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The Physiology of Exercise in Spinal Cord Injury

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The Physiology of Exercise in Spinal Cord Injury

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Contents

Chapter 1
The Physiology of Exercise in Spinal Cord Injury (SCI): An Overview of the Limitations and Adaptations

Hannah W. Mercier and J. Andrew Taylor

Abstract For all human beings, exercise is vital to living well. Exercise promotes physical and psychological health across the lifespan, reducing risk for mortality and decreasing prevalence of health complications which contribute to chronic disease. Exercise requires integrated physiologic responses across the musculoskeletal, cardiovascular, autonomic, pulmonary, thermoregulatory, and immunologic systems. However, persons living with spinal cord injury (SCI) have difficulty achieving the minimal exercise requirements for health benefits since paralyzed skeletal muscles cannot contribute to overall oxygen consumption. Moreover, SCI can be considered as an accelerated systemic form of aging due to the severely restricted physical inactivity imposed, usually at an early age. Indeed, persons with SCI experience profound declines in function across many physiological systems and are considered, as a group, to be sedentary and among the least fit individuals. And, there are numerous considerations for exercise in those with an SCI. Alterations in function across almost all the physiological systems engaged by exercise may be compromised or altered. Nonetheless, exercise can still confer significant benefits and may be among the most important components of a healthy lifestyle for this population.

After SCI, the motor, sensory, and autonomic deficits limit not only the convenience of exercising, but notably the capacity to exercise. Due to the decreased ability to ventilate independently and limited innervated skeletal muscle, 6 % of persons with tetraplegia are unable to achieve aerobic exercise after discharge

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(National Spinal Cord Injury Statistical Center 2015). Apart from this small percentage, research has documented that exercise can result in notable training adaptations and clearly protects against risk of death and disease, and reduces the limits that SCI imposes on the body (Huonker et al. 1996; Washburn and Figoni 1998; Knutsson et al. 1973). As physiological changes unique to SCI become better understood, innovative technological solutions for exercise interventions and tailored methods for measuring the effects of training will become increasingly available. This chapter provides an overview to the limitations on exercise physiology for those living with SCI, as well as considerations and current challenges for facilitating exercise performance.

1.1 Motor Limitations and Potential Adaptations

Among the physiological changes in SCI most apparent is reduced or complete loss of volitional muscular control below the level of injury. This limited motor control results from cessation, partial or complete, of supraspinal input to the spinal cord. There is a potential for motor recovery in the lower extremities, however the spinal cord can generate automatic movements without conscious or volitional control (Roy et al. 2012). Spinal circuitry "learns" what motor action (standing, stepping) is taught and practiced (de Leon et al. 1998a, b), and it can "forget" the movement when practice is ceased (de Leon et al. 1999; Cha et al. 2007). Furthermore, there is evidence that the spinal circuitry can alter motor actions in response to the sensory input received at a given moment, even "predicting" subsequent motor actions through central pattern generation (Roy et al. 2012; Edgerton et al. 2004). The spinal cord demonstrates plasticity in generating motor control when it is trained repetitively. Remarkably, even those with motor complete SCI, via electrical stimulation and repetitive training, can exert control on lower extremity motor action based on proprioceptive information (Harkema et al. 1997; Grillner and Zangger 1979; Roy et al. 2012). Finally, pharmacological and epidural stimulation interventions can amplify residual descending input to facilitate motor recovery (de Leon et al. 1998a, b). Recognizing these adaptations and spinal circuitry resiliency, rehabilitation has advanced motor function recovery after SCI using assisted motor training, spinal cord epidural stimulation, and/or pharmacological agents in recent years (Roy et al. 2012). These opportunities for regaining lower extremity motor function present even more reason to exercise and thus prevent secondary health complications that would complicate participation in locomotor training.

Within 6 weeks of SCI, paralyzed skeletal muscles atrophy significantly (Gorgey et al. 2015). They convert to fast-type muscle fibers, becoming weak and highly fatigable (Scott et al. 2006). In addition to limiting exercise performance, the loss of skeletal muscle mass and extreme lower limb physical inactivity in SCI induce structural and functional changes in the heart and circulatory system which lead to increased cardiovascular disease risk. There is strong evidence for the beneficial

effects of functional electrical stimulation (FES) to activate larger amounts of muscle mass and achieve the benefits of regular aerobic exercise, including muscular hypertrophy (Crameri et al. 2002; Gerrits et al. 2001; Pollack et al. 1989; Goss et al. 1992; Deley et al. 2015; Panisset et al. 2016). Hybrid FES exercise, which incorporates volitional contractions of the upper body in synchrony with FES to paralyzed muscles, also serves as a total body exercise (Krauss et al. 1993). Though evidence of comparative effectiveness is limited, greater gains in aerobic capacity have been found using hybrid FES exercise compared to upper body exercise alone (Verellen et al. 2007). Activating the paralyzed muscles with FES during exercise also has benefits to cardiac output as the lower limb contractions act as a muscle pump (Davis et al. 1990). In addition, abdominal binding (West et al. 2012), compression garments, and anti-gravity suits (Hopman et al. 1992) can be used to counteract the lack of sympathetically mediated vasoconstriction that lead to blood pooling in inactive and splanchnic areas.

1.2 Cardiovascular Implications

An accelerated age-related decline in the cardiovascular system occurs after SCI (Phillips et al. 2012; Miyatani et al. 2009), resulting in risk for cardiovascular disease three times greater than the able-bodied and risk for stroke approximately four times greater (Cragg et al. 2013). Factors contributing to this increased physiological risk for cardiovascular disease include autonomic dysfunction, physical inactivity, and poor metabolic profile. Exercise can induce cardiac remodeling which diminishes the functional and structural deficits after SCI (Brown and Weaver 2011; Gibbons et al. 2016). Moreover, arterial cross sectional area is larger among athletes with paraplegia compared to those who are sedentary (Huonker et al. 1998). In fact, increases in arterial diameter have been noted after just two weeks of FES cycling exercise (Thijssen et al. 2006) and arterial wall stiffness may be reversed by exercise (de Groot et al. 2005).

Autonomic dysfunction after SCI produces an unstable cardiovascular system and diminished blood pressure and heart rate responses to exercise. Low resting blood pressure and orthostatic hypotension are related to impaired cerebrovascular and cognitive function, syncope, fatigue, and nausea (Phillips et al. 2014a, b; Claydon, Steeves et al. 2006). Though the symptoms are not distinct from those in able bodied persons (Cleophas et al. 1986; Frisbie and Steele 1997; Sclater and Alagiakrishnan 2004), orthostatic hypotension may limit the positions possible for exercise in persons with SCI. In contrast, autonomic dysreflexia occurs in response to noxious afferent stimuli below the level of lesion, such as bowel or bladder distention, tight clothing, pressure ulcers, or even standard therapeutic electrical stimulation, and can lead to dangerously high blood pressure. Exercise has been shown to be a safe therapeutic approach for attenuating the severity of autonomic dysreflexia (DiCarlo et al. 1994; Halliwill 2001), though interestingly, athletes with

SCI have induced autonomic dysreflexia to generate increased blood pressure and improve exercise performance (Harris 1994).

1.3 Ventilatory Limitations

An SCI results in frequent respiratory problems due to lesser innervated respiratory musculature. For example, the capacity to generate cough is compromised due to impaired innervation of the abdominal muscles at most SCI levels. On the other hand, less active muscle mass, especially in individuals with high level SCI may not impose enough stress on the respiratory system to elicit ventilatory constraint or inspiratory muscle fatigue during exercise. Indeed, athletes with high level SCI may demonstrate lung hyperinflation during exercise without increased ventilatory constraint or inspiratory muscle fatigue. This may permit increased expiratory flow and reduced airway resistance, but also increase diaphragmatic fatigue and impede venous return. There is evidence that various exercise modalities can improve respiratory function among those with SCI (Sheel et al. 2008; Silva et al. 1998; Phillips et al. 1989; Terson de Paleville et al. 2013). The positive effects of exercise training in SCI may reside in an increase in respiratory muscle strength and endurance in addition to adjacent effects of reduced ventilatory demand during exercise via peripheral adaptations. If ventilatory response could be improved, higher intensities which are more effective at improving cardio-metabolic risk may be achievable (Kemi et al. 2005; Swain and Franklin 2006). However, it should be noted that hybrid FES exercise that results in greater skeletal muscle work may allow for oxygen demand that exceeds respiratory capacity in high level SCI (Brurok et al. 2011; Qui et al. 2016).

1.4 Thermoregulatory Considerations

Impaired thermoregulation occurs both at rest and during exercise after SCI, due to a loss of sympathetic innervation and decreased ability to vasoconstrict or shiver below the level of injury. Persons with SCI have a greater risk of heat-related illness, though some cooling technologies used with able bodied persons have been successfully applied to SCI athletes. Cooling of the hands and feet have been used to direct blood flow to the active muscles and facilitate exercising at higher aerobic demands (Griggs et al. 2014). In contrast to the peripheral “detraining” of sweat glands among those with SCI (Ogawa and Asayama 1978), exercise training enhances nitric oxide-dependent vasodilation (Thijssen et al. 2007; Green et al. 2004) and thus the ability to thermoregulate.

1.5 Alterations in Body Composition and Inflammation

Persons with SCI at the same BMI as able-bodied individuals are approximately 13 % fatter due to loss of skeletal muscle and characteristic increases in adipose tissue after injury (Spungen et al. 2003). Adipose has a profound influence on metabolic syndrome (Grundy 2008), chronic low grade inflammation, and cardiovascular disease. However, beneficial changes in body composition can result from various forms of exercise (electrical stimulation, arm crank ergometry, resistance training, and combinations of these). Following the decreased physical activity and obesity that often occur with SCI is greater risk for a state of chronic low grade inflammation (Myers et al. 2007). Persons with SCI have higher inflammatory markers, such as resting cortisol levels (Campagnolo et al. 1999) which in turn increases their propensity to develop cardiovascular disease and diabetes (Gleeson et al. 2011). While acute inflammatory responses are worse for those with high cervical SCI, the anti-inflammatory effects of exercise are attainable for both persons with tetraplegia and paraplegia (Bakkum et al. 2015; Griffin et al. 2009, Turiel et al. 2011; Rosety-Rodriguez et al. 2014). Indeed, exercise holds benefits for lowering BMI, fat mass, and inflammation even at levels that would be considered recreational (Paulson et al. 2013; Kouda et al. 2012; Yamanaka et al. 2010).

1.6 Impact on Bone Fracture Risk

Inactivity and less weight bearing after SCI profoundly limit the mechanical stimulus to bone and increase the risk for low-load fractures during daily living (Lala et al. 2014). Furthermore, poor fracture healing leads to further complications such as deconditioning and pressure ulcers from bed rest (Gifre et al. 2014; Frotzler et al. 2008). Bone loss is greatest in long bones below the level of injury, and is most treatable during the acute phases of SCI. In fact, present literature suggests that there are limited effective interventions to prevent or restore bone loss in those with chronic SCI. Though they involve some component of weight bearing, FES rowing (Gibbons et al. 2014), FES cycling (Frotzler et al. 2008; Lai et al. 2010), and activity-based training (Astorino et al. 2013) demonstrate only modest benefits to bone mineral density specific to the area trained, but with no lasting effects. Furthermore, both increases and decreases in bone mineral density have been identified with the use of electrical stimulation (Gorgey et al. 2015; Gater et al. 2011). Mechanical stresses placed on skeletal muscles during exercise should stimulate osteoblast activity and bone formation. However, load has rarely been quantified during specific exercises and this would assist in developing interventions that would maximize fracture prevention, minimize bone resorption, and promote bone growth.

1.7 Pain

Eighty percent of persons with SCI experience chronic pain, with a third having levels of pain that interfere with activities of daily living and work (Cardenas et al. 2004; Dijkers et al. 2009). A significantly greater proportion of those with SCI, compared to able bodied persons, are prescribed more than one analgesic-narcotic medication and are five and-a-half times more likely to be issued two or more analgesic-narcotics (Kitzman et al. 2016). Considering these rates of use and the high rates of potential adverse events (Kitzman et al. 2016), exercise may be a relatively affordable, safe, and empowering method of reducing pain. However, pain is also a barrier to exercise (Ditor et al. 2003; Hicks et al. 2003; Subbarao et al. 1995). Nonetheless, if psychological and behavioral means are available to support exercise participation, those with SCI may experience lesser pain. For example, regular aerobic exercise decreases pain after just three months, and with greater effects after nine months (Hicks et al. 2003; Martin-Ginnis et al. 2003). Indeed, when those with SCI ceased participating in an exercise program, they experienced increased pain (Ditor et al. 2003). Those who self-propel wheelchairs and transfer numerous times daily (Morrow et al. 2010) typically have weak posterior shoulder muscle strength (Mulroy et al. 1996; Wilbanks and Bickel 2016; Olenik et al. 1995). Strong evidence supports exercise as an intervention to decrease shoulder pain, one of the common chronic pain conditions among persons with SCI. In fact, by decreasing pain even just marginally, exercise also improves psychological well-being and decreases the severity of depression (Stanton and Reaburn 2014).

1.8 Conclusion

As elegantly stated by Henry Barcroft, “the condition of exercise is not a mere variant of the condition of rest, it is the essence of the machine.” Indeed, across the systems impacted by SCI, exercise offers at least modest adaptations to the physiological limitations of injury. Those with SCI who exercise achieve a variety of benefits related to lifelong health and wellness goals: from the cellular level to more distal functional and psychosocial outcomes. Discussed more in detail in the forthcoming chapters are the challenges in measuring these physiological changes which may have relatively large impact in the lives of persons with SCI. Although regular exercise is important for more complete recovery, more than half of those with an SCI experience barriers to exercising, and many do not meet criteria to induce significant health benefits. Given that exercise is unique as rehabilitative for bodily function and as representative of integrated physiological control, the fields of rehabilitation and physiology should work together to develop innovative solutions for those with SCI to optimize exercise interventions.

