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Scientific Review

Risk factors for atherogenesis and cardiovascular autonomic function in persons with spinal cord injury

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CARBOHYDRATE METABOLISM

Introduction

Persons with spinal cord injury (SCI) have been recognized to have several metabolic changes that adversely impact their risk for cardiovascular disease. An increased prevalence of disorders of carbohydrate metabolism and dyslipidemia may be related predominantly to paralysis with immobilization and associated loss of lean body tissue and gain in relative adiposity. Studies have reported an increased risk of vascular disease in those with SCI. As such, an understanding of the constellation of carbohydrate and lipid changes that occur after SCI is relevant to the clinical practice of medicine in this population.

Oral glucose tolerance testing and associated studies

Impaired glucose tolerance and diabetes mellitus are more prevalent in individuals with SCI than in those who are able-bodied.[1–4] In most of the individuals with SCI and abnormal carbohydrate tolerance, resistance to insulin mediation of glucose uptake by peripheral tissues may be demonstrable. In the presence of insulin resistance, the normal homeostatic response to glucose challenge is increased pancreatic β-cell secretion of insulin. If the compensatory response of the pancreas is insufficient to control the serum glucose concentration, worsening of carbohydrate tolerance will ensue.

Bauman *et al*[3] performed a 75 g oral glucose tolerance test in 100 male veterans with SCI and in 50 able-bodied veteran controls. According to criteria established by the World Health Organization,[5] 22% of those with SCI were diabetic whereas only 6% of the control group were diabetic. Eighty-two per cent of the controls had normal oral glucose tolerance, compared with 38% of those with quadriplegia and 50% of those with paraplegia. Subjects with SCI had significantly higher mean plasma glucose and insulin values at several points during the oral glucose tolerance test when compared with controls (Figure 1). In subgroups, determinants of insulin sensitivity were measured: per cent lean body mass, per cent fat mass, and cardiopulmonary fitness. Values for insulin sensitivity were linearly related with those of fitness (VO_2 max) determined from a progressive incremental upper-body exercise stress test. Insulin sensitivity was suggestively correlated with lean body mass, and negatively correlated with body fat. Thus, in a relatively small subgroup of untrained subjects with paraplegia, the strongest determinant of insulin sensitivity was cardiopulmonary fitness.

In 201 non-veteran subjects with SCI, Bauman *et al*[2] studied the relationship of oral carbohydrate tolerance after a 75 g glucose load to several variables, including level and completeness of lesion, gender, ethnicity, age, duration of injury, and anthropometric measures. Of the total group, 27 (13%) had diabetes mellitus and 56 (29%) had impaired glucose tolerance.[2,6] The subjects with complete tetraplegia had signficantly worse carbohydrate tolerance (Figure 2) and were more frequently classified with a disorder of carbohydrate tolerance than the other neurological deficit subgroups.[2] There were no significant gender differences for serum glucose concentration, although the plasma insulin levels were significantly higher for men at the intermediate time points, suggesting a relative state of insulin resistance. Stepwise regression analyses demonstrated that peak serum glucose was associated with

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increased per cent total body fat, complete tetraplegia, older age, and male gender; the peak plasma insulin was associated with increased per cent total body fat and male gender. In this study, glucose tolerance appeared to be independent of ethnic classification.

Prevalence of and pathogenic considerations for diabetes mellitus

Approximately 6.6% of the US population between the ages of 20 and 74 have diabetes mellitus,[7] the vast majority being classified as type II. At least three factors are involved in the pathogenesis of type II diabetes mellitus: a genetic predisposition, impaired insulin action, and a defect in pancreatic β-cell function.[8] The genetic basis of type II diabetes appears to be multifactorial. However, insulin resistance appears to be the universal defect present in individuals with a hereditary predisposition to develop type II diabetes mellitus. The tendency to develop diabetes may be increased by environmental factors, as in persons with SCI. If insulin resistance is present, the pancreas will compensate by increasing insulin release to maintain euglycemia, and hyperinsulinemia may ensue. Impaired glucose tolerance is usually associated with insulin resistance.[9–11] The possible progression of impaired glucose tolerance to diabetes in persons with SCI has not been studied. The progression from a disorder in carbohydrate handling to diabetes depends on a multiplicity of factors, including the genetic composition of the cohort, environmental factors, length of follow-up, and means of assessment.

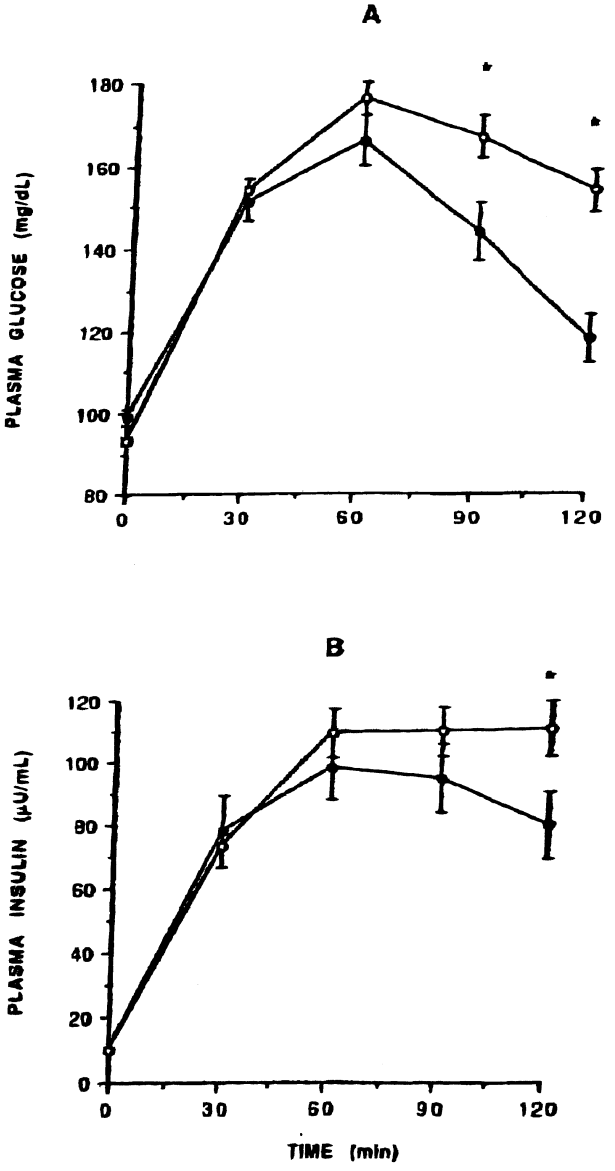

Figure 1 Comparison of oral glucose tolerance between SCI and control groups. Mean plasma (**A**) glucose and (**B**) insulin values $\pm$SEM during a 2-h oral glucose tolerance test performed on 100 subjects with SCI (○) and 50 control subjects (●). An asterisk (*) above the time point displays significant differences ($P<0.05$) between the SCI and control groups (*from* Bauman *et al*[3] with permission)

