Original Article

The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured†

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Study objectives: To describe the distribution of clinically apparent cardiovascular disease (CVD) in people with long-term spinal cord injury (SCI) according to neurologic level and severity of injury.

Design: Historical prospective study.

Setting: Two British Spinal Injuries Centers.

Participants: Five hundred and forty-five individuals surviving at least 20 years with SCI were divided into three neurologic categories by level of injury and Frankel/ASIA grade as follows: Tetra ABC, Para ABC, and All D.

Main outcome measures: Cardiovascular disease outcomes defined by ICD/9 codes 390–448 and obtained through medical record review. Cardiovascular disease outcomes measured included All CVD, coronary heart disease (CHD), hypertension, cerebrovascular disease, valvular disease, and dysrhythmia.

Results: After age-adjustment, the rates of All CVD were 35.2, 29.9, and 21.2 per 1000 SCI person-years in the Tetra ABC, Para ABC, and All D groups, respectively. Rates of All CVD increased with increasing age in all neurologic groups. Tetraplegic level of SCI conferred an excess 16% risk of All CVD (95% Confidence interval [CI], 0.93–1.46), a fivefold risk of cerebrovascular disease (relative risk [RR] 5.06; 95% CI, 1.21–21.15), and 70% less CHD (RR 0.30; 95% CI, 0.13–0.70) when compared with paraplegics. More complete SCI was associated with an excess 44% All CVD risk (95% CI, 1.16–1.77).

Conclusions: Risk of All CVD increased with increasing age, rostral level of SCI, and severity of SCI. More rostral level of SCI was associated with cerebrovascular disease, dysrhythmia, and valvular disease. Conversely, there was an inverse relationship between level of SCI and CHD. *Spinal Cord* (2001) 39, 310–317

Keywords: spinal cord injury; cardiovascular disease; coronary heart disease

Introduction

Until recently, the majority of individuals with SCI have had significantly shorter life expectancies compared with the general population.^{1,2} Improved acute and chronic medical management has contributed to lengthened survival, which has allowed for the occurrence of more chronic disease in this population. As potential exposure to chronic diseases increases due to advancing age, health care providers are faced with the challenges associated with primary and secondary prevention, diagnosis, and management of older individuals with spinal cord injury (SCI) at risk for contemporary chronic diseases.

In the United States, cardiovascular disease (CVD) is the most common cause of mortality, being responsible for more deaths than cancer, accidents, and HIV infection combined.³ Nearly one million deaths were attributable to CVD in 1995, approximately one sixth of these being in individuals younger than 65 years of age. Approximately half of all CVD mortality is due to coronary heart disease (CHD). Morbidity is even more widespread, with CVD affecting more than 58 million and CHD affecting nearly 14 million Americans.³ Comparably, with improved survival in SCI we anticipate that CVD and CHD risk will continue to increase and account for greater morbidity and mortality in this population.

The purpose of this study is to describe the distribution of clinically apparent CVD and CHD in

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long-term SCI according to neurologic level of injury. Due to the effect of altered autonomic function, metabolism, and physical activity levels on CVD risk factor status, we hypothesize that CVD risk increases with age, more rostral level of SCI, and more complete (Frankel/ASIA grade ABC) SCI.

Methods

This historical prospective study was performed through a collaboration of Craig Hospital, the National Spinal Injuries Centre (NSIC) in Aylesbury, UK, and the Regional Spinal Injuries Centre (RSIC) in Southport, UK. The spinal injury centers in the United Kingdom were chosen since they had complete medical records on extensive numbers of persons with SCI followed for many years and because a large proportion of their patient population remained in the system of care.

We identified a group of individuals who incurred their SCI prior to 1970 and followed them prospectively via medical record review and patient interview for at least 20 years, until completion of the study in 1993. This cohort consisted of 834 individuals who met the following criteria:

- age 15–55 years old at the time of injury,
- initial admission to one of the two British SCI centers within 1 year of injury, and
- residence in a 13-county catchment area at the time of injury.