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Chapter 2
Physiology of Motor Deficits and the Potential of Motor Recovery After a Spinal Cord Injury

V. Reggie Edgerton and Roland R. Roy

Abstract The focus of this chapter is to highlight some fundamental concepts on the physiology of movement control after a spinal cord injury (SCI). We will discuss how these concepts are defined by the order of motor unit recruitment within a motor pool and how the relative recruitment across multiple motor pools defines the movements performed. We then will describe how these factors are affected by SCI. Understanding how these particular "neural decisions" might be modified by SCI will provide greater insight in assessing the etiology of the movement dysfunctions and thus in finding potential resolutions in a given individual at a given time post-injury (Fig. 2.1).

2.1 Introduction

The focus of this chapter is to highlight some fundamental concepts on the physiology of movement control after a spinal cord injury (SCI). We will discuss how these concepts are defined by the order of motor unit recruitment within a motor pool and how the relative recruitment across multiple motor pools defines the movements performed. We then will describe how these factors are affected by SCI. Understanding how these particular "neural decisions" might be modified by SCI will provide greater insight in assessing the etiology of the movement dysfunctions and thus in finding potential resolutions in a given individual at a given time post-injury (Fig. 2.1).

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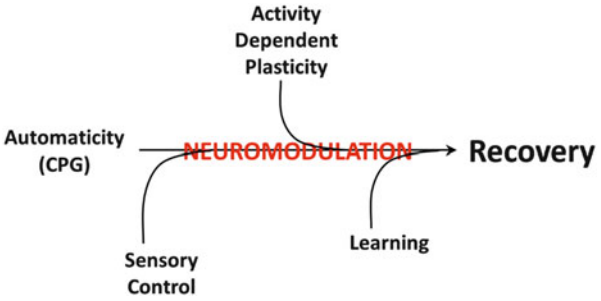

Fig. 2.1 Schematic that emphasizes the importance of multiple physiological concepts being combined in efforts to enhance the recovery of function after a SCI. Each of these concepts is discussed in some detail in the text

An initially useful perspective in understanding what is lost and what potentially can be recovered after a SCI is to consider the different sources and kinds of control of different types of motor tasks as occurs normally compared to the sources and kinds of control after a SCI. One useful general principle to consider is that the sources of control of movement are remarkably redundant. Another useful concept in understanding the potential for recovery is the dominance of the automaticity of the control strategies that are built into our nervous system, even for very complex movements. Although the level of automaticity that persists in routine movements is generally not recognized, the pervasiveness of this phenomenon can be readily understood when considering the persistent conservation of basic evolutionary mechanisms within the neuromotor systems. For example, we routinely and continuously assess the extensive details of every aspect of our movements in the context of what has occurred only a few milliseconds beforehand to essentially those that occurred probably even prenatally. In a sense our nervous system takes advantage of many different types of mechanisms that have evolved and have been conserved in our species. One might view this process as "evolutionary learning" and explain why the automaticity of control is such a pervasive and important feature of our control systems. Undoubtedly there are multiple mechanisms of learning and forgetting within the sensorimotor system that function within a wide range of time frames, all of which may be retaining some aspect of the experience of movement. It seems likely that these learning and forgetting processes occur throughout the neural networks that sense and control movement.

What are the sources of control of movement that are lost in part or in total after a SCI? After a complete separation of the caudal and rostral segments of the spinal cord, the lost sources of control certainly include the supraspinal centers in the brain that normally play a predominant role in these processes. In this context, all sensory information plays an important role in the control of movement. Stated another way, all sensory systems at some point project directly or indirectly to the motor networks. For example, sensory information related to vision, hearing, odor, and taste are normally available. After a SCI, however, there is some degree or even total loss of "*direct*" control of these systems innervated by the spinal segments distal to the lesion. Thus these physiological systems must rely on the processing

and translation of proprioception and cutaneous sensory input derived from the more caudal spinal segments, i.e., those below the level of the lesion. But additionally a paralyzed individual with a lesion at a mid-thoracic level may have lost normal access to multiple sensory modalities, although vision can remain a critical source of control of the upper body and thus enable the individual to ski and sail. An example of the level of redundancies in the neural control of movement has been demonstrated in an individual who is blind and paralyzed but can still walk proficiently with the aid of an exoskeletal device combined with transcutaneous spinal cord stimulation (Gad et al. 2015). This fact leads back to the importance of the plasticity within and among the different networks that can contribute to the control of movement after a SCI.

The experimental evidence is clear, however, that the potential control mechanisms that remain most important after a SCI is proprioception and cutaneous input. "Potential" is a key word here because to reclaim this source of control, significant plasticity must occur via a range of neuromodulatory interventions, including activity-dependent rehabilitation. This activity-dependent rehabilitation provides the opportunity for the spinal networks to learn what it practices, e.g., stepping and standing (Edgerton et al. 1997). The precision in movement that can be observed based on the neural networks that receive, process, and translate proprioceptive and cutaneous input in real-time is embedded within the sensorimotor networks throughout the spinal cord. Given the redundancy in the sources of control of movement, the loss of vision, hearing, taste and even equilibrium are much less prohibitive in one's level of mobility given that proprioception and cutaneous information is usually preserved after a SCI.

What, then, are the challenges in regaining motor function after a SCI? There is a severe loss in the ability to respond directly and precisely to the routine, ongoing, but highly comprehensive, sensing of the environmental surroundings. As noted above, proprioception and cutaneous inputs caudal to the lesion provide the information needed to assess the kinetics environment and to recognize the consequences of these kinetics. The robust feed-forward mechanisms within that spinal circuitry make it possible to translate this information in real time to generate the appropriate kinetics and kinematics of the complex musculoskeletal system without any input from supraspinal sources. A second factor is that the spinal circuitry can learn and improve motor skills with practice. Thus it appears that for rehabilitative strategies to be effective for recovering sensorimotor function they must (1) reengage the sensorimotor networks that generate a movement and (2) provide the opportunity to repeatedly engage the circuitry so that it can learn the task that it is being trained.

2.2 Adaptation of Neuromuscular Properties After a SCI

After a SCI, there are dramatic changes in the neuromotor units below the level of the lesion. In this section related to animal studies we will focus primarily on the effects of a complete spinal cord transection or spinal cord isolation, i.e., complete spinal cord transections at a mid-thoracic and a high sacral level plus bilateral deafferentation between the transection sites resulting in electrical silencing of the muscles innervated by the motoneurons located in the isolated spinal cord segment (Roy et al. 2007a). For the human we will focus on studies involving a severe SCI. In both cases we then will highlight activity-dependent rehabilitation strategies that influence the recovery of function at the neuromotor level.

2.3 Animal Studies

2.3.1 Adaptations Post-injury

Motoneurons located below the lesion after a complete spinal cord transection or within the isolated region of the spinal cord after spinal cord isolation have lower rheobase currents and higher spike after hyperpolarization amplitudes and input resistances compared to motoneurons in control animals (Button et al. 2008). In addition, these motoneurons also show depolarization of the resting membrane potential and voltage threshold (Beaumont et al. 2004; Cope et al. 1986; Hochman and McCrea 1994), decreased after hyperpolarization duration (Cope et al. 1986; Hochman and McCrea 1994; Czeh et al. 1978), and a rightward shift in the frequency–current relationship (Beaumont et al. 2004). Interestingly, the soma size and oxidative capability as reflected by quantitative histochemical determinations of succinic dehydrogenase activity are unaffected even months after either spinal cord transection or isolation (Roy et al. 2007b; Chalmers et al. 1992; Krikorian et al. 1982). There is some disassembly of neuromuscular synapses and a mild decrement in neuromuscular junction function after a spinal cord transection and, although transmission remains largely intact for supramaximal stimulation, these decrements could be related to the increased fatigue observed under non-supramaximal stimulation conditions (Burns et al. 2007; Ollivier-Lanvin et al. 2009). In addition, a slight increase (Cope et al. 1986) or no change (Mayer et al. 1984; Munson et al. 1986) in motor axon conduction velocity after a spinal cord transection has been reported.

There are a number of morphologic, phenotypic, and mechanical changes in the skeletal muscles below the level of the lesion. The muscles and muscle fibers atrophy, lose force capacity, show an increase in myosin ATPase activity, become "faster" phenotypically and mechanically, and have a decrease in fatigue resistance (Edgerton et al. 1996; Roy et al. 1991). After spinal cord transection there is an increase in the expression of the fastest MHC isoforms in both predominantly slow

and fast muscles, but with the response being more robust in slow muscles (Roy et al. 1991, 1999; Roy and Acosta 1986; Talmadge 2000). In general, the muscles also show a lower oxidative capacity, although the predominantly slow soleus muscle in cats and rats maintains its oxidative capacity as reflected by the staining patterns of succinate dehydrogenase and the levels of citrate synthase and resistance to fatigue.

Similar changes have been observed at the motor unit level. In general a higher percentage of motor units produce less force (Cope et al. 1986; Mayer et al. 1984; Gallego et al. 1978; Celichowski et al. 2006), have faster twitch mechanical properties (Cope et al. 1986; Mayer et al. 1984; Talmadge et al. 2002), show reduced levels of oxidative enzymes (Pierotti et al. 1994) and higher levels of glycolytic enzymes (Pierotti et al. 1994), and are more fatigable (Mayer et al. 1984; Munson et al. 1986; Celichowski et al. 2006) after either spinal cord transection or isolation. In addition, the motor units change towards a faster phenotype (Cope et al. 1986; Talmadge 2000; Gallego et al. 1978) and this is reflected in an increase in the percentage of fast motor units post-injury (Pierotti et al. 1994). The fibers comprising a single motor unit post-injury are of the same myosin immunohistochemical type and show a similar range in oxidative and glycolytic enzyme activities as in intact animals (Pierotti et al. 1994; Roy et al. 2008).

Combined all of these changes result in the neuromuscular system becoming weaker and less resistant to fatigue. Thus the strategy from a therapeutic and rehabilitation viewpoint is to counter or minimize these deficits.

2.3.2 Rehabilitation Strategies

Several forms of motor training have been somewhat successful in ameliorating the deficits in the neuromuscular system after a complete SCI in animals. For example, treadmill training (Roy et al. 1998a), "passive" cycling exercise (Dupont-Versteegden et al. 1998), stand training (Roy et al. 1998a; Jiang et al. 1990), and robotic loading during a step cycle (Nessler et al. 2011) have reduced the amount of atrophy and phenotypic changes in the muscles below a complete mid-thoracic spinal cord transection. Several motoneuron properties affected after a SCI such as depolarization of the resting membrane potential and voltage threshold, decrease in the excitability for rhythmic firing, increased amplitude of both the action potential after-hyperpolarization and synaptic input to motoneurons are normalized by either step training (Petruska et al. 2007) or cycling using a motorized ergometer (Beaumont et al. 2004; Gardiner 2006).

We have used the spinal cord isolation model to begin to determine the optimal type, duration, and frequency of contractile activity for maintaining muscle properties post-injury. This model has allowed us to impose a known amount and type of contractile activity on the otherwise silent muscles. The hindlimbs of spinal cord isolated cats were moved through a simulated step cycle and the soleus muscle was stimulated while being lengthened, shortened, or during an isometric phase for

30 min/day, 5 days/week for 6 months: isometric contractions was the most effective mode for maintaining the muscle properties close to normal (Roy et al. 2002). Interestingly, passive cycling thorough the same range of movement ameliorated the effects of spinal cord isolation on the soleus mass, force capability, and maximum shortening velocity (Roy et al. 1998b). Using the same model in rats, we then showed that the same amount of daily contractile activity distributed at 2–3 intervals during the day was more effective in maintaining the properties of the soleus and medial gastrocnemius muscles than one bout per day (Kim et al. 2007, 2010; Haddad et al. 2003a, b).

2.4 Human Studies

2.4.1 Adaptations Post-injury

Human studies generally have reported similar changes as those observed in animals in the neuromuscular system post-injury. Compared to normal controls, there is a decrease in muscle cross sectional area (Shah et al. 2006; Mohr et al. 1997; Ragnarsson 1988) and peak torque (Krieger et al. 2005; Jayaraman et al. 2008; Lotta et al. 1991; Castro et al. 1999a, b), lower oxidative capacity (Gerrits et al. 2003; Rochester et al. 1995), and a decrease in fatigue resistance to repetitive activation reflecting a decrease in the percentage of slow fatigue resistant fibers in the muscle groups below the lesion (Talmadge 2000; Mohr et al. 1997; Rochester et al. 1995; Grimby et al. 1976; Martin et al. 1992; Olsson et al. 2006; Gerrits et al. 1999, 2001; Shields et al. 1997; Gaviria and Ohanna 1999; Butler and Thomas 2003).

In chronic SCI, the muscles below the lesion generally have faster contractile properties, e.g., a shorter contraction and half-relaxation time, most likely reflecting changes in muscle fiber composition toward a predominance of fast glycolytic fibers (Rochester et al. 1995; Gerrits et al. 1999, 2001; Shields et al. 1997). Single fiber analyses from chronic spinal cord injured subjects also show an increased contraction velocity (Malisoux et al. 2007).

There is a high incidence of diabetes in individuals with a SCI (Duckworth et al. 1980; Bauman et al. 1999; Lavela et al. 2006). Functional electrical stimulation (FES) paradigms help regulate common pathways involved with glucose metabolism (Petrie et al. 2014). For example, FES during exercise can decrease blood glucose levels and improve glucose utilization (Jeon et al. 2002) resulting in a decrease in the glucose intolerance and insulin resistance associated with paralysis (Bauman and Spungen 1994).