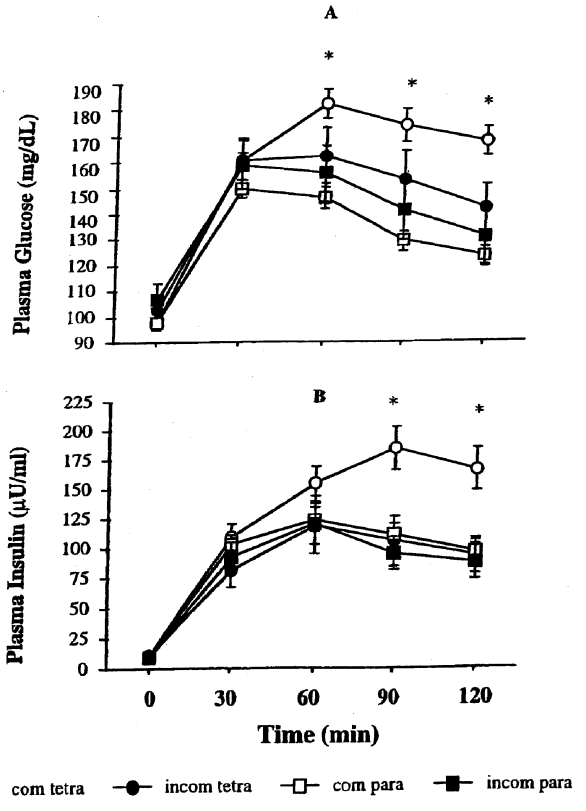

Figure 2 Comparison of oral glucose tolerance by neurological deficit. (**A**) Serum glucose concentration *vs* time after a 2-h oral glucose tolerance test. (**B**) plasma insulin levels *vs* time after a 2-h oral glucose tolerance test. An asterisk (*) above the time point displays significant differences ($P<0.05$) between the motor complete tetraplegia group and the three other groups with neurological deficit (incomplete tetraplegia, complete paraplegia, incomplete paraplegia) (*from* Bauman *et al*[2] with permission)

Since fasting plasma glucose has been shown to highly correlate with basal rates of hepatic glucose output,[12] and the average fasting plasma glucose is only mildly elevated in subjects with SCI, peripheral insulin resistance is the major factor responsible for glucose intolerance in this disorder. Subjects with impaired glucose tolerance or diabetes mellitus may have fasting plasma glucose values within the normal range and be without symptoms of any carbohydrate disorder. In one study[13] in which able-bodied individuals were screened for diabetes, of those diagnosed with impaired glucose tolerance or diabetes mellitus, 66% and 51%, respectively, exhibited fasting plasma values below 115 mg/dL. The presently accepted classifications for the diagnosis of the disorders of oral carbohydrate tolerance are those of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[6] Despite the absence of the typical symptoms related to the hyperglycemia of diabetes, insulin resistance and relative hyperinsulinemia will predispose such individuals to an atherogenic condition.

Determinants of insulin resistance

Muscle

Since the predominant peripheral action of insulin is upon muscle, and paralysis results in an absolute decrease in the quantity and quality of muscle mass, it is important to address the known morphological, physiological, and biochemical effects of SCI on muscle. Denervation of skeletal muscle has been shown to cause insulin resistance.[14] Schmalbruch *et al*[15] studied the morphology of rat soleus muscle denervated for 6–10 months. These investigators found that in chronically denervated muscle, the original fibers were lost and those surviving were adversely affected by repeated cycles of regeneration and necrosis. Denervation has an adverse effect on muscle fiber type.[16] Electrical stimulation has been shown to improve muscle fiber structure and function.[15,17,18] In animal models, investigators have reported the deleterious effect of denervation on post-receptor insulin action,[19] exercise-induced glucose uptake,[20] insulin receptor binding,[21,22] receptor phosphorylation,[21] and the glucose transporter protein (GLUT-4).[23–25]

In a recent study,[26] individuals with tetraplegia were found to have a marked reduction in whole body glucose transport that appeared to be due to a proportional reduction in muscle mass. In contrast to several studies in animal models of muscle denervation, the glucose transport system in skeletal muscle in those with tetraplegia remained remarkably intact despite severe morphological changes, including a predominance of type IIb fibers.[26] Lillioja *et al*[27] demonstrated a significant correlation between insulin resistance by the euglycemic clamp technique and per cent of type IIb muscle fibers. Type IIb muscle fibers are less sensitive to insulin action, and these fibers have a reduced capillary density, which may also be responsible for a reduction in glucose uptake, both insulin-dependent and insulin-independent.

Level of Activity

Prolonged inactivity has been shown to be associated with hyperinsulinemia and impaired glucose tolerance.[28,29] An epidemiological study by Helmrich *et al*[30] demonstrated that the incidence rates for diabetes mellitus declined as energy expenditure increased. For each 500-kcal per week increment in energy expenditure, the age-adjusted risk of diabetes mellitus was reduced by 6%. In another epidemiological study of over 20 000 US male physicians by Manson *et al*,[31] an inverse association was found between regular exercise and the subsequent development of diabetes mellitus, supporting the study by Helmrich.[30] Placing healthy subjects at bed rest voluntarily for 7 days resulted in a moderate deterioration in oral glucose tolerance and increased plasma insulin levels both fasting and in response to an oral glucose load.[32] If obese subjects who have insulin resistance and elevated plasma insulin levels are placed at bed rest, they will manifest a further worsening of carbohydrate tolerance.[33] After bed rest, euglycemic clamp studies[32] revealed a rightward shift of the insulin dose response curve at which half-maximal stimulation occurred with no significant change in the maximal response in the rate of glucose uptake. Hepatic glucose output suppression by insulin was not changed by bed rest. These investigators[32] suggested that short-term immobilization and its effects on carbohydrate metabolism occur primarily in skeletal muscle. Bed rest does not appear to be associated with a decrease in insulin receptor binding.[33] Postreceptor defects in insulin action may also be operative. Single leg casting for 1 week in man has been shown to reduce insulin-stimulated glucose uptake in the immobilized limb.[34] In normal subjects, carbohydrate intolerance associated with bed rest may be reversed within 1 week of ambulation.[28,35] Goodyear *et al*[36] reported that the number and activity of the glucose transporter protein, GLUT-4, was increased after exercise. In addition, glycogen synthase activity was increased, resulting in increased synthesis of glycogen and increased nonoxidative glucose disposal. By hind-limb perfusion technique or the incubation of isolated skeletal muscle,[37,38] muscle contraction, independent of insulin, increased glucose transport. Thus, denervation appears to be responsible for a post-receptor defect in insulin action, as well as the loss of contraction-stimulated glucose disposal.

Adiposity

There is a generally recognized association between adiposity and insulin resistance, hyperinsulinism, and abnormalities in carbohydrate metabolism. Yalow *et al*[39] reported higher plasma insulin concentrations in

obese individuals compared with lean controls. This observation has been confirmed in numerous animal and human models of obesity. Studies have shown that the hyperinsulinism of obesity is due to decreased response of the peripheral tissues to insulin.[40–42] Generally, caloric restriction may partially reverse these abnormalities. In adult-onset obesity, the size of the fat cell appears to correlate with insulin resistance.[43,44] Adipocyte hypertrophy is associated with decreased insulin mediated glucose uptake, presumably due to a reduction in the number of insulin receptors,[45] as well as postreceptor defects.[46] Studies of body fat topography have suggested that distribution of body fat may be an important factor in the association of obesity with other metabolic disorders in able-bodied individuals.[47–54] In persons with SCI, the usual clinical measures under estimate the degree of adiposity. Several methods of body composition have been employed in subjects with SCI[55] and appear to offer reasonable estimates of total or regional body fat. Studies in the able-bodied have established an association between hypertension, hyperinsulinemia, obesity, and disorders of glucose tolerance.[56–61] In persons with SCI, investigators have begun to establish associations between obesity (total and regional), glucose intolerance, hyperinsulinemia, lipid abnormalities, and hypertension.[1,3,62–64] Possibly reflecting a state of insulin resistance, an increased prevalence of hypertension has been reported in persons with chronic paraplegia.[65] Hyperuricemia is also an inherent component of this metabolic syndrome.[66] In a subset of subjects with SCI with hyperinsulinemia and hypertriglyceridemia, hyperuricemia was also present.[67]