Subjects were excluded if they did not survive at least 20 years after SCI. These criteria ensured a population-based sample with a minimum 20 years duration of SCI by completion of the study, while minimizing the effect of aging prior to SCI.

Data collection via medical record review was initiated in 1990 and conducted retrospectively to the time of SCI. Additionally, participants were interviewed in 1990 and 1993 regarding their medical history. This served as another means by which medical information was obtained. More than 20 000 documented diagnoses were abstracted and sorted according to the International Classification of Disease-Adapted, Part 9 (ICD/9) codes.⁴

Endpoints included withdrawal due to death, diagnosis with CVD or loss to follow-up. Vital status of 93% of the study population was determined through searches of medical records, the National Health Service, and the Office for National Statistics.

CVD diagnoses were established *a priori* according to American Heart Association (AHA)³ definitions. The AHA defines CVD according to International ICD/9 codes 390–459 and 745–747. We chose to define clinically apparent CVD according to ICD/9 codes 390–448, thereby excluding congenital CVD, since this would be unrelated to the SCI. Cardiovascular disease diagnoses were further categorized into CHD, cerebrovascular disease (cerebrovascular acci-

dent and transient ischemic attack), hypertension, dysrhythmia, valvular disease, and ‘other CVD’. CHD events included myocardial infarction (MI), angina, and coronary atherosclerosis, consistent with the definition of CHD by the AHA.³ The ‘other CVD’ group was comprised of individuals with diagnoses of cardiomegaly, congestive heart failure, thrombophlebitis, endocarditis, deep venous thrombosis, and venous insufficiency. Since CVD diagnoses were determined via medical record review or patient report, subclinical disease was not included.

For the analyses, participants were stratified into three neurologic groups according to the Frankel⁵/American Spinal Injury Association (ASIA)⁶ classification system as follows:

- tetraplegia Frankel/ASIA Impairment grade A, B, or C (Tetra ABC),
- paraplegia Frankel/ASIA Impairment grade A, B, or C (Para ABC), or
- all Frankel/ASIA Impairment grade Ds (All D).

The All D group had a bimodal distribution of level of SCI, with 37% occurring between C4 and C7 and 40% occurring between T11 and L4. There were no individuals with Frankel/ASIA Impairment Grade E SCIs enrolled in the study. This type of stratification by injury level has been described elsewhere.^{2,7}

Univariate investigations of the cohorts with respect to demographic characteristics were performed. This comparison allowed for the detection of any underlying differences between the groups that might have contributed to an altered risk of CVD. ANOVA was used to compare potential demographic and CVD risk factors between the neurologic groups. The 0.05 level was used to denote statistical significance.

Person-time follow-up for each subject was calculated from the time of SCI to the date of CVD diagnosis, death from any cause, last known follow-up, or completion of the study. All person-time information used as the denominator in the calculation of incidence is reported in SCI person-years, as opposed to total lifetime person-years.

The population-based longitudinal approach described above permitted calculation of incidence of CVD outcomes, since SCI person-time data was available from the time of SCI to completion of the study or censoring due to death or loss to follow-up. Incidence rates were calculated by dividing the number of new CVD events by the total SCI person-time for each neurologic category. Age-adjustment was performed using the direct method with the total SCI population as the standard.

The RR was used as a measure of the strength of the association between neurologic level and the risk of cardiovascular events. Relative risk was calculated as the incidence rate of disease in individuals in a particular neurologic category divided by the corresponding rate in a specific reference group. To assess the effect of level of injury, the Tetra ABC group was

compared to the reference Para ABC group. To assess the effect of severity of injury (using Frankel/ASIA grade as the proxy), the Tetra ABC and Para ABC groups were combined and compared to the reference All D group. Because the All D group had significant proportions of both tetraplegics and paraplegics, we felt that combining the two ABC groups and comparing them to the All D group would provide a more accurate assessment of the effect of severity of injury. These comparisons were based on our hypotheses that more rostral level and more complete SCI are related to CVD. Statistical significance was demonstrated by calculating 95% CIs for the RRs.