2.4.2 Rehabilitative Strategies

A variety of functional electrical stimulation (FES) modalities with some form of loading on the musculature have been somewhat effective in restoring the neuromuscular deficits associated with a SCI. FES paradigms involving isometric resistance training (Dudley et al. 1999), cycling (Duffell et al. 2008; Crameri et al. 2002; Baldi et al. 1998; Scremin et al. 1999), and lifting ankle weights with isotonic contractions (Rodgers et al. 1991; Mahoney et al. 2005; Gorgey and Shepherd 2010) have resulted in improvement in neuromuscular function. For example, training programs involving FES cycling (Mohr et al. 1997; Liu et al. 2007; Pacy et al. 1988; Hjeltnes et al. 1997; Sloan et al. 1994), FES ambulation (Klose et al. 1997; de Abreu et al. 2009), FES resistance training, and vibration exercise (Melchiorri et al. 2007) produced significant increases in muscle mass, with training frequencies ranging from 2–7 per week, for 8–52 weeks duration.

The contractile properties also revert toward normal values. The muscles become slower contracting (Rochester et al. 1995; Harridge et al. 2002), there is an increase in muscle force (Crameri et al. 2002; Gerrits et al. 2002; Hartkopp et al. 2003), an increased fatigue resistance (Rochester et al. 1995; Martin et al. 1992; Harridge et al. 2002; Gerrits et al. 2002; Hartkopp et al. 2003; Shields and Dudley-Javoroski 2006, 2007), and half-relaxation time returns to normal (Rochester et al. 1995). Electrically induced stimulation increases the glycolytic and mitochondrial oxidative enzyme levels (Kjaer et al. 2001) and there is an increase in both SDH activity (Rochester et al. 1995; Martin et al. 1992) and citrate synthase activity (Mohr et al. 1997; Crameri et al. 2002; Chilibeck et al. 1999).

Chronic FES training regulates metabolic gene signaling pathways in human paralyzed muscle (Petrie et al. 2014). Although acutely paralyzed muscles in humans appear to be fatigue resistant and oxidative, they transform into highly fatigable, glycolytic muscle after one year of paralysis (Shields 1995). Long term studies have shown that the size, fatigue resistance, oxidative enzyme levels, and contractile speed can be sustained using FES that includes loading of the musculature (Shields and Dudley-Javoroski 2006, 2007; Shields et al. 2006; Adams et al. 2011). It appears that variable frequency trains are more effective than constant frequency trains because they are less fatiguing (Deley et al. 2015) and that the inclusion of doublets enhances the torque production (Chang and Shields 2011).

Body weight support treadmill training has been shown to be very effective in recovering locomotor function (Roy et al. 2012), and there is some indication that this may be related to changes in the neuromuscular properties. Recently, it has even been shown that body weight–supported treadmill training (without FES) can increase muscle cross-sectional area (Giangregorio et al. 2005, 2006) and muscle fiber size and oxidative capacity in incomplete SCI subjects (Stewart et al. 2004; Adams et al. 2006).

FES also has a profound effect on fiber phenotype: there have been reports of a decrease in the proportion of type IIX fibers (the fastest fiber phenotype) and type II

MHC and an increase in the proportion of type IIA fibers (a more oxidative fast fiber type) and IIA MHC (Crameri et al. 2000, 2002; Kjaer et al. 2001; Andersen et al. 1996) and may even increase the percentage of type I fibers (Martin et al. 1992). There is a high incidence of diabetes in individuals with a SCI (Duckworth et al. 1980; Bauman et al. 1999; Lavela et al. 2006). FES paradigms help regulate common pathways involved with glucose metabolism (Petrie et al. 2014). For example, FES during exercise can decrease blood glucose levels and improve glucose utilization (Jeon et al. 2002) resulting in a decrease in the glucose intolerance and insulin resistance associated with paralysis (Bauman and Spungen 1994).

The effects of SCI on motor unit properties have been thoroughly reviewed recently by Thomas et al. (2014). Motor unit properties are viewed as important to address in this Chapter, focused on the neural elements of SCI, because of the acute and chronic control that spinal motoneurons have on muscle fiber phenotype and function. Motor unit firing rates define to a large degree the forces that are generated by the muscle unit. Although the effects of SCI on the maximum rate of firing can differ within and across muscles, the most common observation is a reduction in firing rate (Zijdewind and Thomas 2012). After SCI, voluntary force has been reported to increase in the triceps brachii by increasing the motor unit discharge rate. While increases in unit firing rates and force also occur in the thenar muscle, the low maximal rates suggest that the strongest voluntary contractions will be sub-maximal relative to the uninjured state (Hager-Ross et al. 2006). Firing rate variability also increases after SCI during voluntary contractions adding to the difficulty in controlling force (Wiegner et al. 1993; Thomas and del Valle 2001; Zijdewind and Thomas 2003).

The more critical factors in motor unit recruitment in generating force are that more units must be recruited to perform a given task due to the lesser force associated with muscle atrophy and reduced firing frequencies of the units. In addition, both of these factors require more dependence on more fatigable motor units. In spite of these functional deficits associated with fatigue some of the weakness and fatigability of paralysed muscles can be prevented or reversed by motor training (Shields and Dudley-Javoroski 2006; Peckham et al. 1976; Stein et al. 1992).

2.5 Bases for Automaticity in the Control of Movement

The idea of biological systems having isolated networks with rhythmic input that can generate cyclic motor output, commonly called central pattern generation (CPG), is centuries old. Experiments by Brown (1914) and Shik et al. (1966) extended this idea by demonstrating that highly adaptive stepping behavior could be generated by the spinal cord when cutaneous and proprioceptive inputs were available. These experiments, underscored the level of automaticity in the control of posture and locomotion in the mammalian spinal cord. The results showed that

supraspinal input to spinal neurons that they called 'controllers' respond to a tonic drive from the brain and generate complex rhythmic patterns that activate the limb musculature to generate a highly coordinated locomotion pattern. Later Shik and Orlovsky (1976) proposed a two-level automatism control system for locomotion: a nonspecific tonic input that determines the intensity (speed and grade) of locomotion, while the other level makes fine adjustments in the control of the limbs, including maintaining equilibrium. This control system interacts with sensory inputs such as proprioception and cutaneous feedback to execute well-coordinated stepping.

These observations were followed rapidly with numerous studies focused on the CPG phenomenon in mammals. The automatic aspects of these functions reflect a feature of evolution that enables postural and locomotor responses to be generated by the spinal cord without relying on what would be a much more delayed decision-making process by higher neural centers. A greater reliance on the brain to process the ongoing kinetics and kinematics events would require additional time and would impose disadvantages in the execution of a variety of postural and locomotor tasks. This would be particularly true when the response time is critical for survival. In this sense, "evolutionary learning" has played a key role in the automaticity of neural control exhibited during the execution of even routine motor tasks. Thus, the nervous system, even without conscious control, demonstrates a sophisticated level of automaticity that is smart and highly adaptable and plastic.

We now know that the spinal circuitry of an adult cat with the spinal cord completely severed at a mid-thoracic level can learn a task that it is practiced (de Leon et al. 1998a, b) and that it can forget the task if it is not practiced (de Leon et al. 1998a). For example, when spinal cats are trained to step their stepping ability improves (de Leon et al. 1998b), whereas when they are trained to stand their standing ability improves (de Leon et al. 1998a). This specificity of training is further demonstrated by the finding that standing ability, but not necessarily stepping ability, is improved after stand training (de Leon et al. 1998a). In fact, in some instances spinal cats trained to stand will step more poorly than spinal cats that are not trained at all.

2.6 Sensory Input to the Spinal Cord Defines the Dynamics of the Physiological States in Controlling Movement After a SCI

The circuitries responsible for CPG receive and interpret sensory information in a highly dynamic manner. Whether a group of muscles is excited or inhibited by a given afferent input during locomotion depends on the phase of the step cycle. For example, a stimulus applied to the dorsum of a cat's paw (as in a stumbling response) will excite the flexor muscles of the ipsilateral limb when applied during the swing phase, whereas the same stimulus will excite the extensor muscles when

applied during the stance phase of the step cycle (Forssberg et al. 1975). These types of observations further support the concept that the spinal cord is smart: the spinal cord makes decisions based on the physiological state of the spinal networks as defined by the sensory inputs it receives. This enabling capability of the spinal interneurons caudal to a complete spinal cord transection to sequentially activate the specific groups of neurons necessary to sustain rhythmic stepping is manifested by modulating the net excitability of some combination of spinal locomotor networks yet to be defined. Thus, the CPG can coordinate motor pool activation based on the sensory input received and can process this information in real time so that effective sequences of motor commands are generated.

2.7 Fundamental Elements of Controlling Movement After a SCI

The basic biological principles for the generation of and improvement in movement triggered by activity-dependent mechanisms that are known to be important in the injured are qualitatively the same as those in the uninjured. For example, all elements in the control of performing a specific motor task can be reduced to two simple conceptual variables that the central nervous system must control. The first variable that must be controlled during the intended movement, and the one that is by far the best understood mechanistically, is the order of recruitment of motor units within each motor pool. This feature of the neural control of movement has evolved evolutionarily so that the order of recruitment is defined largely by what has become known as "the size principle" of motor unit recruitment (Henneman and Olson 1965; Henneman et al. 1965a, b). Briefly, this means that, for the most part, the motor units within a given motor pool, i.e., those motoneurons that project and activate a given muscle, are recruited in a highly predictable order.

The order of recruitment during any motor task is consistently and predictably related primarily to the force that can be generated by all of the muscle fibers innervated by its parent motoneuron. When the threshold current is sufficient to activate a motoneuron, it generates a series of action potentials at some variable frequency, i.e., an EMG burst, in all of the muscle fibers it innervates (referred to as a muscle unit). The main variables which define the force generated by the muscle fibers of a motor unit is determined primarily by the number of muscle fibers within the motor unit, secondarily by the frequency of excitation of those muscle fibers, and finally by the myosin phenotype of the muscle fibers. There are numerous other phenotypic characteristics of the motoneuron and muscle fibers that relate to size, but none of these match the predictability of the order of recruitment more precisely than simply the number of muscle fibers within a given motor unit (Bodine et al. 1987; Cope and Sokoloff 1999).

Obviously, however, the predictable order of recruitment is not likely to be assessed with respect to the neural networks recognition of the targeted number of

muscle fibers within each motor unit. So what factor(s) are used to make a "decision" as to which motoneuron will be recruited next? Firstly, it appears that the anatomical and physiological properties of the spinal neuronal networks as well as the motoneurons themselves are designed in such a way that the likelihood of each motoneuron reaching its motor threshold is a function of the total amount of the depolarizing current that reaches the motor pool. Multiple experiments performed by Henneman and colleagues (Henneman and Olson 1965; Henneman et al. 1965a, b) demonstrated that this order of recruitment is primarily a function of the amount of current reaching the motoneuron and the electrophysiological properties of the motoneuron, i.e., impedance that is a function of the volume of the motoneuron combined with the specific excitability of the cell membrane. In essence the order of recruitment is defined by Ohm's law combined with the evolved intrinsic design of the sensorimotor networks within the spinal cord.

The second physiological function that defines the specific motor tasks that will be generated is the relative current synaptically projecting to a given motor pool. The net excitability reaching each motor pool will determine the relative forces generated by that motor pool and the net vector of these forces from each motor pool define the kinematics of the movement. Unlike our understanding of the mechanisms of the size principle which clearly defines the order of recruitment within a motor pool, there is minimal understanding as to how the nervous system "decides" how much excitatory vs. inhibitory current will be projected to a given motor pool. This physiological phenomenon is even more intriguing when considering the extensive anatomical overlap of multiple motor pools within the ventral horn of the spinal cord.

2.8 SCI and Motor Unit Properties and Recruitment Order

Although the order of recruitment of motor units within a given muscle after an injury does not appear to be as precise and as predictable as before the injury, this physiological principle essentially remains intact. Factors that could partially disrupt this order may include selective changes in the electrophysiological properties of a given motoneuron. Such changes could be caused by anatomical or physiological disruption of the normally massive dendritic tree of each motoneuron and changes in ionic channel density and distribution, and membrane receptor systems that normally control the excitability of a given motoneuron. As noted above, however, in spite of these types of changes identified after a SCI, this important physiological principle is usually sufficiently robust to persist. Evidence that a relatively normal recruitment order remains even years after a SCI is provided by the generally gradual increase in amplitude followed by a gradual decrease in amplitude of the EMG signals recorded from a given muscle during a motor task. This is true in individuals with a severe incomplete or a complete SCI. Further evidence consistent with a significant order of recruitment being sustained after a SCI is based on the relatively normal metabolic quotient ($CO_2 \backslash O_2$) maintained

during movement, indicating a relatively normal level of dependence on free fatty acids as opposed to carbohydrates as the energy source for the muscle contractions (Herman et al. 2002). In contrast when the muscles of SCI subjects are stimulated directly, thus bypassing the intrinsic spinal networks that normally control motor unit recruitment, the subjects tend to fatigue very rapidly, in large part, because of the selective recruitment of those motor units with muscle fiber phenotypes (fast, fatigable) that are much more susceptible to high rates of fatigue.

2.8.1 Frequency of Motor Unit Firing

There are little data on how the frequency of firing of individual motor units is affected for any duration of time after a SCI. One exception is the recording of the frequency of firing of motor units after a cervical lateral hemisection in a nonhuman primate for durations as long as 24 weeks post-injury. These data (unpublished observation) show that after the initial 6–8 weeks of recovery from having little motor control while performing a simple upper limb motor task, a relatively normal firing frequency is present among the motor units. Furthermore these data show a significant, but relatively small, reduction in firing frequency over the duration of the 24-week period post-injury. The decline in the motor unit firing rates observed across animals were similar to those reported after a SCI in humans (Thomas et al. 2014; Zijdewind and Thomas 2003; Johanson et al. 2013; Yang et al. 1990).

2.8.2 Amplitude of Motor Unit Potentials

Changes in the amplitude of the motor unit potentials have also been studied over a 24-week period after a cervical hemisection in nonhuman primates. The results were mixed in that the amplitude increased over time in some units, but remained relatively constant or slightly declined in other units. These results (unpublished observation) were interpreted to reflect a change in the number, size, and density of muscle fibers of an individual motor unit and the proximity of its fibers to the implanted recording electrodes. The consistency in shape and amplitude of the action potentials recorded with chronically implanted electrodes was impressive, indicating no significant change in the relative territory and of the spatial position and distribution of the muscle fibers relative to the recording electrodes. This consistency provides some level of confidence that the action potential amplitudes were a reasonable estimate of the relative size, i.e., number and size of muscle fibers, of the motor unit. In addition, unless there was some direct disruption of the integrity of the motoneuron as a result of the SCI one would not necessarily expect any significant reorganization, i.e., change in the number of fibers due to post-injury partial denervation and/or hyperinnervation, of the muscle unit from which a given pair of electrodes embedded within the muscle is recording.