Recommendations

Any individual with a potential genetic predisposition to diabetes mellitus or diagnosed as having an abnormality in carbohydrate handling should make an effort to reduce the risk of diabetes. Pre-diabetic subjects have an atherogenic pattern of risk factors for coronary heart disease (CHD), possibly due to obesity, hyperglycemia, and hyperinsulinemia, which may present for several years prior to the emergence of diabetes, and these risk factors may contribute to CHD, as much as diabetes itself.[68] Intervention at any stage could potentially prevent or delay progression of cardiovascular disease. Obesity, physical inactivity, and a high-fat diet are recognized risk factors for diabetes which can be modified. Diet therapy, according to the recommendations of the Committee on Food and Nutrition of the American Diabetes Association,[69] should be instituted when appropriate to achieve and maintain a desirable body weight. Combining exercise with diet therapy may be expected to be of greater efficacy than either approach alone.[70,71] The general treatment of diabetes mellitus is beyond this discussion herein, but a description of the classes of pharmacological agents and brief strategies for treatment has been provided in a prior review.[1]

LIPID METABOLISM AND CARDIOVASCULAR DISEASE

Introduction

The levels of high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol have a potent influence on the atherosclerotic process. It is well appreciated that elevation in LDL cholesterol and depression of HDL cholesterol are two important independent risk factors for CHD.[72–75] Individuals with SCI have been reported to have accelerated and premature CHD. In an epidemiological study, Whiteneck *et al*[76] reported that cardiovascular diseases were the most frequent cause of death among persons with SCI more than 30 years after injury (46% of all deaths) and among those more than 60 years of age (35% of all deaths). In a relatively small cohort, Bauman *et al*[77,78] found that the prevalence of asymptomatic CHD was between 60% to 70%, as determined by upper body exercise[78] or dipyridamole thallium scintillation[77] stress testing in subjects with paraplegia (mean age, 52 years) or tetraplegia (mean age, 47 years), respectively. Although the prevalence of CHD in the population of persons with SCI is not established with certainty, every effort should be made to identify risk factors for CHD that are modifiable and appropriately intervene to attempt to reduce potential vascular events. An understanding of the lipid profile in persons with SCI and therapeutic interventions, if indicated, will improve clinical care.

Serum HDL cholesterol

A consensus with regard to the finding of a lower serum HDL cholesterol in those with SCI than in able-bodied persons has generally been accepted.[63,79] Approximately 10% of the US population has HDL cholesterol values less than 35 mg/dL,[80] whereas 24% to 40% of those with SCI have levels below this value.[63,81] Bauman *et al*[63,81] found a depressed mean serum HDL cholesterol level in subjects with paraplegia and tetraplegia compared to mean values in able-bodied controls with almost 40% having levels less than 35 mg/dL.[63,81] In the subjects with SCI and in the controls, strong inverse correlations were demonstrated between serum triglycerides and HDL cholesterol.[63,82] This inverse relationship may reflect the effects of elevated plasma insulin.[83,84] In a study of 541 subjects with chronic SCI,[62] lower levels of serum HDL cholesterol were found in the subjects with tetraplegia than in those with paraplegia.[62] Furthermore, subjects with motor complete injuries had lower values of serum HDL cholesterol than did those with incomplete injuries for each category of neurological deficit (Figure 3).[62] The potential effect of ethnicity on the serum lipid profile was studied in 600 patients with SCI who were being seen for their routine annual physical examination.[85] As has been reported in the able-bodied population, African Americans had significantly higher serum

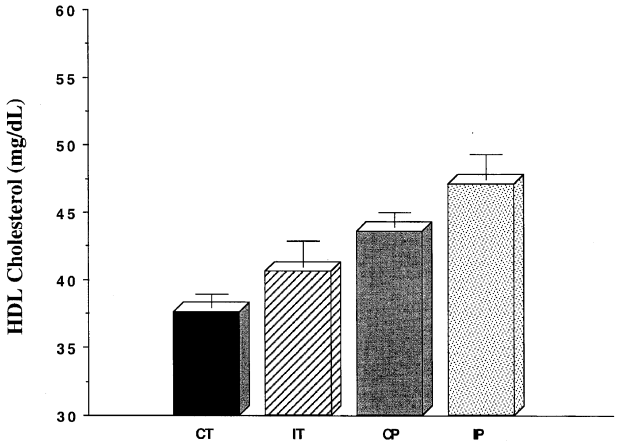

Figure 3 Serum HDL cholesterol levels by neurological deficit. CT represents complete tetraplegia; IT, incomplete tetraplegia; CP, complete paraplegia; IP, incomplete paraplegia. All values are expressed in mean ± SEM. A significant inverse relationship was found for degree of neurological deficit and serum HDL level ($r = 0.19$, $P < 0.0001$). (*drawn from data presented in* Bauman *et al*[62] with permission)

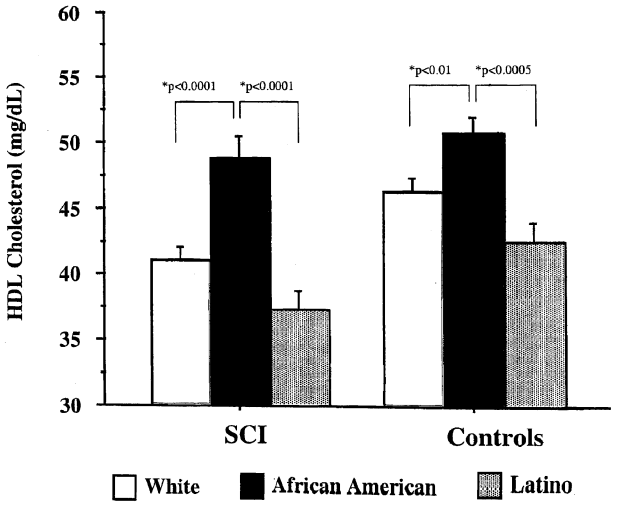

Figure 4 Comparison of serum HDL cholesterol levels among the ethnic groups. The groups with spinal cord injury (SCI) and controls are categorized by ethnicity. The bar graphs represent serum HDL cholesterol levels (*from* Bauman *et al*[81] with permission)

HDL cholesterol values and a lower ratio of serum total to HDL cholesterol than whites or Latinos. In another study of 320 patients with SCI and relative sedentary able-bodied controls,[81] males with SCI had lower HDL cholesterol than the able-bodied but there was no significant difference for females who were predominantly premenopausal. Whites and Latinos with SCI had lower serum HDL cholesterol levels than the ethnically-matched able-bodied group, whereas African Americans with SCI did not (Figure 4). Serum HDL cholesterol levels were inversely associated with body mass index in the SCI group.[62,81] Serum lipoprotein (a) does not seem to be significantly affected by age, duration of SCI, or level and completeness of lesion.[81]

An increased level of cardiopulmonary fitness has been demonstrated to positively influence the serum HDL cholesterol level in subjects with[63,79,86] or without SCI.[87,88] In addition, it would appear that in those with SCI even slightly increased levels of activity may increase HDL cholesterol concentrations.[62] Inactivity, independent of lipid values or other risk factors for CHD, may be an independent risk factor for CHD.[86] Patients should be strongly encouraged to reach and maintain the highest level of daily activity compatible with their injury.