Since we utilized a fixed cohort, survival analysis was performed to estimate the risk of disease according to age at CVD diagnosis or most recent follow-up. Statistical significance for the survival analyses was determined using the log rank test.

Statistical Package for the Social Sciences⁸ was used for data management.

Results

Demographics

Of the 834 individuals who met the inclusion criteria, 289 were removed from the study because their duration of survival following SCI was less than 20 years. Therefore, 545 (65%) who had survived at least 20 years and had complete medical record documentation were included in the study. Of these, 190 (35%) were known to have expired by completion of the study, the majority of these being in the Para ABC and All D groups.

Table 1 summarizes general demographic information of the participants according to the neurologic level of injury. There were 16 857 total person-years, over half being contributed by the Para ABC group. Although the mean age at injury for the Para ABC and All D groups was similar, the Tetra ABC group

was several years younger at the time of SCI ($P=0.8$) and at follow-up ($P=0.8$). The duration of injury ($P=0.7$) and gender distribution ($P=0.4$) was similar between the groups. Of the entire population with SCI, 73% were injured between the ages of 15 and 30 years, 21% between 31 and 45 years, and 6% were 46 years or older at the time of injury.

Risk of cardiovascular disease

There were 458 CVD events that occurred during 16 857 SCI person-years in individuals surviving at least 20 years with SCI. The majority of these events were due to CHD (24%) and hypertension (21%), while dysrhythmias (16%), peripheral vascular disease (15%), congestive heart failure (8%), valvular disease (7%), cerebrovascular disease (2%), and atrial fibrillation (2%) comprised the remainder. Approximately 5% of CVD cases were due to cardiomegaly, endocarditis, and venous insufficiency. Table 2 summarizes the occurrence and age-adjusted risk of CVD events for the entire cohort and by neurologic category. Because the Tetra ABC group was younger than the other two groups at the time of the study, age-adjustment was performed to account for this difference. After adjustment, there was a trend toward increasing risk of All CVD in individuals with more rostral and more complete injuries. Table 3 presents a summary of the age-adjusted RRs for CVD diagnoses. While the effect of level of injury on CVD risk was not statistically significant (RR 1.16; 95% CI, 0.93–1.46), the effect of a more complete injury was associated with 44% greater risk (RR 1.44; 95% CI, 1.16–1.77).

Figure 1 demonstrates that the incidence of CVD increases with age in all of the neurologic groups. Because person-time information used as denominator data was limited in the oldest age groups, thereby contributing to greater instability of those calculations, participants in the two oldest age groups were

Table 1 Description of demographic data if subjects according to neurologic level of injury

Demographic data	All SCI	Tetra ABC	Para ABC	All D
Number	545	99	285	161
Person-years	16 857	2993	9079	4785
Age at injury (mean $\pm$ SD)	27 $\pm$ 9	25 $\pm$ 7	28 $\pm$ 9	29 $\pm$ 11
Age at termination of study (mean $\pm$ SD)	57 $\pm$ 10	53 $\pm$ 8	58 $\pm$ 10	58 $\pm$ 11
Duration of SCI (mean $\pm$ SD)	29 $\pm$ 6	28 $\pm$ 4	30 $\pm$ 7	29 $\pm$ 6
Vital status at termination of study				
Alive (%)	53	77	51	43
Deceased (%)	35	19	40	35
Lost to follow-up (%)	12	4	9	22
Gender				
Male (%)	86	82	88	85
Female (%)	14	18	12	15

SD = Standard deviation

Table 2 Summary of CVD events and age-adjusted rates of CVD per 1000 SCI person-years by neurologic category