2.9 Spinal Learning of a Motor Skill After a SCI

While it is well known that one can improve the performance of a motor task by practicing, it is often thought that this motor learning is largely if not entirely attributed to networks within the cerebellum. It has been known for decades, however, that a simple motor task can be learned by networks within the spinal cord when there is no communication between the spinal networks and the supraspinal networks such as those located in the cerebellum. More specifically, an animal with a complete mid-thoracic spinal cord transection can learn to avoid a noxious stimulus by lifting the paw above a predetermined threshold to not elicit the stimuli (Jindrich et al. 2009). Results from several versions of these types of experiments indicate that the mechanism for this learned behavior at the spinal level is that the spinal networks share many of the factors identifying learning phenomena located within the networks in the hippocampus. It also is known that very complex motor tasks, such as stepping (at higher speeds) and standing (duration of standing), can be learned by spinal animals with repeated training over a period of days to weeks (Fig. 2.2). Other evidence of spinal learning is provided by the reduced variability in the trajectory of the step performance in spinal animals that have been trained to step compared to those not trained (Fig. 2.2c). Furthermore, it appears that one of the neural strategies that contributes to the spinal learning is that the neural networks involved become pruned to some degree so that fewer neurons within the spinal circuitry are activated as the spinal animal improves the ability to perform stepping (Fig. 2.2d). In spinal rats it is necessary to either neuromodulate the spinal circuitry with electrical stimulation or pharmacologically, but we know that the learning that occurs by applying either or both of these neuromodulation strategies depends on the engagement of the spinal circuitry for the task that is being learned. For example, if either neuromodulatory strategy is administered without step training, no learning occurs (Fig. 2.2e). These findings clearly illustrate the importance of training and rehabilitation after the loss of motor function due to some injury.

2.10 Assist-as-Needed Experiments Reflect Inherent Stochastic Variation in Spinal Networks

It is generally recognized that there can be advantages in using robotic devices to assist in the recovery of motor function after a SCI. There have been a number of efforts, however, in which training with a robot has resulted in little improvement beyond that occurring with training without the robot. In the development of these devices it has been demonstrated that the software strategies to control the robot in a manner that can facilitate learning within the neural networks impacted by an injury must consider the interface between the machine and the subject. The fundamental physiological principle in motor learning is that the neural motor networks function

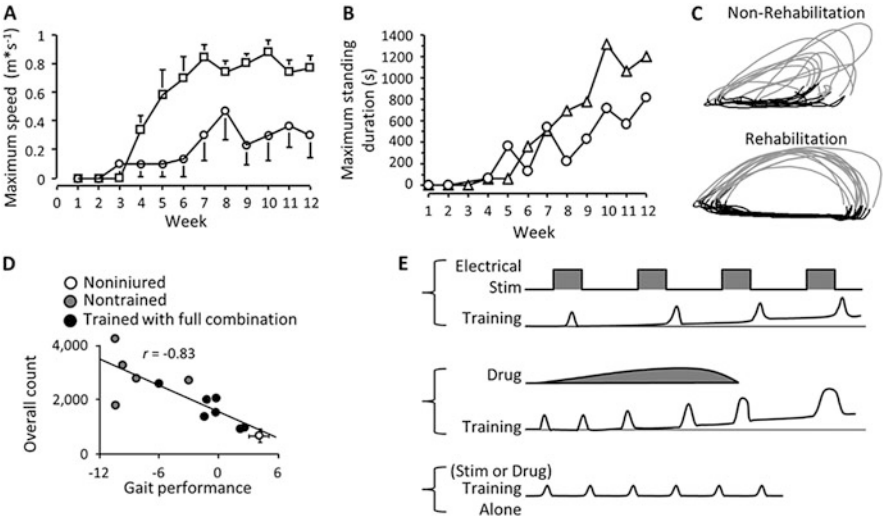

Fig. 2.2 (**a**) Adult spinal (mid-thoracic) cats that were trained to step (*squares*) compared to non-trained (*circles*) show the progression of the recovery of maximum stepping speed over a 12-week period [modified from (de Leon et al. 1998b)]. Values are mean (±SEM): trained significantly higher than non-trained at 6 weeks through 12 weeks. (**b**) Progression of duration of independent bilateral standing in two stand-trained adult cats over a 12-week period after a mid-thoracic spinal transection [modified from (de Leon et al. 1998a)]. (**c**) The trajectory of the paw for multiple consecutive steps of a non-trained spinal rat (*top traces*) compared to a bipedal step-trained spinal rat (*bottom traces*). (**d**) The number of c-fos positive neurons in the lumbosacral spinal cord of uninjured, non-trained spinal, and step-trained spinal rats demonstrating that fewer neurons are activated in the trained rats (modified from (Courtine et al. 2009) (**e**) A schematic illustrating the concept that there is an acute (a single intervention session) and cumulative chronic (repetitive interventions) effect of electrical stimulation or pharmacological modulation on the recovery of stepping in spinal rats when combined with motor training. When these two interventions are used repeatedly without step training, however, there are minimal cumulative effects

in a manner that requires a certain amount of variability in the specific networks that perform even highly repetitive movements. For example, spinal rats were trained to step using robotic arms attached to the ankles to control the trajectory of the ankle: training using a fixed trajectory that mimicked the kinematics of an average, normal step cycle was much less effective than when the robotic arms controlled the ankle in an assist-as-needed mode to allow for step-to-step variation in the kinematics as occurs normally (Fig. 2.3). The key point of these experiments is the following. Imagine that the step cycle is divided into very brief time bins and that the robot is programmed continuously to move from point A to point B within each time bin. Given that variations in stepping trajectories and EMG patterns occur naturally, there is a very high probability that the point that the robot was programmed to reach B within each time bin would differ from that of the spinal circuitry operating essentially on stochastic probabilities. Therefore within each time bin the robot would be correcting the output of the spinal circuitry in the fixed trajectory mode, whereas this would occur less often in the assist-as-needed mode. The result is a

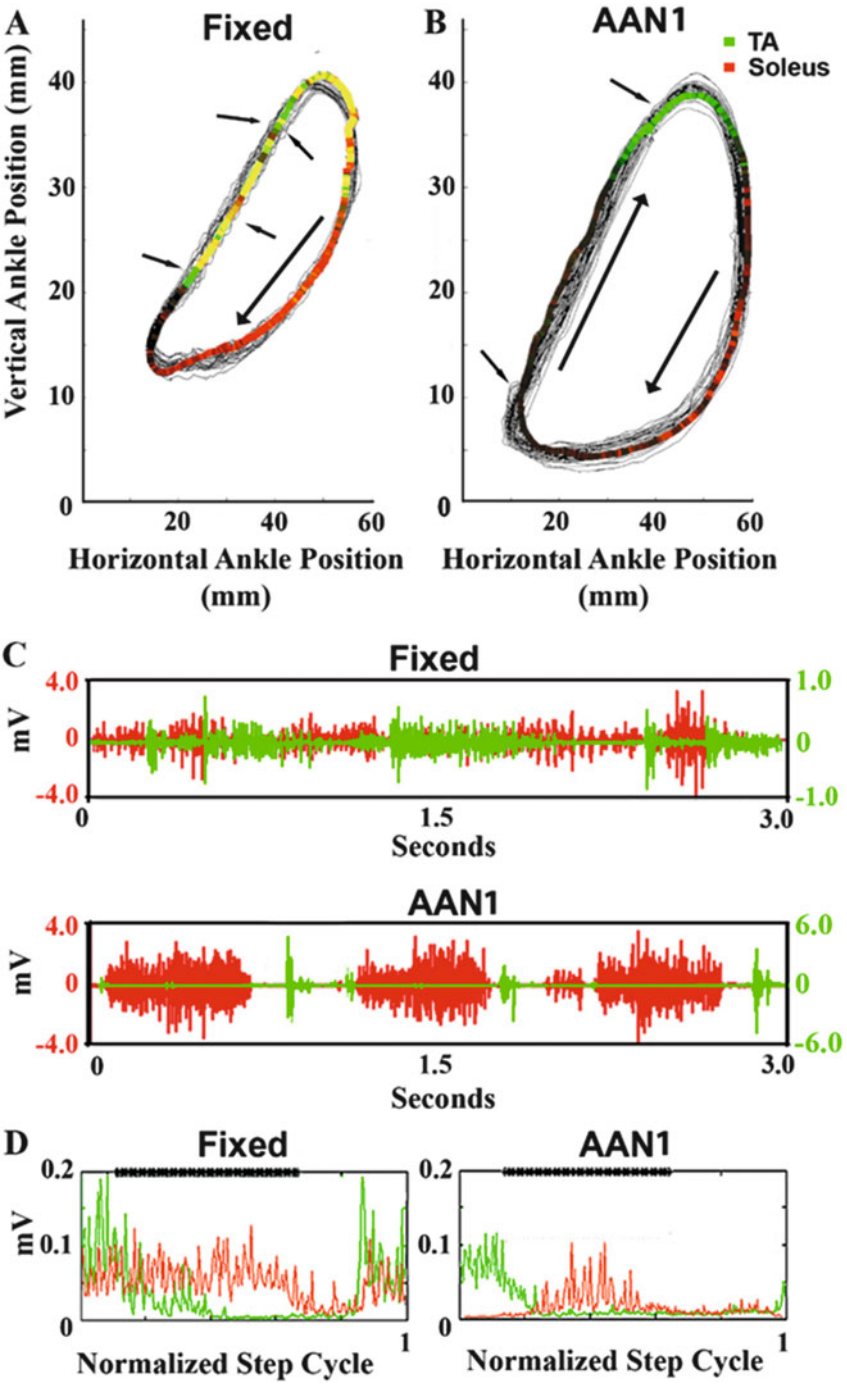

Fig. 2.3 Spinal rats were trained using two strategies to control the trajectory of the paw while being trained. One strategy was to impose a fixed trajectory (**a**) and a second strategy was to control the trajectory in an assist-as-needed (AAN1) strategy. A comparison of the ankle

highly abnormal EMG pattern for an ankle flexor (tibialis anterior) and extensor (soleus) marked by constant co-contractions with the fixed trajectory mode. The marked differences in the incidence of co-contraction between the two modes are obvious. Interestingly these experiments demonstrate that the spinal circuitry must function as a planned (feed-forward) system since feedback is too slow for real time. From this perspective our stepping movements are controlled via feed-forward mechanisms. The activity patterns (EMG recordings) of several hindlimb muscles were consistent with the kinematics data, suggesting that the activity-dependent responses also were consistent with a learning phenomenon at the spinal cord level (de Leon et al. 2002). In effect, these data are consistent with feed-forward mechanisms adjusting the step and muscle activity patterns during the swing phase of the step cycle. Similar results have been observed when applying a downward force during the stance phase of the step cycle in adult spinal rats (Timoszyk et al. 2002).

2.11 Conceptualizing Neuromodulation as a Network Phenomenon

The neural control of movements in vivo appears to be mediated at a systems-level network given the manner in which we can tailor the details of a motor task via epidural and transcutaneous stimulation and with pharmacological agents (Courtine et al. 2009). We can bias a physiological or anatomical segment of a network toward greater or lesser excitability by selecting different combinations of electrodes to stimulate within an array (spatial selection), varying the frequency, intensity, and patterns of the waveforms of the stimulation pulses, and selectively modulating specific combinations of interneurons with agonists and antagonists of different receptors using a multitude of pharmacological cocktails. Although these approaches can yield significant and highly predictable motor outcomes by selectively facilitating different components of the spinal networks, we know little about the neural "pathways" within these continuously changing networks. A common assumption is that the effects of epidural stimulation at the dorsum of the spinal cord are primarily due to the activation of primary afferents and other sensory axons that activate motoneurons monosynaptically or polysynaptically. This can be true

Fig. 2.3 (continued) trajectories recorded over 30 s of stepping. The *arrows* in (**a**) and (**b**) show the direction of the movement of the ankle. The *colored areas* represent the average EMG activity recorded from the soleus and tibialis anterior (TA): *red*, soleus activity; *green*, TA activity; and *yellow*, soleus and TA co-activation. (**c**) shows the raw EMG activity of the soleus and TA during 3.0 s of movement for each paradigm (*top*, Fixed; *bottom*, AAN1). (**d**) shows the averaged integrated EMG for the soleus (*red*) and TA (*green*) from over 30 continuous seconds of stepping for each paradigm (*left*, Fixed; *right*, AAN1). The *asterisks* section in (**d**) represents the stance phase of the step cycle (from Ziegler et al. 2010)

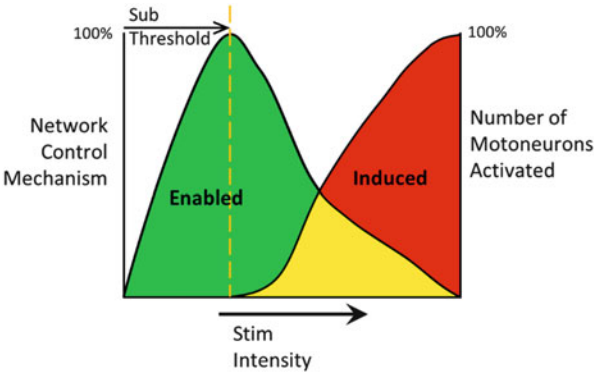

Fig. 2.4 This illustration depicts the changes of the source of control of recruitment of motoneurons among motor pools as a function of stimulation intensity when stimulating epidurally on the dorsum of the spinal cord. At the lower intensities there can be increased control manifested in large part by the interneuronal networks associate with a given motor task (*green*). At the appropriate level of neuromodulation the motor task can be performed as the result of input from proprioception, e.g., as in stepping, and/or from descending sources of activation. With either proprioception or descending input the detailed elements of the fine coordination of motor pools is executed by the interneurons projecting directly or indirectly to the motoneurons within and among motor pools (Gad et al. 2013b). As the intensity of stimulation increases there is a greater probability of direct activation of the motoneurons and therefore bypassing the control that can be exerted by the interneuronal networks (*red*). The intensity of the stimulation for example can increase to the point where all of the motoneurons within a motor pool are activated directly and completely bypass the control that is intrinsic to the pre-motor spinal circuitry. The objective is to modulate the intensity of the stimulation to maximize the control potential within this circuitry and minimize direct activation of the motor pools. This is the fundamental principle of neuromodulation of spinal circuits that 'enable' a motor task to be performed rather than being 'induced' by direct stimulation

with relatively high stimulation intensities, but we propose that this is not the primary means of neuromodulation at lower intensities. For example, the effectiveness of this stimulation strategy is highlighted by the fact that a stimulation strength of 20% less than motor threshold can produce a fivefold increase in the spontaneous motor activity of spinal rats while in their home cage in the near absence of any direct activation of motor units in any muscle (Gad et al. 2013a). The significance of our largely sub-threshold neuromodulatory techniques functioning via those interneurons projecting to the motor pools that generate postural and locomotor movements is that we can take advantage of the highly sophisticated spinal circuitry controlling these motor tasks with remarkable effectiveness in the absence of any input from the brain (Fig. 2.4). With increasing stimulation levels the controlling potential of the interneuronal networks are minimized, resulting in direct activation of motoneurons with each stimulus pulse. In this case, the control system intrinsic to the needed automaticity is bypassed.