Certainly, factors other than immobilization may play a role in determining the serum triglyceride and/or HDL cholesterol levels. High calorie or high fat diets may increase serum triglycerides and depress serum HDL cholesterol levels.[89] Excessive alcohol intake may also depress serum HDL cholesterol levels.[90] Moderate alcohol consumption has been reported[91] to increase serum HDL cholesterol levels. However, in obese subjects this effect of alcohol to raise serum HDL cholesterol levels may not occur.[92] Cigarette smoking has also been shown to be associated with insulin resistance[93] and lower serum HDL cholesterol levels.[94] Heavier cigarette smokers have been reported[94] to have lower serum HDL cholesterol levels than lighter smokers. Current cigarette smoking is an independent risk factor for CHD,[95] and when reduced or eliminated decreases the risk for CHD. In a group of 250 male veterans with chronic spinal cord injury, Spungen *et al*[96] reported that 76.8% had smoked cigarettes but that 31% were current smokers, comparable to that found in the general population.[97] Cigarette smokers with SCI had lower HDL cholesterol levels, regardless of gender, ethnicity, level or completeness of lesion.[98] A low serum HDL cholesterol level is yet another medical indication to encourage a patient to avoid cigarette smoking.

As has been previously mentioned, an inverse correlation generally exists between serum triglycerides and HDL cholesterol: the higher the triglycerides, the lower the HDL cholesterol.[63,81,82] Thus, those patients with serum triglyceride concentrations above 200–250 mg/dL and HDL cholesterol values below 35 mg/dL should receive diet and/or pharmacological therapy in an effort to raise the serum HDL cholesterol level.[99] In such individuals, abstinence from alcohol should be achieved since drinking has been shown to further raise serum triglycerides.[90,100]

Serum LDL cholesterol

Approximately 25% of the able-bodied population has an absolute elevation of the serum LDL cholesterol level. Generally, the level of serum LDL cholesterol in individuals with SCI is similar to control groups. The

recommendations of the National Cholesterol Education Program[95] for therapy are based on the level of serum LDL cholesterol in association with the presence or absence of CHD or risk factors for CHD. Since patients with SCI may have at least two risk factors for CHD or have premature CHD, the target value for LDL cholesterol in those with SCI is lower than that of persons without these considerations. Diet therapy should be instituted initially in the absence of CHD and/or extremely high levels of serum LDL cholesterol. A low fat and low cholesterol diet may be expected to reduce levels of serum LDL cholesterol by 10% to 20%, an effect which will be maintained for only as long as the patient adheres to diet therapy. Pharmacological agents are currently available that have a profound effect on lowering serum LDL cholesterol concentrations with generally minimal adverse reactions.[101,102]

Goal of therapeutic intervention

The objective of the treatment of dyslipidemia is to prevent or reduce the morbidity and mortality associated with CHD. To this end, several treatment programs in the general population have been reported to be successful.[99,101–104] Every effort should be made to increase serum HDL cholesterol levels, by appropriate exercise prescription, avoidance of lifestyle factors that are known to depress serum values, and pharmacological measures, if indicated. If values for serum LDL cholesterol exceed those recommended,[95] then appropriate therapeutic intervention is indicated.

HEMOSTATIC CONSIDERATIONS

Introduction

Compared to able-bodied population, individuals with SCI have been reported to have an increased mortality at an earlier age due to CHD. As discussed in detail in the prior section, a clustering of risk factors associated with CHD have been demonstrated in individuals with SCI,[1–3] including hyperlipidemia, hypertension, diabetes mellitus, and hyperinsulinemia.[1–3,28–31,48,65] Additional risk factors include an increased prevalence of cigarette smoking,[96] and the fact that the vast majority of the SCI subjects are men.[105] In addition to the aforementioned metabolic, gender, and lifestyle risk factors for CHD, an alternative hypothesis in individuals with SCI is that there exist pathologic hematological factors directly involved in contributing to premature and accelerated atherogenesis, similar to those that have been previously demonstrated in the able-bodied population with diabetes mellitus. The increased incidence of trauma-related hypercoaguability and thromboembolism in the acute phase of SCI[106–108] does not appear to persist beyond the early stages of SCI,[109,110] and, as such, is not related to the genesis of CHD. However, there is strong evidence of abnormal platelet function, resulting in the production of atherogenic and thrombogenic factors.

General background on prostacyclin in homeostasis

Prostacyclin (prostaglandin (PG)I_2) and thromboxane A_2 (TXA_2) are cyclooxygenase metabolites of arachidonic acid and the major prostanoids regulating homeostasis of the circulatory system. They appear to counteract each other in ischemic heart disease, when the level of PGI_2 decreases, the level of TXA_2 increases.[111–114] Prostacyclin, produced mostly in the endothelial cells, is a potent vasodilator and inhibitor of platelet aggregation; this prostanoid exerts its effect by binding to specific membrane receptors on the platelets, heart, aorta and kidney. The PGI_2 receptors are abundantly expressed on platelets. In acute CHD, on the platelet surface PGI_2 receptors decrease and TXA_2 receptors increase.[112]

The serum low-density lipoprotein (LDL) cholesterol is important in maintaining a constant concentration of cellular cholesterol. This lipid fraction also provides arachidonic acid for prostaglandin formation and has a profound inhibitory effect on prostaglandin H synthase, the key enzyme of prostaglandin synthesis essential for inhibition of platelet aggregation.[115]

Platelets as sources of active components

Aggregation of platelets induced by agonists such as thrombin, ADP, epinephrine, or collagen, is critical in normal blood coagulation and in the development of atherosclerosis and thrombosis.[116–123] Aggregation of platelets by these agonists is mediated, in part, through the intracellular synthesis of PGG_2 and TXA_2.[124] Platelet aggregation is inhibited by several autacoids including prostanoids, such as prostacyclin (PGI_2) and PGE_1 or PGD_2,[125] blood coagulation factor Xa[126] and endothelium derived relaxing factor/nitric oxide.[127] Among the prostanoids PGI_2 is the most potent inhibitor of platelet aggregation and is generally believed to play a key role in the prevention of CHD.[128] Disruption of the gene for the prostacyclin receptor in mice increases their susceptibility to thrombosis.[129] Aggregation also results in the release of a platelet-derived growth factor (PDGF), and is a well-recognized mitogenic factor in the pathogenesis of atherosclerosis and induction of apoptotic cell death.[130] Recent studies have demonstrated that endothelial injury at the site of stenosis by rupture or fissure of the atherosclerotic plaque initiates a sequence of events that leads to vessel occlusion.[131,132] Incidence of CHD is significantly increased in SCI.[77,78,133] At the sites of endothelial injury, there is an accumulation of TXA_2, ADP, serotonin, activated thrombin, platelet activating factor and tissue factor.[134]

Platelet abnormalities after SCI

Although premature CHD is increased in individuals with SCI, the underlying pathophysiological events are unknown. Recently we have demonstrated that platelets in individuals with SCI are not hypersensitive

to aggregating agonists, such as, ADP, *l*-epinephrine, collagen or thrombin. In addition, they are not resistant to the inhibitory effects of PGE_1/PGI_2.[135] However, the basal level of PDGF in SCI plasma was threefold higher than the normal level (6.41 ± 0.12 *vs* 2.15 ± 0.12 pg/10^6 cells; $P < 0.05$) and platelet-stimulated thrombin generation and PDGF release from SCI platelets was not inhibited by the PGI_2-stimulated increase of cyclic adenosine monophosphate (cAMP) formation.[136]

