead of 12 m/s as the best predictor of carotid–femoral PWV.[44] In the present study, subjects with SCI had similar SBP and heart rate, and lower DBP compared with ABPs. They also had lower BMI and general adiposity, but same waist circumference and central adiposity. In other words, in subjects with SCI, there was a loss in lean body mass and a gain in central distribution of adipose

tissue, which is known to be related to arterial stiffness.[45] Such a relationship is not straight, but it is mediated by the endocrine properties of the adipose tissue.[46,47] In the meta-analysis of Ben-Shlomo *et al*., including prospective observational data from 17,635 patients, it was estimated that 12% of the projected increase in CVD due to raised BMI may be attributable to arterial stiffness.[48] Liao *et al*. using a noninvasive ultrasonic echo-tracking method, found that among a cohort of 6992 patients, those who developed hypertension over 6 years of follow-up had higher carotid arterial stiffness at baseline, and its predictive value was independent of baseline BP: one standard deviation decrease in arterial elasticity was associated with a 15% increased risk of hypertension.[49]

As we reported previously,[18] subjects with SCI exhibit initially LV concentric remodeling and dysfunction. In the present study, subjects with SCI also had reduced LV longitudinal contraction (Sm) on TDI probably because the additional patients enrolled were affected by a higher thoracic spine injury with greater impairment of the sympathetic nervous system, along with right ventricular and atrial involvement. Subjects with SCI showed decreased right ventricular contractility (TAPSE, Sm), smaller right atrial volume, slightly more tricuspid regurgitation, and higher PASP. Reduced dimensions of the right atrium are likely related to decreased cardiac preload, whereas depressed right ventricular performance, as assessed by TASE and right Sm, could be related directly to sympathetic dysfunction, responsible for lower inotropic capacity and related to cardiac involvement from cardiovascular risk factors.[50]

After 7 years of follow-up, 6 subjects with SCI developed arterial hypertension. Hypertensive patients with SCI were found to have higher baseline adiposity, in particular central adiposity, and worse E/A ratio. Local carotid stiffness was higher in subjects with SCI who developed hypertension regardless of age and BP, but the difference did not remain statistically significant after adjustment for body weight (i.e., BMI and waist circumference). In this case, the increase in arterial BP may be mediated by arterial stiffness through increased body weight. In the logistic multiple regression analysis, BMI was found to be the only independent predictor of development of high BP. Bauman *et al*. suggested a relationship between arterial stiffness and arterial hypertension in this particular population.[9] In the Whitehall II study, Brunner *et al*. demonstrated that central adiposity was a strong independent predictor of aortic elasticity.[45] In the recent multicenter cross-sectional study of Adriaansen *et al*., which included people with chronic SCI, BMI, time since injury, age, diabetes mellitus, and a history of hypercholesterolemia were significant predictors of hypertension.[6]

Study limitations

Our study has some main limitations. First, although enrolled subjects come from the largest Rehabilitation Hospital of our region, it is a single-center experience. Second, many laboratory data (e.g., cholesterol) were unavailable and their impact on the development of hypertension could not be analyzed. Third, at 7 years of follow-up, SCI subjects did not undergo repeat TTE and carotid stiffness assessments.

Conclusions

To the best of our knowledge, this is the first longitudinal study that evaluated local arterial stiffness in subjects with SCI and no overt CVD with assessment of right ventricular function. Subjects with SCI have higher carotid stiffness with left and right ventricular involvement. Moreover, those who develop arterial hypertension exhibit higher baseline local carotid stiffness, independent of age, and SBP but related to increased adiposity. SCI subjects have a higher incidence of high BP than the general population and according to our findings, BMI is the main determinant of the development of high BP either directly or through the increase in arterial stiffness. Despite the limited sample size, we can say that arterial stiffness measured as one-point carotid stiffness might be not only a parameter related to physiological arterial aging but also a marker for future development of arterial hypertension mediated by body weight.

Dietary control and regular physical activity might help to prevent excessive weight gain and future development of hypertension and cardiovascular events, and this holds particularly true for subjects with SCI. Further studies are needed to confirm our results.

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Conflicts of interest

There are no conflicts of interest.

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