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Chapter 3
Role of Activity in Defining Metabolic and Contractile Adaptations After SCI

Gaelle Deley

Abstract Spinal cord injury (SCI) can lead to moderate to severe muscle paralysis, loss of lower-limb functionality and often results in a reduced physical activity. As a consequence, people with SCI demonstrate numerous metabolic and contractile transformations such as leg muscles atrophy, a transformation from slow, fatigue-resistant fibers to fast, fatigable fibers, a decreased vascularization. Appropriate exercise and most especially exercise using functional electrical stimulation (FES) is now well-known to have beneficial effects on muscle characteristics, force output, exercise capacity, but also bone mineral density and cardiovascular parameters. For example, increases in muscle mass and strength, oxidative capacity and vascularization have been reported after several weeks of FES exercise (FES-strengthening, FES-cycling or FES-rowing) in people with SCI.

Spinal cord injury (SCI) induces substantial changes in paralyzed muscles. Although variable, most muscles below the neurologic level of injury rapidly become atrophied and convert toward predominantly fast type IIx fibers due to the removal of chronic efferent neural activity. As a result, muscles become weak, highly fatigable, and have a fast contractile speed. With that said, significant evidence now exists to support the beneficial effects of physical activity, and more precisely electrically induced activity on the paralyzed muscles for people with SCI. The aim of this chapter is to examine the role of activity in defining metabolic and contractile adaptations after SCI. We will first present the main

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metabolic and contractile alterations observed after SCI and then describe the impact of physical activity (i.e., electrically induced activity) on these alterations. More precisely, we will focus on muscle atrophy, changes in myotypology, muscle metabolism, vascularization and contractile properties.

3.1 Metabolic and Contractile Alterations After SCI

Figure 3.1 presents the main alteration observed after spinal cord injury, with a particular focus on muscle changes.

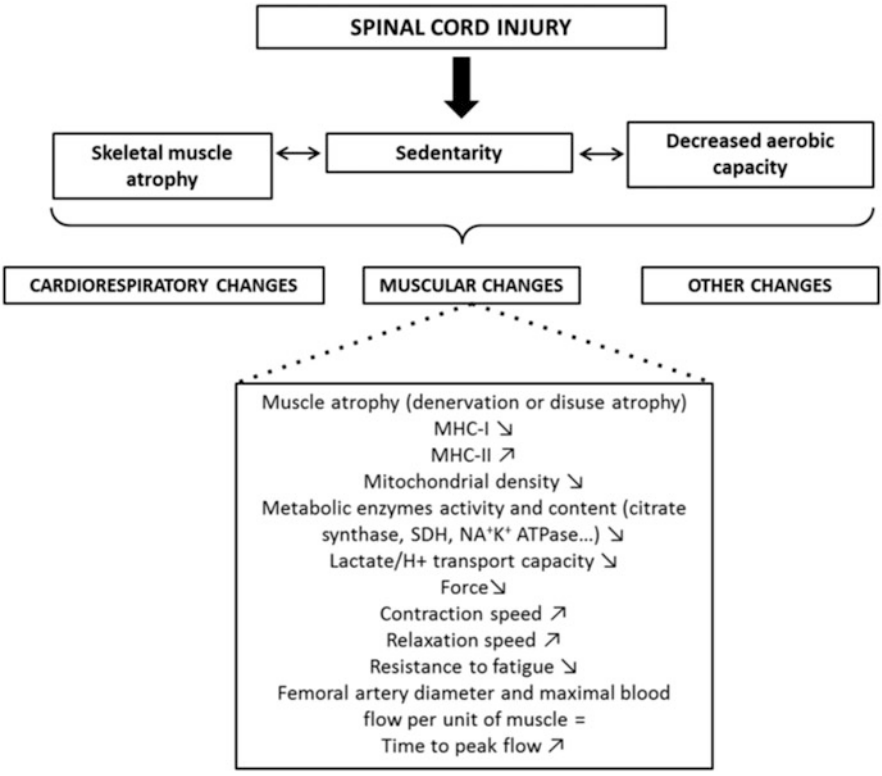

Fig. 3.1 Main alterations observed in people with spinal cord injury. *MHC* myosin heavy chain, *ATP* Adenosine Tri-Phosphate, *SDH* Succinate DeHydrogenase, *right up arrow* increases with spinal cord injury, *right down arrow* decreases with spinal cord injury. Adapted from Deley et al. (2015)

3.1.1 Muscle Atrophy

Significant muscle fiber atrophy, a reduction in the size and/or number of muscle fibers, occurs after SCI. For example, mean area of the Vastus Lateralis muscles of $3.535 \pm 1.795\ \mu m^2$ have been reported in people with complete SCI whereas values averaged $5.392 \pm 1.327\ \mu m^2$ in able-bodied control subjects (Ditor et al. 2004). This atrophy occurs rapidly with significant changes in cross-sectional area and muscle volume within 6 weeks of injury (Gorgey and Dudley 2007). Atrophy occurs in type II fibers before type I fibers (Lotta et al. 1991). Muscle atrophy may be secondary to denervation atrophy or disuse atrophy. Denervation atrophy after SCI results from injury to motoneurons in the spinal cord or to the motor nerves in the ventral roots through which they exit (Gordon and Mao 1994). Disuse atrophy occurs as a result of loss of muscle activation due to disruption to the central and segmental synaptic drive to intact spinal motoneurons (Peckham et al. 1976; Gordon and Pattullo 1993). Muscles are usually referred to as paralyzed in both cases.

Denervation Atrophy Muscles that lose all of their innervation undergo drastic and rapid wasting. Generally, the proportion of muscles that suffer complete denervation after SCI is small (Peckham et al. 1976). However, many muscle fibers sustain partial denervation as a result of the damage to motoneurons in an affected spinal cord segment. For example, in patients with C5 complete tetraplegia, the paralyzed thenar muscles lose as much as 50 %–90 % of their normal complement of motor innervation. Prevention or reversal of denervation atrophy in these cases will depend on the capacity of the nerves of surviving motoneurons nerves to grow and reinnervate as many denervated muscle fibers as possible. As it will be detailed in the second part of this chapter, muscle fibers may survive and contract in response to electrical stimulation to develop enough force to perform functional movements.

Disuse Atrophy Muscle wasting after spinal cord injury is generally attributed to the muscle inactivity induced by the loss of the synaptic inputs from spinal cord segments to spinal motoneurons. However, several studies suggest that much of the disuse atrophy of the paralyzed muscles occurs secondary to changes in muscle length or loading conditions, rather than to the decline in neuromuscular activity (Gordon and Pattullo 1993; Roy et al. 1991). The magnitude of disuse atrophy is variable after spinal cord lesions but does not necessarily correlate with the decline in neuromuscular activity (Gordon and Pattullo 1993). Although neural activity is generally reduced after spinal cord lesions it can also vary considerably depending on the type of lesion and the level of spasticity (Gordon and Pattullo 1993; Roy et al. 1991; Alaimo et al. 1984).

Disuse atrophy is more pronounced in muscles that normally bear weight, especially those crossing single joints since they contain a large proportion of slow fatigue-resistant muscle fibers, which are largely responsible for maintaining posture (Gordon and Pattullo 1993). For example, in patients with C5 complete

tetraplegia, the paralyzed tibialis anterior muscles develop isometric forces very similar to those in nondisabled individuals whereas the quadriceps femoris muscle, which normally lifts the lower limb by extending the knee, shows significant atrophy after SCI (Peckham et al. 1976). A similar atrophy occurs after space flight, hind-limb suspension, and limb immobilization, wherein muscles undergo shortening contractions that are not resisted by a normal 1oad (Gordon and Pattullo 1993). These findings also suggest that changes in loading or length of paralyzed muscles after spinal cord lesions are responsible, at least in part, for the atrophy that occurs.

3.1.2 Myotypology

In addition to muscle atrophy, people with SCI also demonstrate a fiber-type transformation with a shift toward a homogeneous muscle composed of predominantly type II fibers (Dudley-Javoroski and Shields 2008). According to most studies, in the quadriceps muscle, the fiber-type transformation, with down-regulation of type I fibers and upregulation of type IIA and IIx fibers, begins between 4 and 7 months post SCI (Biering-Sorensen et al. 2009). Similar results were found for the soleus and gastrocnemius muscles. It has also been suggested that early post SCI (<1 month) myosin heavy chain (MCH) isoform composition remains relatively stable (Burnham et al. 1997). A transitional period is seen between 1 and 20 months post SCI with a progressive drop in the proportion of slow MHC isoform fibers and a rise in the proportion that co-express both the fast and slow MHC isoform. By approximately 70 months post SCI, a new steady state has been reached characterized by almost exclusively fast MHC isoform expression.

However, some studies have reported that type I fiber decrease is not always correlated with the length of time post-injury. For example, Ditor et al. (2004) found that the vastus lateralis muscles of those with SCI had a higher proportion of their area represented by type I fibers compared with values in the literature for healthy able-bodied (52.6 $\pm$ 25.3 % vs. 36 $\pm$ 11.3 %, respectively) (Gorgey and Dudley 2007). These authors suggested that muscle spasticity as a result of upper motor neuron injuries explain these results. Thus, although it is clear that SCI induces a fiber-type transformation toward type II fibers, it also appears that there might be important, unexplained interindividual differences.

3.1.3 Muscle Metabolism

As mentioned above, there appears to be a general reduction in absolute activity of metabolic enzymes after SCI, with a shift in the metabolic profile of muscle fibers toward the fast glycolytic type. Oxidative enzymatic activity starts to decline a few months post-SCI and may reflect the transformation from slow to faster muscle

fibers. For example, low values of citrate synthase activity and mitochondrial DNA in the vastus lateralis of individuals with paraplegia have been reported as compared to controls (Wang et al. 1999). In addition, these authors found that the significant relationships between citrate synthase activity, mitochondrial DNA content and aerobic exercise capacity were sustained in individuals with paraplegia with no intrinsic muscle disease. More recently, magnetic resonance spectroscopy (^{31}P-MRS) has reported ~50 % reduction in the rate of phosphocreatine recovery after exercise in skeletal muscle of persons with SCI (McCully et al. 2011).

Gerrits et al. (2003) reported a 67 % decrease in succinate deshydrogenase (SDH) activity in type II fibers and a 48 % decrease in type I fibers in the tibialis anterior muscle in those >2 years post injury (Gerrits et al. 2003). In addition, Castro et al. (1999) suggested that there is a relative independence of metabolic enzyme levels and inactivation within the first months after SCI; long-term but not short-term inactivation (and the consequent unloading of human skeletal muscle) reduces aerobic-oxidative enzyme levels (Castro et al. 1999). Na^+, K^+-ATPase concentration has also been demonstrated to be decreased in the paralyzed vastus lateralis as compared with control subjects (141.6 ± 50.0 vs. 339 ± 16 μmol/g wet weight) and a significant negative correlation to years since injury (Ditor et al. 2004). Sarcolemmal lactate/H^+ transport capacity is also lower in SCI individuals than in normally physically active subjects suggesting that prolonged muscle inactivity reduces the lactate/H^+ transport capacity of human muscle (Pilegaard et al. 1998).

Proteins associated with the Ca^{2+}-ATPase of the sarcoplasmic reticulum, responsible for re-sequestering Ca^{2+} into the sarcoplasmic reticulum from the myoplasm, also undergo transitions following SCI (Scott et al. 2006). Talmadge et al. (2002) demonstrated that the fast isoform of sarcoplasmic reticulum Ca^{2+}-ATPase is upregulated soon after SCI in paralyzed human muscle and that the proportion of fibers with the slow isoform of sarcoplasmic reticulum Ca^{2+}-ATPase alone was decreased by 30 % at 6 weeks and 65 % at 24 weeks (Talmadge et al. 2002). At the same time, the hybrid sarcoplasmic reticulum Ca^{2+}-ATPase fibers, containing both slow and fast sarcoplasmic reticulum Ca^{2+}-ATPase, was increased nearly fivefold by 24 weeks. However, no significant difference was found in the proportion of fibers containing only MHC I between SCI and control individuals at either time-point (6 weeks and 24 weeks).