The PGI_2-induced inhibition of platelet aggregation has been shown to be mediated through the binding of the prostanoid to its specific receptors on the cell surface[137–140] activating the membrane-bound adenylate cyclase, and increasing cellular cAMP levels leading to the inhibition of platelet function and vasodilation. Prostacyclin and PGE_1 bind to the same receptors on platelets and to the purified receptor from platelets.[137–139] When studying platelets from subjects with SCI, equilibrium binding of the tritiated probe ^{3}H-PGE_1 was on average persistently less than 50% of the mean control level.[135]

Scatchard analysis of PGI_2/PGE_1 platelet binding has shown the presence of one high-affinity-low-capacity receptor population, and one low-affinity-high-capacity receptor population. Binding of the agonist to the low-affinity receptors (Kd in μM ranges) increases the cAMP level in platelets, which inhibits platelet aggregation.[137,138] Binding of the agonist to the high-affinity receptors also increases cAMP levels, probably in a compartmentalized manner and in a smaller quantity when compared with the synthesis of the compound through the low-affinity binding.[140] Also, the synthesis of cAMP by high-affinity prostaglandin binding is under feedback inhibition by the nucleotide itself.[140] The binding of PGI_2 to its high-affinity, but not to its low-affinity receptors is inhibited by guanidine triphosphate.[141] In individuals with SCI, Kahn *et al*[135] has recently shown that inhibition of platelet aggregation by increasing cAMP through low-affinity PGI_2 receptor binding exclusively failed to inhibit either PDGF release or platelet-stimulated thrombin generation[136] (Figures 5 and 6) and was postulated to be due to the loss of high-affinity PGI_2 receptors.

Novel IgG identified in SCI

Platelets from subjects with SCI had markedly decreased binding of ^{3}H-PGE_1 to high affinity prostacylin binding sites without affecting the low-affinity binding sites[142] (Figure 7). Incubation of nonSCI platelets in plasma from SCI subjects resulted in a similar inhibition of binding of the radiolabelled ligand to high-affinity binding sites.[142] Such treatment of normal platelets resulted in the failure of the prostanoid to inhibit platelet-stimulated thrombin generation and PDGF release without any impairment of the stimulation of cAMP formation or PGI_2-induced inhibition of platelet aggregation.[136] These results suggested the presence of an inhibitor in SCI plasma capable of partial impairment of platelet PGI_2 interactions. This inhibitor of PGI_2 platelet binding has been identified as a prostacyclin receptor antibody (IgG) that specifically blocks the high-affinity PGI_2 receptors on the platelet surface[142] and has been

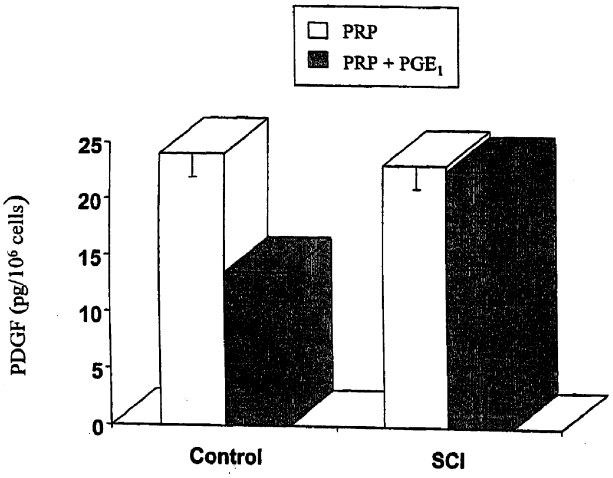

Figure 5 Effect of PGI_2 on platelet-stimulated thrombin generation in platelet rich plasma (PRP) from control and SCI subjects. PRP anticoagulated with sodium citrate was obtained from normal and SCI volunteers. PRP was treated with or without PGI_2 (10 mM) before relative rate of thrombin generation was determined. The rates of thrombin generation were measured in PRP and platelet-poor plasma by determining the recalcification time (*derived from data from* Kahn *et al*[135] with permission)

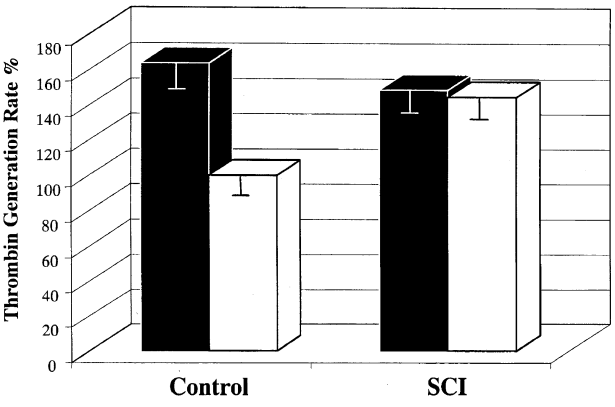

Figure 6 Effect of PGI_2 on release of PDGF in PRP from subjects with SCI and controls. Platelet-derived growth factor (PDGF) was determined by ELISA. For platelet aggregation to occur, thrombin ($0.05 \pm .2\,\mu$/ml) was added to platelet-rich plasma (PRP) stirring at a rate of 1200 rpm at 37°C. Reaction was stopped by adding 5% TCA and supernatant was collected by centrifuging the mixture at 8000 *g*. For inhibition of platelet aggregation 100 nM PGE_1 was added[136]. (*derived from data from* Kahn *et al*[141] with permission)

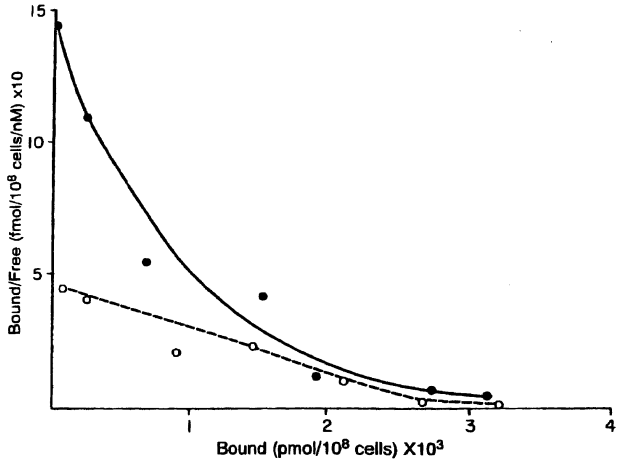

Figure 7 Scatchard plots of prostaglandin E_1 binding to platelets from subjects with SCI and controls. Note the absence of high-affinity binding of ^{3}H-PGE_1 on platelets from subjects with SCI (*from* Kahn *et al*[135] with permission)

demonstrated to be responsible for the previously described platelet/coagulation abnormalities.

Insulin or Ca^{2+} channel blockers have been shown to restore the decreased high-affinity PGI_2 receptors to normal ranges in the platelets from subjects with SCI, and these agents also 'corrected' the efficacy of the PGI_2 receptors in the inhibition of PDGF release and thrombin generation.[135,136] These results indicated that the up- or down-regulation of the high-affinity receptors on the platelet surface resulted in the increased or decreased effects of PGI_2 on platelet function. The increase of cAMP in platelets is generally believed to be associated with both the inhibition of platelet aggregation and the release reaction.[143] However, in SCI platelets the increase of cAMP through the low-affinity PGI_2-receptors was not sufficient for inhibition of thrombin generation or in the PDGF release; thus, the binding of the prostanoid to its high-affinity PGI_2 platelet receptors appears to be necessary for these actions of PGI_2.[136] The decrease of high-affinity PGI_2 receptors on the platelet surface in subjects with SCI (independent of cAMP synthesis) may be speculated to be of importance in potentiating the atherosclerotic process in persons with SCI.