Diagnosis	All SCI		Tetra ABC		Para ABC		All D	
	Number	Rate	Number	Adj Rate	Number	Adj Rate	Number	Adj Rate
All CVD	458	27.2	64	35.2	279	29.9	115	21.2
CHD	109	6.5	5	2.1	63	6.6	41	7.4
MI	47	2.8	1	0.3	31	3.2	15	2.6
Angina	12	0.7	0	—	4	0.4	8	1.7
Coronary atherosclerosis	46	2.7	3	1.0	25	2.7	18	3.1
LBBB	4	0.2	1	0.3	3	0.3	0	—
Hypertension	98	5.8	5	1.7	71	7.6	22	4.5
Cerebrovascular disease	8	0.5	4	1.5	3	0.3	1	0.2
Dysrhythmia	73	4.3	20	13.1	42	3.3	11	1.3
Valvular disease	34	2.0	10	5	14	1.5	10	1.7
Other CVD	136	8.1	20	9.2	86	1.4	30	1.5

Table 3 Age-adjusted relative risks and 95% confidence intervals for CVD diagnoses by level of SCI and Frankel/ASIA grade of SCI

Characteristic	Comparison of Level of SCI		Comparison of Frankel/ASIA Grade of SCI	
	Tetra ABC vs Para ABC	95% CI	All ABC vs All D	95% CI
All CVD	1.16	0.93–1.46	1.44	1.16–1.77
CHD	0.30	0.13–0.70	0.80	0.58–1.10
MI	0.11	0.10–0.74	1.08	0.58–1.99
Coronary atherosclerosis	0.49	0.17–1.39	1.43	1.15–1.77
Hypertension	0.22	0.09–0.54	1.37	0.85–2.20
Cerebrovascular disease	5.06	1.21–21.15	3.11	0.38–25.01
Dysrhythmia	3.94	2.45–6.35	2.54	1.15–5.63
Valvular disease	3.25	1.57–6.73	1.29	0.62–2.70

Figure 1 Incidence density of CVD by 10 year age group and neurologic category

Figure 2 Proportion surviving without CVD by age and neurologic group

combined. Survival analysis for CVD by age and neurologic category is shown in Figure 2, and demonstrates a greater probability of survival without CVD in the All D group compared to the two other groups. The difference between the All D group and the other two more neurologically complete groups was statistically significant ($P=0.04$) and initially became evident in those as young as 40 years of age.

Risk of coronary heart disease

Myocardial infarction, angina, and coronary atherosclerosis were combined to form the CHD group. After age-adjustment, the risk of CHD was 2.1, 6.6, and 7.4 per 1000 SCI person-years in the Tetra ABC, Para ABC, and All D groups, respectively. Of the 109 CHD events, 47 (43%) were MI, while only 12 (11%) individuals reported angina. While MIs were responsible for nearly half (49%) of the CHD events in the Para ABC group and 37% of those in the All D group, they accounted for only one of five (20%) CHD events in the Tetra ABC group. More rostral level of SCI was associated with a lower risk of MI (RR 0.11; 95% CI, 0.10–0.74) whereas Frankel/ASIA grade did not affect risk (RR 1.08; 95% CI, 0.58–1.99). The relationship between increasing risk of CHD with advancing age was evident in the Para ABC and All D groups, but not in the Tetra ABC group.

Forty-six of the total 109 CHD diagnoses were due to coronary atherosclerosis, accounting for a rate of 2.73 cases per 1000 SCI person-years. There was a trend toward increasing risk in those with more caudal (RR 0.49; 95% CI, 0.17–1.39) and more complete SCI (RR 1.43; 95% CI, 1.15–1.77).

Risk of hypertension

There were no participants who experienced hypertension prior to age 20, and none with tetraplegia experienced hypertension prior to 30 years old. The incidence of hypertension increased with advancing age in the Para ABC group, peaking in the 60–69 year olds. A similar pattern was seen in the All D group, with the incidence of hypertension highest in 60–69 year olds (18.1 per 1000 SCI person-years). Rostral level of SCI conferred a protective effect (RR 0.22; 95% CI, 0.09–0.54) whereas severity of injury did not affect risk (RR 1.37; 95% CI, 0.85–2.20). Further, within the Tetra ABC group there was not a clear pattern of increasing incidence with increasing age.