3.1.4 Muscle Contractile Properties

It is well known that the ability of muscles to produce and sustain force depends on their fiber type composition and metabolic profile (as well as the general nutritional and cardiovascular state of the organism). These fibers vary in their oxidative and glycolytic enzyme profiles and their corresponding susceptibility to fatigue (Enoka 1988). Thus, it can be easily understood that the histochemical changes associated with changes in contractile properties prevent paralyzed muscles from performing repeated, high-intensity contractions (Dudley-Javoroski and Shields 2008).

For example, Scott et al. (2006) found that the paralyzed muscles of subjects with SCI contract faster (+14 %), relax faster (+38 %), are weaker (−62 % of peak twitch force) and less resistant to fatigue (fatigue ratio −35 %) than non-paralyzed individuals (Scott et al. 2006). These authors also reported that compared to control subjects, those with SCI had twitch-to-tetanus ratios that were 84 % and 127 % greater in nonfatigued and fatigued conditions, respectively. They suggested that possible explanations for the increased twitch-to-tetanus ratio of paralyzed muscle are shifts in fiber type toward the fast-twitch phenotype, changes in muscle stiffness, and changes in muscle length.

Several studies have shown markers of oxidative capacity to be correlated with increased muscle fatigue in those with SCI (Gerrits et al. 2003; Rochester et al. 1995a). As mentioned above, other possibilities include the fiber-type transformation with a shift to predominantly type II fatigable fibers (Gerrits et al. 2003; Talmadge et al. 2002; Rochester et al. 1995a) and ensuing impairments in Ca^{2+} handling (Castro et al. 2000). However, characteristics of muscle fatigue in people with SCI seem to vary with fatiguing protocols, stimulation intensity, and the muscle being investigated. For example, during 2 min of intermittent tetanic stimulation, a decrease in muscle excitability does not appear to be a significant contributing factor to the greater fatigue after SCI and the mechanisms more likely relate to changes in excitation–contraction coupling and/or muscle oxidative capacity. Another factor inducing rapid fatigue in paralyzed muscles may be impaired muscle blood flow, which would limit oxygen and energy supply to the exercising muscle and allow accumulation of potassium and metabolic products such as lactate and inorganic phosphate.

Gerrits et al. (2000) showed that fatigue resistance was negatively correlated with time since injury. The lesser fatigue resistance at some point stabilizes, and subsequently muscle will show properties characteristic of fast fatigable muscles. At the same time, speed-related contractile properties change toward faster contractile properties in muscles. More precisely, fatigue resistance has been shown to decrease rapidly for the first 1.7 years post-injury, with smaller decreases occurring in subsequent years (Shields and Dudley-Javoroski 2006). As many rehabilitation strategies (for example, functional electrical stimulation) are dependent on the muscle being able to perform repeated contractions, a greater understanding of the processes of muscle fatigue in paralyzed muscles might allow an optimization of rehabilitation efforts.

3.1.5 Vascularization

Olive et al. (2003) found that femoral artery diameter (0.48 ± 0.06 vs 0.76 ± 0.14, SCI vs. able-bodied) and femoral artery maximal blood flow (1220 ± 240 vs 2050 ± 520 mL min^{-1}) were lower individuals with SCI than in able-bodied individuals (Olive et al. 2003). However, these reductions are only evident for absolute values since femoral artery diameter and maximal blood flow per unit muscle volume did not differ between individuals with SCI and able-bodied

individuals. These authors also found a fivefold greater half-time to peak blood flow at the beginning of exercise and a threefold greater recovery of blood flow at the end of exercise in individuals with SCI vs. able-bodied. However, they concluded that increased muscle fatigue in those with SCI was not associated with the magnitude of the muscle blood flow response to electrical stimulation. The prolonged time to peak blood flow may contribute.

3.2 Effects of Activity on Muscle Adaptations After SCI

Exercise recommendations for individuals with SCI include the use of Functional Electrical Stimulation (FES) to facilitate exercise and allow the achievement of greater exercise intensities (Jacobs and Nash 2004). Indeed, FES artificially activates paralyzed muscles and it may offset the rapid process of skeletal muscle atrophy, regional adiposity and impaired metabolic profile. Recent research has noted the utility loading the paralyzed skeletal muscles to improve musculoskeletal, metabolic and cardiovascular health in persons with SCI (Gorgey et al. 2012). Figure 3.2 presents the main adaptations to exercise in people with SCI with FES exercise.

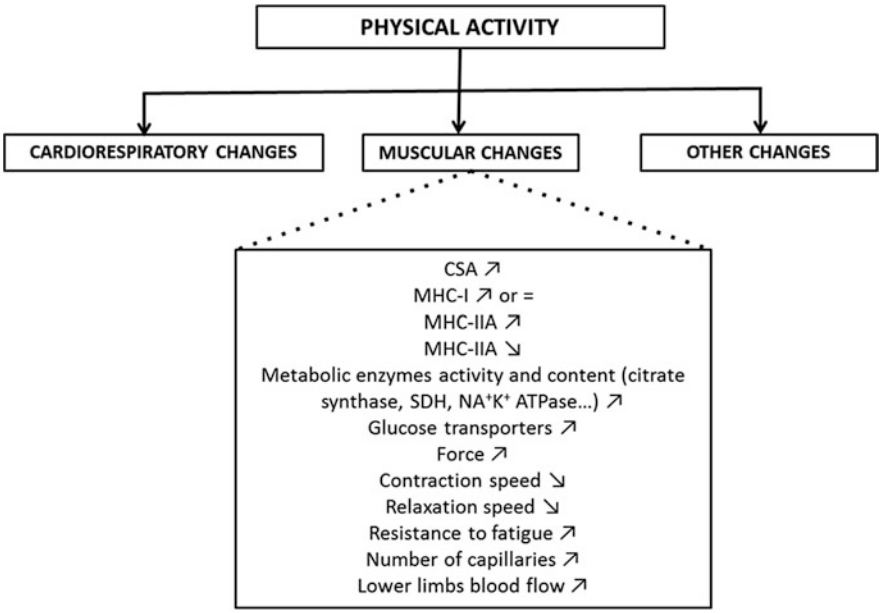

Fig. 3.2 Main effects of physical activity in people with spinal cord injury. *MHC* myosin heavy chain, *ATP* Adenosine Tri-Phosphate, *SDH* Succinate DeHydrogenase, *right up arrow* increases after training, *right down arrow* decreases after training, "*equal to*" unchanged after training. Adapted from Deley et al. (2015)

3.2.1 Electrical Stimulation (ES)

Generally speaking, ES involves application of a series of intermittent stimuli to skeletal muscles, with the main objective to trigger visible muscle contractions by activating the intramuscular nerve branches (Hultman and Sjöholm 1983). Functional electrical stimulation (FES) applies this electric current to activate the damaged or disabled neuromuscular system in a coordinated manner to generate a functionally useful movement such as leg flexion/extension for cycling or rowing (Liberson et al. 1961). It serves to generate a train of impulses that grossly imitates the neural triggers that would have normally passed through the spinal cord to the appropriate peripheral nerves below spinal cord lesion. These stimuli thus initiate action potentials in the peripheral nerves, which in turn activate muscle contractions in the associated muscles fibres (Rattay et al. 2003). Pulses, delivered via adhesive electrodes positioned on selected muscles, are defined by several characteristics such as pulse width, duration, frequency, waveform and duty cycle (the total time to complete one on/off cycle). These characteristics directly influence torque production but also the rate of muscle fatigue. Indeed, muscle fatigue may be an important factor for FES programs, limiting practical utilization (Isakov et al. 1986). The ideal stimulation pattern for activation during FES, according to the purpose (strengthening, cycling or rowing), would therefore be one that produces sufficiently high forces while minimizing fatigue [for review see Deley et al. (2015)].

3.2.2 Effects on Muscle Atrophy

Several studies have found that ES and FES exercise may reverse or limit muscle atrophy, and muscle fibers may shift their morphological characteristics more toward that similar to sedentary, able-bodied individuals. For example, Dudley et al. (1999) found that a program of electrically-induced knee extensions, performed twice weekly over an 8-week period is effective to reverse muscular atrophy of the quadriceps muscles (Dudley et al. 1999). Further, Baldi et al. (1998) found that FES cycling was more effective than unloaded ES-induced isometric contractions in preventing muscle atrophy in those with SCI less than 3 months post injury (Baldi et al. 1998). In addition, several studies have shown that FES-cycling training leads to a hypertrophy of the thigh and calf muscles (Chilibeck et al. 1999; Kjaer et al. 2001). It has also been reported that the mean cross sectional area (CSA) of muscle fibers is higher in those trained with FES-cycling or FES-rowing as compared with untrained able-bodied individuals and is similar to trained able-bodied individuals after 8 weeks of cycle training (Andersen and Henriksson 1977).

Studies have evaluated the effects of FES-cycling training on changes in spastic muscle tone with equivocal results. One study found that FES-cycling training effectively reduces spasticity (Krause et al. 2008) whereas another study reported

lesser duration and frequency of spasticity, but greater spasticity intensity (Arnold et al. 1992). This could result from greater muscle strength after FES-cycling training.

Lastly, in denervated and degenerated muscle biopsies, more than 50 % of myofibers have a diameter smaller than 10 μm, whereas FES-trained subjects demonstrate more than 50 % of myofibers with a diameter larger than 30 μm. This seems to result from both an increase in size of the surviving fibers and a regeneration of new myofibers (Kern et al. 2004). In addition, myofibrils that were completely disarranged without training appear structurally normal after training. The excitation-contraction coupling apparatus is reorganized and its association with the myofibrils appears to be normal. This coordinated reorganization may provide the structural basis for the improved capacity of FES-trained muscle to respond to electrical impulses. Figure 3.3 presents the effects of 10 weeks of FES-cycling on both the overall CSA and the fiber distributions in people with SCI.

3.2.3 Effects on Myotypology

FES training appears to modify the histochemical properties of the muscle through conversion of type IIb fibers to type IIa (Mohr et al. 1997). Several studies reported that FES-cycling training converted the skeletal muscle fiber-type toward more oxidative muscle fibers (Andersen et al. 1996; Rochester et al. 1995b), with

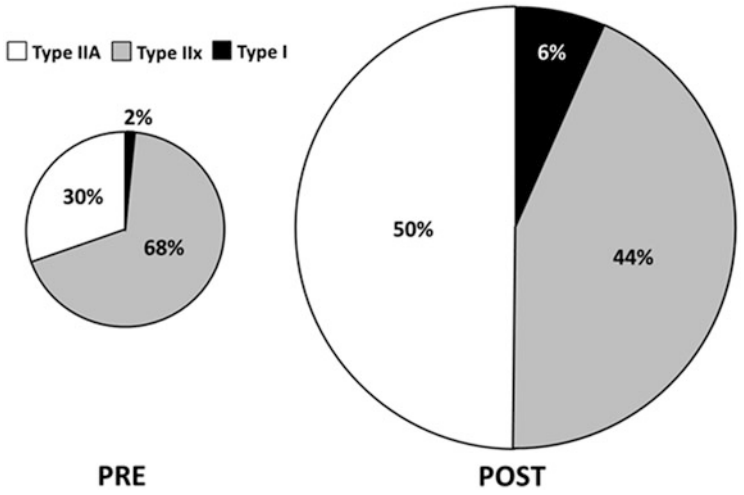

Fig 3.3 Effect of 10 weeks of FES-cycling in people with Spinal Cord Injury. The diameter of the circles is representative of the overall cross sectional area (Vastus Lateralis muscle) before (PRE) and after (POST) training (+129 %). The repartition of fiber types is also presented before and after training. Adapted from Crameri et al. (2002)

concomitant increases in concentration of oxidative enzymes and mitochondria in the paralyzed muscle groups. Moreover, Crameri et al. (2002) found an overall 129 % increase in cross-sectional area of all muscle fibers with a threefold increase in type IIx fibers and a 36 % increase in type IIa fibers after 10 weeks of FES-cycling (Crameri et al. 2002). However, MHC IIx significantly decreased (from 67.9 % to 44.1 %) over the 10 weeks, while a corresponding significant increase (from 30.4 % to 49.6 %) in MHC IIa was detected. In addition, Andersen et al. (1996) reported that 12 months of FES-cycling training induced a marked switch in MHC expression from about equal amounts of MHC IIa and MHC IIb to an almost dominance of MHC IIa: after 12 months almost all fibers (91.2 %, $P < 0.05$) contained only MHC IIa. The number of fibers containing only MHC IIb was 2.3 % and the fibers co-expressing MHC IIa and IIb had decreased to 4.6 %. The amount of fibers containing only MHC I never exceeded 0.5 %. On the other hand, Harridge et al. (2002) found that 4–9 weeks of chronic stimulation (2–6 h per day) does not evoke any significant change in relative MHC content, but found evidence of upregulation of the mRNA for the MHC I isoform and downregulation of the MHC IIx isoform (Harridge et al. 2002). Hence, a longer-duration training program may be necessary to cause changes at the protein level.

3.2.4 Effects on Metabolism

Several experiments have found important effects of ES training on muscle metabolism in those with SCI. For example, Gerrits et al. (2003) reported that 12 weeks of daily electrical stimulation training resulted in a significant increase of 76 $\pm$ 26 % ($P < 0.05$) in total SDH activity in the trained vastus lateralis muscle suggesting increased oxidative capacity (Gerrits et al. 2003). Moreover, Crameri et al. (2002) found increased hexokinase (+100 %) and citrate synthase activity (+132 %) after 10 weeks of FES-cycling (Crameri et al. 2002), and Chilibeck et al. (1999) reported increased glucose transporter (GLUT-1 and GLUT-4) protein levels in paralyzed skeletal muscles of individuals with SCI after 8 weeks of FES-cycling (Chilibeck et al. 1999). Hence, it is not surprising that 12 months of FES-cycling three times a week induced increases in glycolytic enzymes (hexokinase (HK): +150 %, lactate dehydrogenase (LDH): +40 %, citrate synthase (CS): +100 % and 3-hydroxyacyl-CoA dehydrogenase (HAD): +70 %) activities (Kjaer et al. 2001). After reducing the amount of training to once per week, HK, LDH and CS activities remained elevated above basal levels, whereas HAD returned to pretraining levels. Hence, most improvements in glycolytic and mitochondrial oxidative enzyme activity induced by long-term training can be maintained in SCI individuals even with a marked reduction in training frequency.