PDGF and thrombin in SCI

Thrombin and PDGF are potent mitogenic agents for arterial smooth muscle cells and induce the proliferation of human mesengial cells in the vascular intima.[144,145] Elevated levels of platelet-stimulated thrombin generation and PDGF release would be expected to accelerate the progression of atherosclerosis in individuals with SCI. Thrombin is well appreciated as an important proteinase capable of converting fibrinogen to fibrin. However, in addition, thrombin is the most potent stimulator of platelet aggregation with a vital regulatory function upon hemostasis and thrombosis. Thus, thrombin not only plays an essential role in blood coagulation but also significantly influences the development of CHD.[146,147] Although the effects of thrombin and PDGF are counteracted by several inhibitors present in plasma,[148] these effects are, in part, inhibited by PGI_2 through a platelet-mediated interaction.[149] Thus, through its multi-inhibitory effects, PGI_2 exerts a significant beneficial effect in the prevention of atherosclerosis.[150–153] As previously stated, the failure of PGI_2 to inhibit PDGF release and platelet-stimulated thrombin generation in SCI platelets was due to the loss of the high-affinity PGI_2 receptors on the platelet surface. It follows that restoration of these receptors would be expected to have a beneficial clinical effect. Insulin and calcium channel blockers have been shown to increase both the high- and low-affinity PGI_2 receptors in platelets[136,153,154] and insulin is required for PDGF-stimulated cells to grow.[155] Treatment of SCI platelets with insulin resulted in a sufficient increase in high-affinity PGI_2 receptors to normalize PDGF release and thrombin generation.[136] The post high-affinity binding receptor mechanism by which PGI_2 inhibits PDGF release and thrombin generation is unknown. By defining the mechanisms of platelet abnormalities in SCI that enhance the potential for aggregability and the release of atherogenic mitogens, it may be possible to develop new and effective therapeutic interventions to normalize platelet function and prevent or attenuate the deleterious effects of platelet dysfunction on the vasculature.

AUTONOMIC CHANGES AND DYSFUNCTION

Introduction

Limited data exists for persons with SCI regarding the role of autonomic dysfunction and its direct contribution to impairment of central and peripheral cardiovascular control. Adverse changes in the pattern of cardiovascular autonomic function may potentially lead to the development of hypertension and other cardiovascular disease. The effects of SCI on cardiovascular and autonomic function have been investigated by defining the indices of heart rate variability (HRV) and blood pressure variability (BPV), as well as other noninvasive research tools. Because HRV and BPV reflect the degree of efferent autonomic modulation of the sinus node and vasculature, respectively, these measures may also be applicable in the diagnosis of autonomic impairment in patients without underlying cardiovascular disease.

HRV and BPV analysis

The electrocardiograph (ECG) represents the electrical events of the cardiac cycle in a waveform consisting of a number of well-defined components, of which the R

peak is the most readily discernible. Measuring HRV entails quantification of the beat-to-beat oscillations in the ECG-derived R-R intervals (RRI); it provides an estimate of autonomic modulation of cardiac function.[156–158] One technique used in the determination of HRV, referred to as power spectral analysis, produces spectra of heart rate oscillations in the frequency domain by mathematically transforming a series of sequential RRI into specific frequency components (high frequency: HF_{RRI}, and low frequency: LF_{RRI}). The HF_{RRI} component of HRV is believed to represent solely efferent vagal influences,[159] whereas interpretation of the LF_{RRI} component is more controversial. The general consensus, however, is that this component estimates cardiac sympathetic modulation.[160] A sympathovagal balance (LF_{RRI}/HF_{RRI}) has commonly been used to describe the dual opposing effects of the sympathetic and parasympathetic nervous system on the heart.[161,162] Therefore, HRV provides a quantitative measure for discriminating between the influences of the two branches of the autonomic pathways on cardiac control. This technique has been used to study classes of subjects with varying degrees of autonomic nervous system dysfunction.

Complex intrinsic, neural and humoral mechanisms, in addition to disease, injury, medications, excitement, inactivity and diet, may influence blood pressure. Quantification of beat-to-beat blood pressure oscillations, a sensitive and noninvasive method of blood pressure monitoring, was developed to assess blood pressure changes that can be unpredictable, rapid, or slow and subtle. A technique described by Penáz in 1973[163] allows for noninvasive continuous monitoring while displaying real-time waveforms and beat-to-beat values for systolic, diastolic and integrated mean blood pressure. Power spectral analysis of BPV provides another tool for assessing the relationship between the autonomic and vascular systems.[164,165] The low frequency systolic blood pressure (LF_{SBP}) component of BPV represents sympathetic vasomotor tone, while the high frequency (HF_{SBP}) component depicts the mechanical effects of respiration on blood pressure. Because HRV methods only isolate cardiac vagal activity (HF_{RRI}), a combination of the LF_{SBP} component of BPV and the HF_{RRI} component of HRV provides a more complete picture of parasympathetic and sympathetic cardiovascular regulation.

Cervical autonomic dysfunction

The normal autonomic response to pressor stimuli (i.e., phenylepherine) is augmentation of sympathetic and attenuation of parasympathetic activities. Several investigators[166,167] have shown an exaggerated blood pressure response to various stimuli (increased pressor response) in subjects with complete tetraplegia. Mathias *et al* have suggested that there is an up-regulation of adrenoceptors and/or a hyperresponsiveness of the effector cells.[168] Hypersensitivity was hypothesized to be due to several different mechanisms, including an increased number of receptors, an enhanced response to receptor activation,[168] or possibly post-junctional changes in the effector organs resulting from prolonged inactivity.[169,170] Cannon and Rosenblueth[171] have previously summarized the 'autonomic sensitivity phenomena', and detailed receptor activation and modulation, focusing attention on the 'up' and 'down' regulation of receptor function, which depends on the availability of the neurotransmitter. In subjects with low paraplegia (below thoracic vertebra six) and intact sympathetic outflow, an increased pressor response to stimuli does not occur.[166]

Among groups with varying degrees of autonomic dysfunction (complete and incomplete tetraplegia, and high level paraplegia), Grimm *et al* have demonstrated an inverse relationship between the level and completeness of injury and the components of HRV.[172] The higher and more complete the SCI the lower the levels of both sympathetic and parasympathetic output to the heart (Figure 8). This finding suggests that the two components which regulate autonomic control of the cardiovascular system maintain a balance, even in cases in which one component of the autonomic nervous system is severely compromised. Furthermore, the cardiac sympathovagal balance (LF_{RRI}/HF_{RRI}) was consistently similar among all groups (SCI and able-bodied) regardless of sympathetic interruption.