Risk of cerebrovascular disease

When cerebrovascular accidents and transient ischemic attacks were investigated as to their role in CVD, we found only eight events in all three neurologic groups, corresponding to a crude rate of 0.5 per 1000 SCI

person-years in the SCI population. The risk was greatest in the Tetra ABC group, and more rostral level of injury (RR 5.06; 95% CI, 1.21–21.15) was associated with a heightened risk of disease.

Other CVD

When the rates of dysrhythmias and valvular disease were similarly investigated, we found that rostral level of injury and more complete SCI conferred greater risks of disease. The Tetra ABC group had a fourfold greater risk of dysrhythmia than the Para ABCs (RR 3.94; 95% CI, 2.45–6.35), and a 10-fold greater risk than the All Ds (RR 10.39; 95% CI, 4.40–24.55). Similarly, the risk of valvular disease was associated with more rostral SCI (RR 3.25; 95% CI, 1.57–6.73) and more complete SCI (RR 1.29; 95% CI, 0.62–2.70). The remainder of ‘other CVD’ risk assessed (including cardiomegaly, congestive heart failure, and peripheral vascular disease) was relatively equally distributed between the groups.

Discussion

Recent interest in CVD in those with SCI has primarily involved CHD, with varying reports of risk when spinal injured individuals are compared with the general population. Krum⁹ used logistic regression coefficients derived from analysis of the Multiple Risk Factor Intervention Trial to calculate an overall low cardiac risk in those with SCI compared with age and sex matched controls. When estimating the risk of coronary artery disease according to the Framingham model, Cardus¹⁰ found that the risk in individuals with SCI was similar to that of nontrained, able-bodied individuals. In contrast, Yekuteil¹¹ documented a higher prevalence of CHD in individuals with duration of SCI greater than 10 years compared with relatively healthy age-matched controls derived from a database of pre-employment examinations. These prospective and retrospective studies provide limited evidence suggesting at least comparable risk of CHD in SCI compared with able-bodied individuals.

However, utilizing experimental methodology early evidence suggests that CHD may be higher in SCI than previously anticipated. In a series of studies, Bauman^{12,13} found that 62% of paraplegics without known CHD had positive radionuclide perfusion imaging studies compared with 26% diagnosed by exercise stress test alone. Further, when radionuclide myocardial imaging using thallium-201 was performed to assess myocardial ischemia in a relatively young sample of male tetraplegics with several risk factors for CHD, approximately half were found to have latent CHD without previous symptoms or abnormal EKGs.¹³ Therefore, the actual risk of CHD may be greater than predicted in SCI with subclinical disease accounting for a significant proportion of CHD.

We sought to describe the basic epidemiology of clinically apparent CVD in SCI by utilizing a historical

prospective approach that allowed for calculations of disease rates. Further, we attempted to identify a group of individuals with SCI who were at heightened risk of the major types of CVD, including CHD, MI, coronary atherosclerosis, cerebrovascular disease, hypertension, valvular disease, and dysrhythmia. Level and severity of SCI may affect the risk of CVD through altered autonomic function, diminished physical exercise level imposed by the more severe SCI, altered lipid profile, altered glucose tolerance, and other as yet unidentified risk factors. To date, there has been a paucity of literature examining multiple CVD diagnoses, and a subgroup of people with SCI at heightened risk of CVD has yet to be identified.

We found that both level and severity of SCI contributed to the risk of CVD in SCI. While more rostral level of SCI was associated with a greater risk of All CVD, cerebrovascular disease, dysrhythmia, and valvular disease, there was an inverse association between level of SCI and CHD, MI, and hypertension. More complete SCI was associated with greater risk of All CVD, coronary atherosclerosis, and dysrhythmia. Disparate risk factor status between subgroups of individuals according to the level and/or severity of SCI may provide an explanation for these associations.

While high density lipoprotein (HDL) lower than 35 mg/dL is a known risk factor for CHD,¹⁴ this can be modified through increased physical activity. Low HDL in persons with SCI compared with the able-bodied population, presumably due to greater imposed inactivity, has been well described.^{9,15–18} More recently, Bauman¹⁹ has shown that tetraplegics have lower HDL levels than paraplegics.