3.2.5 *Effects on Contractile Properties*

Muscle strength increases after FES-strengthening protocols (Dudley et al. 1999). Increases in the maximal workload or total power output at the end of exercise tests, as well as decreases in muscle fatigue have also been reported (Shields and Dudley-Javoroski 2006; Dudley et al. 1999; Ingjer 1979). For example, Shields and Dudley-Javoroski (2006) reported greater torque, torque-time integral and fatigue-index of up to 50 % in trained versus untrained limbs (2 years on plantar flexors muscles) (Shields and Dudley-Javoroski 2006). Moreover, Wheeler et al. (2002) found a 25 % enhancement in the distance rowed during an incremental test after 12 weeks of FES-rowing (Wheeler et al. 2002) and Crameri et al. (2002) found that the total work performed during the ergometer testing increased from 51.8 ± 39.3 to 112.9 ± 33.5 kJ after FES-cycling training (Crameri et al. 2002). Contractile properties also increase towards values for able-bodied. Muscles contract slower as shown by a 45 % increase in torque rise time after 2 years of ES training (Shields and Dudley-Javoroski 2006). It has also been suggested that half-relaxation time return to able-bodied values after 4 weeks of ES training (Rochester et al. 1995a).

3.2.6 *Effects on Vascularization*

Crameri et al. (2002) reported an increase in capillarization after after 10 weeks of FES-cycling. Moreover, the capillary/fiber ratio in those with SCI trained with FES-cycling or FES-rowing is only than in trained able-bodied individuals (Ingjer 1979). Interestingly, FES-rowing may result in a ratio higher than both the trained SCI cyclists and able-bodied subjects. These changes in capillarity are reflected in blood flow. Taylor et al. (1993) found that training with the Odstock functional electrical standing system during 3 months produced an average increase of 115 % in thigh blood flow so that these values were similar to those of the control group (Taylor et al. 1993). This increased leg blood flow in SCI may also be due, in part to an endothelin-1 pathway (Thijssen et al. 2007). The same authors also demonstrated that 4 weeks of arm combined with ES-induced leg exercise leads to vascular adaptations in the exercised tissues (thigh) but not in non-stimulated passive tissue (calf) (Thijssen et al. 2005). Similarly, Gerrits et al. (2001) reported a 29 % increase in resting femoral artery blood flow after 4 weeks of FES-cycling (Gerrits et al. 2001). These improvements seem to be directly related to the training program being performed. Indeed, Sabatier et al. (2006), who did not find any modification in femoral arterial diameter and in blood flow after 18 weeks of low volume resistance training, concluded that the volume of training was probably insufficient to evoke any changes (Sabatier et al. 2006).

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Chapter 4
Respiratory System Responses to Exercise in Spinal Cord Injury

Christopher R. West, Andrew W. Sheel, and Lee M. Romer

Abstract In the previous half-century, outcomes for people with spinal cord injury (SCI) have dramatically improved. Nevertheless, respiratory complications are still frequently observed, especially in those with cervical SCI. In this chapter, we synthesize current knowledge regarding the changes in pulmonary and respiratory muscle function that occur after SCI, and emphasise the respiratory responses to exercise. We do not provide extensive background on respiratory function in the acute period post-SCI or discuss clinical pulmonary complications such as cough and sleep disordered breathing. Data are presented for both trained and untrained individuals with SCI and, when available, by level of injury. However, since the majority of respiratory complications are present only in those with cervical and high-thoracic SCI, most studies are delimited to these levels of injury. Finally, despite the well-appreciated sex-based differences in respiratory function that exist in able-bodied individuals, no studies have stratified respiratory outcomes by sex; this is likely due to the fivefold higher incidence of SCI in men vs. women. Thus, the focus of this chapter is on the respiratory responses to SCI at rest and during exercise in men with high-level SCI.

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4.1 Respiratory Function at Rest

The most common measures of respiratory function are those derived from spirometry and manometry. It is well established in the SCI population that there is an injury-level dependent impairment in respiratory function, whereby those with the most rostral injuries exhibit the most severe reductions in function, including vital capacity (VC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), maximum static inspiratory pressure ($P_{I,max}$) and maximum static expiratory pressure ($P_{E,max}$) (Baydur et al. 2001; Estenne et al. 1998; Fujiwara et al. 1999; Lin et al. 2006; Mueller et al. 2008a). Thus, it is generally accepted that individuals with cervical or high-thoracic SCI exhibit pulmonary restriction (Anke et al. 1993; Schilero et al. 2009) that is compounded by reduced lung and chest wall compliance (Goldman et al. 1988; Estenne and De Troyer 1986), paradoxical inward movement of the anterior rib cage during inspiration (Urmey et al. 1986; De Troyer et al. 1986a), and chest wall distortion (Mortola and Sant'Ambrogio 1978; Fugl-Meyer and Grimby 1971a).

Individuals with cervical or high-thoracic SCI exhibit a VC and FEV_1 below the lower limit of normal, and it is not until the injury is caudal to the T8 spinal level that these parameters fall within predicted limits (Linn et al. 2001; Baydur et al. 2001). The level-dependence of pulmonary function after SCI is due largely to the motor innervation of the respiratory muscles. The motor nerves of the diaphragm and scalenes (primary muscles of inspiration) exit the spinal cord between C3-C5 and C3-C7, respectively, whereas the motor nerves of the major muscles of expiration (abdominal muscles and internal intercostals) are distributed throughout the T7-L1 region (Fig. 4.1). Hence, injury below T7 will permit some degree of abdominal muscle function, which likely explains why pulmonary function approaches normal values in individuals with injury at or caudal to this level. The paralysis of typical inspiratory and expiratory muscles in cervical SCI appears to be partially compensated for by activation of the trapezius (inspiratory) as well as the clavicular portion of the pectoralis major and the latissimus dorsi (both expiratory) (De Troyer et al. 1986b; Terson de Paleville and Lorenz 2015; Fujiwara et al. 1999). Nevertheless, those with cervical and high-thoracic SCI still exhibit a disproportionate decrease in expiratory muscle strength ($P_{E,max}$) relative to inspiratory muscle strength ($P_{I,max}$) (West et al. 2012a). This is important insomuch as it may result in a disproportionate reduction in VC, which is primarily an expiratory manoeuvre, relative to total lung capacity (TLC), which is primarily an inspiratory manoeuvre. Indeed, it has been reported in athletes with cervical SCI that all individuals studied exhibited a VC below the lower limit of normal, whereas significantly fewer exhibited a TLC below the lower limit of normal (West et al. 2012a). Thus, defining pulmonary restriction from a low VC alone may increase the likelihood of a false positive test.

Individuals with cervical or high-thoracic SCI are commonly reported to have a TLC below the lower limit of normal (Anke et al. 1993; Roth et al. 1997; Stepp et al. 2008; Estenne et al. 1993; Hart et al. 2005; Fugl-Meyer and Grimby 1971b;

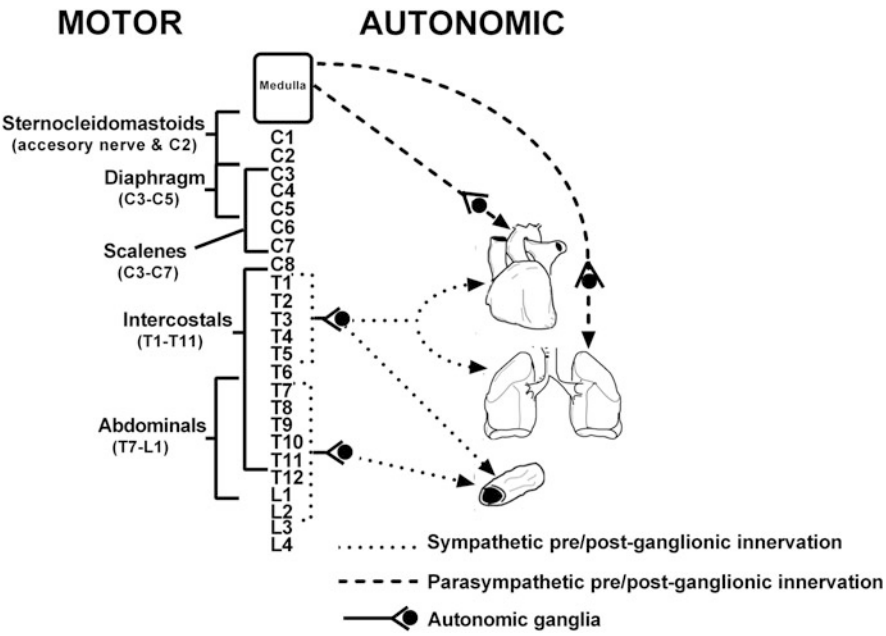

Fig. 4.1 Schematic overview of the motor control of the respiratory muscles (*left*) and the autonomic control of the lung (and airway), heart, and vasculature. Note that an individual with low cervical SCI (C7-C8) will exhibit full preservation of the primary muscles of inspiration, but complete paralysis of the accessory muscles of inspiration and the major muscles of expiration. As the level of injury moves caudally down the thoracic cord there is a greater preservation of accessory inspiratory muscle function as well as expiratory muscle function. Note also that an individual with complete cervical SCI at any level will exhibit loss of descending sympathetic control of the cardiopulmonary organs (lung, heart, vasculature), predisposing to bronchoconstriction, chronotropic and inotropic incompetence, and a subsequent reduction in cardiopulmonary capacity. Adapted from Krassioukov (2009)

Huldtgren et al. 1980), which is the definition of pulmonary restriction according to current guidelines (Pellegrino et al. 2005). Along with a reduced TLC, residual volume (RV) is typically increased while functional residual capacity (FRC) is maintained at near normal levels. Interestingly, Paralympic athletes with cervical SCI who compete in wheelchair rugby also exhibited a reduced TLC relative to able-bodied predicted values, suggesting that chronic exercise training exerts little effect on lung volumes after SCI (West et al. 2012b). However, the percent-predicted values for $P_{E,max}$ were higher than those typically reported for non-athletic individuals with similar injuries (e.g., Mateus et al. 2007), suggesting that exercise training may enhance expiratory function, perhaps via strengthening of the accessory muscles of expiration (Estenne et al. 1989; Fujiwara et al. 1999). To our knowledge, no study has reported resting lung volumes in athletes with thoracic SCI. A summary of resting lung volumes by level of injury for untrained individuals with SCI is provided in Fig. 4.2.

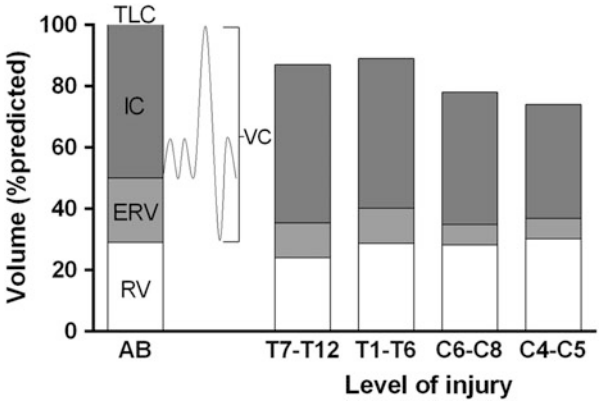

Fig. 4.2 Effect of level of injury on total lung capacity (TLC), inspiratory capacity (IC), expiratory reserve volume (ERV), residual volume (RV) and vital capacity (VC) expressed as percent-predicted of able-bodied (AB) TLC. Note that all individuals with SCI, regardless of level of injury, exhibit a decline in TLC and VC, but the relative degree of impairment is level-dependent. For low-thoracic (T7-T12) and high-thoracic (T1-T6) SCI, IC is relatively well preserved because the major muscles of inspiration are innervated from the cervical and upper-thoracic spinal cord. Conversely, ERV is severely compromised because the motor innervation for the major muscles of expiration (i.e., abdominal muscles) arises from the lower-thoracic spinal cord. For low-cervical (C6-C8) and high cervical (C4-C5) SCI, both IC and ERV are compromised due to the paralysis of accessory muscles of inspiration and major expiratory muscles. Adapted from Stepp et al. (2008)

Pulmonary obstruction was initially not thought to be present in the majority of individuals with cervical or thoracic SCI. According to current guidelines, an obstructive defect is defined as a FEV_1-to-VC ratio below the lower 5th percentile of the able-bodied predicted value (Pellegrino et al. 2005). However, this method is dependent upon lung volume history, such that a low VC may result in a normal FEV_1-to-VC ratio. Recent technological advances have enabled airway resistance to be measured during tidal breathing at rest. Using both body plethysmography and flow oscillometry it is now well documented that many individuals with cervical SCI exhibit pulmonary obstruction (Mateus et al. 2006; Radulovic et al. 2008a; Schilero et al. 2005; Singas et al. 1996), whereas individuals with thoracic SCI do not (Schilero et al. 2005; Radulovic et al. 2008b). The primary mechanism purported for the obstructive defect in cervical SCI is overriding parasympathetic (cholinergic) tone, secondary to the loss of descending control of the sympathetic pre-ganglionic neurons in the upper-thoracic cord which ultimately innervate the lungs and airway (Fig. 4.1) (Mateus et al. 2006). An alternative mechanism for the presence of pulmonary obstruction is the loss of regular stretch of airway smooth muscle due to pulmonary restriction. Intriguingly, Paralympic wheelchair rugby players with cervical SCI have near normal levels of airway resistance (West et al. 2012b; West and Romer 2010), which may be a consequence of the repeated stretch associated with increased ventilation during exercise causing a modification of the contractile mechanism of airway smooth muscle or via a remodelling of the

airway smooth muscle (Scichilone et al. 2010). More recently, however, Paralympic wheelchair rugby players with cervical SCI have been show to exhibit preservation of descending sympathetic axons in the face of motor- and sensory-complete SCI (West et al. 2013). Thus, the preservation of descending sympathetic fibres may explain, at least in part, the 'normal' airway resistance noted in wheelchair rugby players with cervical SCI. A direct comparison between exercise trained and untrained individuals with SCI is needed to confirm this postulate.