Several investigators[173–175] have examined the effects of complete cervical transection on HRV in an effort to determine whether LF_{RRI} (an estimate of cardiac sympathetic tone) is measurable, but their

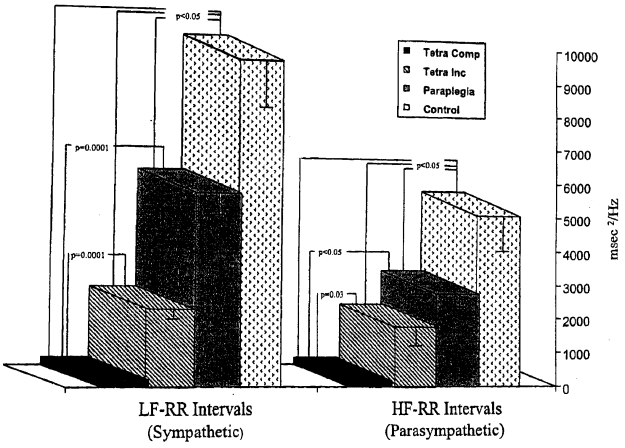

Figure 8 Composite of provocative maneuvers for mean LF(RRI) and HF(RRI) values in subjects with spinal cord injury and able-bodied controls. Provocative maneuvers in the composite variable included head-up tilt, cold pressor and isometric contraction. Group with complete tetraplegia represented by dark gray box, incomplete tetraplegia hashed box, paraplegia light gray box and able-bodied controls dotted box. LF(RRI) = low frequency R-R interval. HF(RRI) = high frequency R-R interval (*adapted from* Grimm *et al*[172] with permission)

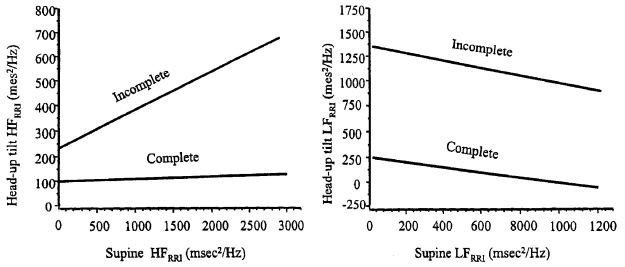

Figure 9 Regression of head-up tilt on low frequency (LF) and high frequency (HF) components of heart rate variability. Intercepts and slopes shown for regression of composite provocative LF component of HRV against the supine LF measure (right side) and HF component of HRV against the supine HF measure (left side). For LF measure, the complete tetraplegia group exhibited a systematically lower composite provocative LF component than the incomplete tetraplegia group. For the HF measure, the complete tetraplegia group failed to show a change in the HF component during provocation whereas the group with incomplete tetraplegia demonstrated a significant positive slope. (*from* Grimm *et al*[175] with permission)

findings have been inconsistent. Grimm *et al* reported a LF_{RRI} component at rest and during head-up tilt in subjects with complete tetraplegia; the provocative response of both components (LF_{RRI} and HF_{RRI}) was significantly reduced relative to those with incomplete tetraplegia[175] (Figure 9). This observation suggests that the loss of neural efferent sympathetic innervation to the cardiovascular system in individuals with complete tetraplegia results in a compensatory decrease in vagal tone to the heart, a parasympathetic response promoting autonomic stability. The presence of the LF_{RRI} component in the group with complete tetraplegia may represent sympathetic-like oscillations or, conceptually, may also represent excitation of supraspinal reflexes and/or an up-regulation of receptor function.[174] Finally, the significant differences in the LF_{RRI} component at rest and during provocation between the complete and incomplete groups with tetraplegia imply that the measurement of HRV may be useful to distinguish between complete and incomplete injuries, and may assist in the neurological assessment of persons with SCI.

Thoracic autonomic dysfunction

Long-term immobilization, whether as a result of SCI or other forms of illness, can cause deleterious physiologic alterations to most organs and systems of the body.[176–178] Ineffective orthostatic circulatory regulation is associated with notable problems for patients with SCI and may contribute to the increased prevalence of cardiovascular disease in this population.[64] The combination of the loss of peripheral sympathetic vasomotor tone, reduce lower extremity skeletal muscle pump, attenuated venous return, and depressed baroreceptor sensitivity results in significant alterations of the cardiovascular system.

Arterial baroreceptors exert a ubiquitous influence on the heart and circulation. Their primary function is to buffer transient changes in arterial pressure. A fall in arterial pressure (as occurs during an orthostatic maneuver) is detected by the sensory nerve endings in the walls of the aortic arch and the carotid sinuses, triggering nerve discharge to the medulla and resulting in deactivation of the baroreceptors. To more clearly define baroreflex responses, investigators have experimentally applied selective stimuli, such as lower body negative pressure, the neck chamber technique, and bolus injections of vasoactive drugs. The Valsalva maneuver has also been used as a noninvasive means to study baroreflex mechanisms, and it is a well-established method for assessing the integrity of cardiovascular reflexes and autonomic function. In healthy individuals, stimulation of the sinoaortic baroreceptors by the Valsalva maneuver has been demonstrated to provide a quantitative assessment of cardiovascular baroreflex sensitivity (BRS)[179–182] and the extent to which baroreceptor-cardiac reflexes contribute to changes in cardiovascular autonomic control. The Valsalva maneuver may be employed to compare autonomic responses of healthy subjects and those with potential cardiovascular impairment.[182]

Investigators[183] have demonstrated an attenuated BRS through phase IV of the Valsalva maneuver in subjects with paraplegia compared to age-matched able-bodied controls. This finding suggests that there is an impairment in pressure regulation below the level of lesion resulting from compromised sympathetic outflow, a change in regulation of receptor sensitivity has occurred as a result of the inability to orthostatically challenge the baroreceptors, and/or an apparent attenuation of vagal control of the heart (also observed by the finding of a reduced HF_{RRI}). These adverse autonomic findings may be potential precursors to overt clinical hypertension or contribute to other cardiovascular dysfunction and disease in individuals with paraplegia.

Central cardiac-autonomic function

Central cardiac control is preserved by both efferent vagal and sympathetic fibers, with stimulation of one system corresponding to an inhibition of the other. Autonomic control of the cardiovascular system is intrinsic and complex, and compromise to either branch of the autonomic nervous system will considerably affect cardiac regulation. In contrast, the sympathetic branch exclusively maintains peripheral vascular control. Distribution of blood flow is controlled, in part by excitation or withdrawal of sympathetic activity. Functional deficits between the cardiovascular and autonomic nervous systems have been described in various pathophysiologic disorders. Clearly, in persons with SCI, cardiovascular autonomic impairment is related to the level and extent of lesion.

In cervical and high thoracic transection (above T-6), cardiac sympathetic output is partially to completely ablated, while in those with lower cord injury, central sympathetic function remains intact but there is peripheral sympathetic denervation. Regardless of the level of SCI, patients often display clinical disorders resulting from autonomic dysfunction, highlighting the importance of the relationship between the autonomic and cardiovascular systems in maintaining integrity and homeostasis.

Recently, Grimm *et al*[184] demonstrated that subjects with tetraplegia have significantly reduced resting central cardiac function (ie, cardiac output and stroke volume) relative to individuals with paraplegia and to sedentary and active able-bodied controls. Subjects with lower cord injury (below T-10) exhibited similar central cardiac function as age-matched sedentary able-bodied controls. A strong relationship between vagal-cardiac tone (HF_{RRI}) and stroke volume was established for the total group ($r=0.78$, $P<0.001$) (Figure 10), and by an analysis of covariance it was determined that the slopes of this relationship were not significantly different among the four groups. These observations suggest that efferent vagal control of resting central cardiac function is maintained despite autonomic dysfunction, and that as levels of vagal activity increase, stroke volume rises proportionally among all groups regardless of the degree of autonomic impairment or level of activity. Finally, the comparable levels of cardiac vagal output and stroke volume found between the paraplegia and sedentary groups suggest that, despite peripheral sympathetic status, the absence of regular physical activity has a similar impact on central autonomic and cardiac function.

Peripheral vascular function

The autonomic nervous system, specifically sympathetic tone, contributes to the control of central venous pressure and vascular compliance by causing contraction of smooth muscle of the vessel walls. In individuals with SCI, autonomic dysfunction, immobility and inactivity play critical roles in affecting peripheral vascular circulation. Changes in sympathetic outflow are controlled by various receptors (ie, arterial baroreceptors, chemoreceptors and cardiopulmonary receptors), as well as alterations in the activity of higher brain centers (ie, nucleus tractus solitarius).[185] As a consequence sympathetic outflow is selectively modified and adjusts appropriately to the needs of the vascular system. In view of the number and complexity of these control mechanisms, caution must be exercised when interpreting results obtained from noninvasive beat-to-beat blood pressure oscillations (represented by LF_{SBP}).