Additionally, fasting hyperglycemia and glucose intolerance have been shown to be more prevalent in SCI,^{20–22} likely secondary to immobility and potential other unknown causes.

Autonomic dysreflexia may play a role in increasing the risk of CVD in those at risk via an atherogenic effect on the blood vessels due to repeated episodes of vascular contraction.²³ It is well established that AD occurs predominately in those with SCI rostral to the T6 level. Therefore, if AD does affect CVD status, the individual with more rostral SCI would potentially be exposed to greater risk of disease.

When we examined the specific types of CVD we found interesting differences between the neurologic groups, with an inverse relationship between neurologic level and clinically apparent CHD. Diagnostic bias could contribute to this relationship, because individuals with SCI rostral to T4 may not recognize cardiac pain due to disruption of sympathetic afferent fibers traveling with cardiac pain fibers. Consequently, the diagnosis of CHD requires heightened clinical suspicion in the Tetra ABC group and a subset of the Para ABC with injuries rostral to T4. This may imply that accepted screening methods may be indicated even in the absence of observable signs and symptoms in SCI,

especially in tetraplegics and paraplegics with more cephalic injuries.

Conversely, this risk of CHD could be truly lower in those with more rostral SCI. Clinically, we frequently observe hypotension in individuals with more rostral lesions, often secondary to altered autonomic control. This lack of hypertension observed in individuals with tetraplegia could be a protective influence for CHD.

All groups had low rates of cerebrovascular disease, and risk appeared to correlate with increasing completeness and more rostral level of injury. Also, the risk of dysrhythmia and valvular disease was similarly higher in those with more complete and more rostral SCIs. A propensity toward dysrhythmias has been documented acutely after SCI,²⁴ though it has not been shown that chronic SCI is associated with dysrhythmia in the absence of underlying CHD.²⁵ While dysrhythmia could be associated with heightened cerebrovascular disease risk, the reason why valvular disease is elevated according to level and Frankel/ASIA grade is unclear.

Since we obtained our data through medical record review and patient report, this study is subject to inherent limitations. Misclassification of outcome can occur when those who actually had CVD (including subclinical disease) were not correctly identified, or those without CVD were incorrectly identified as having disease. It is more likely that misclassification of outcome occurred in the former manner as opposed to the latter, thereby leading to an underestimate of the true risk of disease. Further, we chose to include subjects only after they had survived with their spinal injury for at least 20 years. Because any resulting survival bias would have eliminated those individuals dying of CVD prior to entry into the study, we may have underestimated the risk of disease.

Further, due to altered sensation, misclassification is more likely to occur in the Tetra ABCs and a subset of the Para ABCs with more rostral injuries, again underestimating the true risk of disease in those groups. Differences in medical practice between Great Britain and the US would not be expected to affect the results, since any diagnostic misclassification due to medical practice should have been consistent across neurologic groups.

This study is strengthened by the historical prospective design, population-based approach, and capability for long-term follow-up of the cohort. Further, we were able to calculate risk of disease by neurologic category and by age, allowing us to describe groups at higher risk of disease within the SCI population. Because SCI is a rare condition, it is often challenging to meet these objectives.

Our primary hypothesis that risk of All CVD is greater in those with a more rostral level of injury and more complete injury was confirmed, although this relationship was not consistent across all subtypes of CVD. The risk of All CVD, CHD, MI, hypertension, cerebrovascular disease, dysrhythmias, and valvular

disease were related to level of SCI, while the risk of All CVD, coronary atherosclerosis, and dysrhythmia were associated with Frankel/ASIA grade.

This study demonstrates the growing significance of CVD in an SCI population that is surviving to older ages than has been observed in previous years. Although CVD is not the primary cause of morbidity and mortality in SCI, the risk is growing and we anticipate this trend will continue. With this understanding, more intense surveillance for CVD in SCI might be considered in the future, potentially preventing further secondary disability and mortality. Individuals with a more caudal level of SCI may be candidates for more intense blood pressure and CHD monitoring, while those with more rostral SCI may be candidates for dysrhythmia and cerebrovascular disease surveillance.

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