With these considerations appreciated, Wecht *et al*[186] reported similar levels of resting sympathetic vasomotor tone (LF_{SBP}) in individuals with lower cord injury relative to sedentary able-bodied controls. Other investigators[187] have also reported comparable circadian blood pressure rhythms in subjects with low thoracic injury compared to controls. Furthermore, in able-bodied individuals systemic vascular tone in inactive tissue is believed to be controlled predominantly by myogenic activity, with sympathetic vasoconstrictor influences providing only minimal (approximately 15% to 20%) input to vascular tone at rest.[188] Plasma levels of norepinephrine are also frequently used as an index of peripheral sympathetic activity and are influenced by the balance between

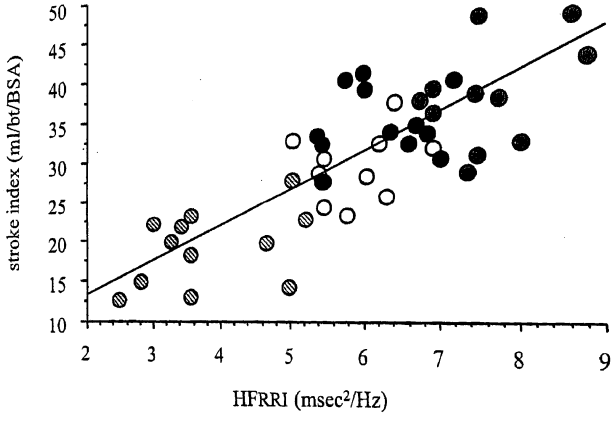

Figure 10 Regression between high frequency component of R-R intervals (HFRRI) and stroke index. Hashed circles represents the tetraplegia group; opened circles paraplegia group; closed circles sedentary able-bodied and gray circles active able-bodied controls ($r=0.78$, $P<0.001$) (*derived from data from* Grimm *et al*[184] with permission)

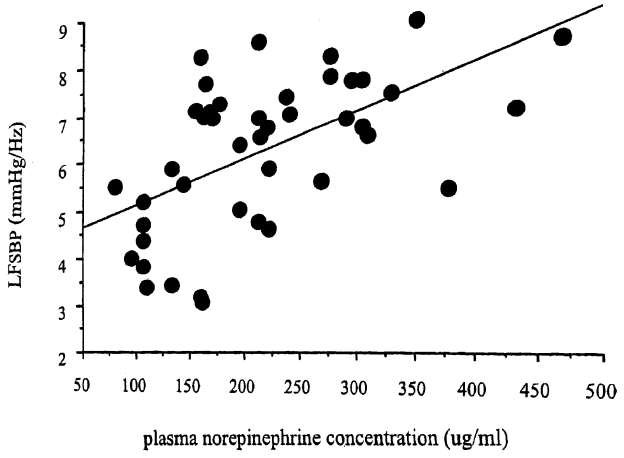

Figure 11 Regression analysis between the low frequency component of systolic blood pressure (LFSBP) and plasma norepinephrine levels. The total group is plotted ($r=0.55$, $P<0.01$). (*derived from data from* Grimm *et al*[184] with permission)

release of norepinephrine from sympathetic nerve endings, re-uptake into the endings and catabolism of the amine. In support of LF_{SBP} findings, subjects with paraplegia demonstrated comparable resting plasma norepinephrine levels to the control group with a significant correlation between the two parameters ($r=0.55$, $P<0.01$) (Figure 11). Similar observations in subjects with paraplegia for plasma norepinephrine values have been reported,[189] with the relatively low level (all below T-10) and incompleteness of injury, in part, explaining the absence of differences between the two groups.

Adaptations to pressure changes within the vasculature, represented by a venous resistance index,[190] are largely modulated through neural and mechanical influences and result from vessel distensibility, elastic recoil and smooth muscle contraction. Using venous occlusion plethysmography, and in contrast to the comparable LF_{SBP} findings, investigators have reported significantly reduced venous vascular function below the level of injury in subjects with tetraplegia or paraplegia relative to able-bodied controls (0.34 ± 0.11 or $0.51\pm 0.21\%$ *vs* $0.255\pm 0.92\%$ respectively; $P<0.05$).[186,191] Venous compliance, a measure of the responsiveness of the vascular system, was approximately fivefold lower in the SCI groups than controls, indicating that the combination of autonomic disruption, immobility and inactivity caused considerable reduction in vessel compliance and responsiveness. The clinical implications of these findings suggest that orthostatic intervention and/or regular physical activity may improve vascular integrity and, potentially, peripheral and central venous pressure in individuals with SCI.

Conclusions

Persons with SCI have been reported to have premature CHD. The etiology of the accelerated atherogenesis, which is strongly suggested from the literature, appears to be multifactorial. Metabolic hemostatic, and autonomic considerations were discussed in this review.

A dysmetabolic syndrome that has been associated with CHD in the able-bodied population occurs with increased prevalence in individuals with SCI. Those with SCI tend to have insulin resistance due to inactivity and adverse body compositional changes. Insulin resistance is associated with abnormalities in glucose tolerance and lipid disorders. There is an increased frequency of glucose intolerance and diabetes mellitus in those with SCI compared with the ambulatory population. Those with the greatest neurological deficit appear to have the worst oral carbohydrate tolerance. Serum HDL cholesterol levels are depressed in persons with SCI. The concentration of serum HDL cholesterol appears to be inversely related to the level of neurological deficit. Intervention at any time after SCI to address the deterioration in carbohydrate metabolism and adverse lipid changes should be expected to have a salutary effect on the vasculature. Obesity, inactivity and diets high in fat are appreciated to increase the risk of diabetes mellitus, and each of these may be modified. Efforts should be made to increase HDL and lower LDL cholesterol levels by avoidance of lifestyle factors that negatively impact these lipid fractions and pharmacological therapy, if indicated.

Hemostatic factors may be relevant in the occurrence of atherogenesis in those with SCI. A novel prostacyclin receptor antibody that specifically blocks the high-affinity prostacyclin receptors on the platelet surface has been described. Persons with SCI have been demonstrated to have elevated circulating platelet-derived growth factor levels and lack the normal inhibition of platelet-derived growth factor release from platelets by prostacyclin. In addition, the rate of platelet-stimulated thrombin generation is not inhibited by prostacyclin. Both thrombin and platelet-derived growth factor are potent mitogenic agents for arterial smooth muscle cells. In addition, thrombin has other potentially deliterious effects on the vasculature, including inducing platelet aggregation and fibrin production. The failure of the inhibition of platelet-derived growth factor release from platelets and platelet-stimulated thrombin generation is due to the loss of the prostacyclin receptors on the platelet surface. With our increased understanding of the mechanisms responsible for platelet dysfunction in those with SCI, new and effective therapies may be considered.

Except in persons with lower spinal cord level injuries (below thoracic level 6), the central autonomic nervous system has been demonstrated to adapt to interruption of sympathetic innervation by down-regulation of cardiac vagal tone, thereby maintaining sympathovagal balance. The attenuation of the baroreceptor sensitivity to provocative stimulation (Valsalva maneuver) in persons with paraplegia may have profound implications for the development of cardiovascular dysfunction, with an increased tendency to develop hypertension and the attendant risk for CHD. There is preliminary evidence to suggest that orthostatic maneuvers and/or physical exercise may improve peripheral and central cardiovascular hemodynamics.

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