The reflexive control of airways in SCI is complex and remains poorly understood. It is known that most (~80 %) people with chronic cervical SCI with no pre-injury history of asthma or smoking have airway hyperresponsiveness to methacholine or histamine (Dicpinigaitis et al. 1994; Fein et al. 1998; Singas et al. 1996). Inhalation of a beta$_2$-agonist or an anticholinergic agent is associated with a significant increase in FEV_1 in those with cervical SCI (DeLuca et al. 1999; Almenoff et al. 1995). This suggests that airway hyper-responsiveness occurs secondary to overriding bronchoconstrictive (parasympathetic) predominance, although the specific pathogenesis of airway hyperreactivity in SCI is unclear. Whilst chemically-induced hyperresponsiveness has been shown, it has also been reported that individuals with cervical SCI are hyperreactive to physicochemical agents (e.g., ultrasonically nebulized distilled water) that do no act directly on airway smooth muscle (Grimm et al. 1999). This implies that the overall airway responsiveness is a nonspecific phenomenon similar to that observed in individuals with asthma (Grimm et al. 1999). Finally, there is some evidence to suggest that at least part of the reduced pulmonary function in SCI is related to airway inflammation. For example, exhaled nitric oxide (a marker of airway inflammation) and airflow obstruction in people with high SCI are comparable to persons with mild asthma and significantly higher than able-bodied controls (Radulovic et al. 2010).

4.2 Breathing Patterns During Exercise

During dynamic lower-limb exercise in healthy able-bodied individuals, minute ventilation ($\dot{V}_E$) increases proportionally with metabolic rate up to the 'anaerobic' threshold, after which there is a disproportionate increase in $\dot{V}_E$ required to expel non-metabolically produced CO_2. The increase in $\dot{V}_E$ at the onset of exercise occurs via increases in both respiratory frequency (f_R) and tidal volume (V_T). During mild-to-moderate intensity exercise (below ~50 % maximum O_2 uptake; $\dot{V}O_{2max}$), V_T increases and expands into both the inspiratory and expiratory reserve volumes with a concomitant increase in f_R. At ~50–60 % of $\dot{V}O_{2max}$, V_T begins to plateau and further increases in ventilation are achieved almost exclusively through f_R only. This exercise-induced "tachypnea" alters the duty cycle, with a disproportionate decrease in expiratory time relative to inspiratory time. As such, the inspiratory duty cycle during progressive exercise rises from approximately 0.40 to 0.55 (McParland et al. 1992). In individuals with cervical SCI there is a small increase in V_T at the onset of exercise, after which $\dot{V}_E$ is achieved predominately through f_R.

The presence of a tachypneic breathing pattern appears robust for trained and untrained individuals with cervical SCI and across different exercise modalities, including upper-limb exercise on an arm-crank ergometer (Van Loan et al. 1987; Taylor et al. 2010) and wheelchair propulsion on a treadmill (West et al. 2014a; Leicht et al. 2014). The negligible increase in V_T in cervical SCI is likely due to expiratory muscle weakness, which limits the degree to which the V_T can expand into the expiratory reserve. For untrained and trained individuals with thoracic SCI, V_T during exercise is typically greater than reported for cervical SCI (Bougenot et al. 2003; Van Loan et al. 1987; Leicht et al. 2014). However, varied participant inclusion criteria with respect to the specific level of thoracic SCI typically result in a wide spectrum of ventilatory responses.

In healthy able-bodied subjects, the increase in V_T at the onset of dynamic lower-limb exercise is achieved by an increase in end-inspiratory lung volume (EILV) and a reduction in end-expiratory lung volume (EELV). The EELV only rises above relaxation volume (FRC) when subjects approach their mechanical limits to generate expiratory flow (Babb 2013). In subjects with cervical SCI, however, there is a sudden and sustained increase in EELV (and EILV), both during arm-crank ergometry (Taylor et al. 2010) and treadmill propulsion (West et al. 2014a), despite limited or no evidence of expiratory flow limitation (Fig. 4.3). This dynamic lung hyperinflation may occur because the muscles that assist with expiration in cervical SCI (e.g., pectoralis major) are also prime-movers during upper-body exercise (Lin et al. 2004). A competing hypothesis is that dynamic hyperinflation may be the "normal" response to upper-body exercise (Alison et al. 1998). Potential benefits of dynamic hyperinflation for those with

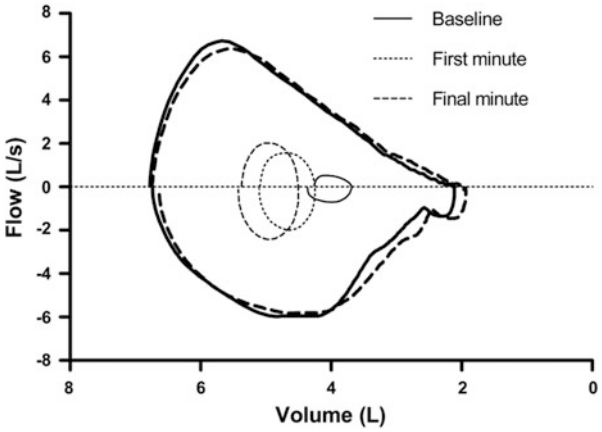

Fig. 4.3 Group mean ensemble average tracings of tidal flow-volume loops at resting baseline (*solid line*) and during the first (*dotted line*) and final (*dashed line*) minute of exercise plotted within the largest maximal flow-volume loop obtained at baseline (*solid line*) and <2 min after exercise (*dashed line*). Note that despite limited evidence of expiratory flow limitation, EELV and EILV increased early during exercise (i.e., leftward shift of the tidal flow-volume loops) and remained elevated through to the final minute of exercise. Reproduced from Taylor et al. (2010)

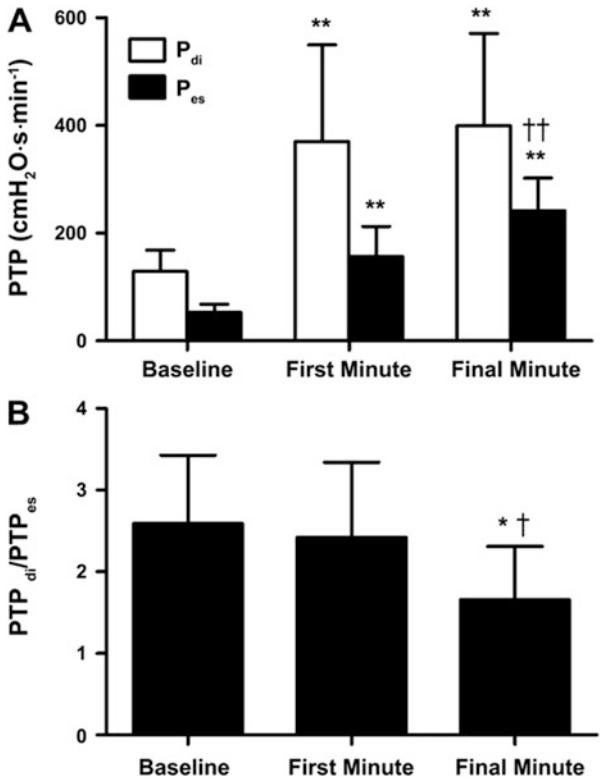

Fig. 4.4 Diaphragm pressure-time product (PTP_{di}; **a**), esophageal pressure-time product (PTP_{es}; **a**), and PTP_{di}-to-PTP_{es} ratio (**b**) at resting baseline and during arm-crank exercise. Note that diaphragm pressure production (PTPdi) increased from baseline to the first minute of exercise and levelled off thereafter, while total inspiratory muscle pressure production (PTPes) increased through to the final minute of exercise. Thus, the relative contribution of the diaphragm to the total inspiratory muscle force output (PTPdi/PTPes) decreased as exercise progressed. Data are presented as group mean ± SD. *$P < 0.05$, **$P < 0.01$, significantly different from baseline; †$P < 0.05$, ††$P < 0.01$, significantly different from first minute. Reproduced from Taylor et al. (2010)

cervical SCI include a "passive" increase in expiratory flow via the increased elastic recoil characteristics of the lung and chest wall at high lung volumes and a decrease in airway resistance via increased parenchymal tug. A negative consequence of dynamic hyperinflation, however, is a reduced ability of the diaphragm to generate pressure, which cause a gradual increase in the rib-cage and neck muscle contribution to inspiration (Yan and Kayser 1997). Indeed, when wheelchair rugby players with cervical SCI perform high-intensity constant-load arm crank exercise, the relative pressure contribution of the inspiratory rib cage and neck muscles increases over that of the diaphragm (Taylor et al. 2010) (Fig. 4.4). Since wheelchair rugby players with cervical SCI do not exhibit objective evidence of exercise-

induced diaphragmatic fatigue, it is possible that the accessory inspiratory muscles are reflexively recruited due to a progressive need for the diaphragm to be 'spared' so that it can take on a greater role in postural support during the latter stages of exercise. There is also evidence of exercise-induced tachypnea and a predominant neck/chest wall contribution to inspiration in untrained individuals with cervical SCI (Sinderby et al. 1996). The potential implications of dynamic hyperinflation are considered in Sect. 4.4.

4.3 Control of Exercise Hyperpnea

During dynamic exercise in humans and other mammals, alveolar ventilation increases in direct proportion to the exercise-induced increase in metabolic rate in order to prevent a reduction in arterial partial pressure of O_2 (PaO_2) or an increase in arterial partial pressure of CO_2 ($PaCO_2$). Despite over a century of study there is still debate on the mechanisms that regulate exercise hyperpnea, but some general conclusions can be drawn. An exhaustive treatment of this topic is beyond the scope of this chapter, but the interested reader is directed to recent comprehensive reviews (e.g., Forster et al. 2012). To summarize what is known about the control of breathing during exercise in SCI, we first present an overview of the key characteristics of exercise hyperpnea in the non-SCI state and the main hypotheses on the controlling mechanisms.

With the onset of exercise there is an immediate increase in ventilation. It is generally agreed upon that the rapid rise in ventilation occurs too quickly to be explained by chemical factors within the blood. There is evidence to show that at the onset of large-muscle mass exercise there is an increase in central nervous system ventilatory drive and a coupling between locomotion and ventilation. Animal models with simulated locomotion have provided evidence of such a feed-forward mechanism, whereby there is simultaneous activation of medullary respiratory neurons and motor pathways (Eldridge et al. 1981, 1985). In addition to a feed-forward mechanism there are several sensory inputs that contribute to ventilatory control. The muscles of locomotion provide a ventilatory stimulus in proportion to the chemical and mechanical conditions of the working muscle [for review see Kaufman and Forster (1996)]. In brief, thinly myelinated (group III) or unmyelinated (group IV) muscle afferents can be stimulated to elicit reflexive increases in ventilation. Mechanical, chemical, and thermal stimuli are all known to stimulate these fibres and contribute to the ventilatory response to exercise. In particular, group IV afferents are stimulated by the accumulation of metabolic by-products within skeletal muscle, thereby leading to increases in ventilation. Finally, it has long been suggested that the hyperpnea of exercise is mediated, in part, via humoral stimuli, with the principal candidates including increases in venous CO_2 and "CO_2 flow" to the lung, increases in cardiac afferent output, direct stimulation of the carotid body in response to chemical stimuli, or a change in the sensitivity of the carotid body. Unfortunately, much of the evidence supporting

these mechanisms is correlative and/or conflicting, which makes it difficult to determine cause and effect.

Exercise hyperpnea in people with SCI has been studied, but interpretation of the available literature is difficult due to the inherent difficulties of studying the control of breathing in vivo coupled with significant between-study differences with respect to participant inclusion criteria. However, a general three-component model of the regulation of exercise ventilation is a useful start point with which to examine where ventilatory control might be different in SCI relative to able-bodied individuals. The model consists of (1) a central rhythm generator and integrator, (2) neural inputs into this integrator from locomotor areas of the central nervous system and from the periphery, and (3) efferent motor output to the respiratory muscles. With SCI we must also consider that exercise is typically conducted with the arms, although there are exceptions (e.g., functional electrical stimulation-assisted cycling and body weight supported treadmill exercise). With this in mind, it appears that the ventilatory response to upper-body exercise is relatively well matched to metabolic demand in SCI. To illustrate this point we have selected one human study as an example. Hopman et al. (2004) had able-bodied controls, and persons with thoracic or cervical SCI perform incremental arm-crank exercise while breathing normoxia, hyperoxia or hypoxia. Predictably, the power output, $\dot{V}O_2$, and heart rate were always highest in able-bodied individuals, lowest in those with cervical SCI and intermediate in those with thoracic SCI. Minute ventilation followed a similar pattern among groups, but, importantly, was tightly coupled to metabolic demand. Collectively, these findings suggest that when persons with SCI perform arm exercise the neural inputs (i.e., muscle afferents, chemoreceptors) to the control of ventilation are such that the response meets demand. To the authors' knowledge, direct testing of feedforward/central command has not been conducted in SCI, but given the appropriateness of the ventilatory response to upper-limb exercise there is reason to postulate that it too is intact.

4.4 Respiratory Limitations

Few studies have explored potential respiratory limitations to exercise in individuals with SCI. An early study in Paralympic athletes with cervical and thoracic SCI reported a ratio of peak exercise ventilation to 15 s maximum voluntary ventilation (MVV) of ~40 % in athletes with cervical SCI, ~55 % in athletes with high-thoracic SCI, and ~66 % in those with the lowest lesions (Wicks et al. 1983). Thus, the authors concluded that the reduced ventilatory capacity might not play a significant role as a limiting factor to exercise in Paralympic athletes with cervical SCI. However, the validity of the MVV test as a true measure of ventilatory capacity has been criticised (Johnson et al. 1999). A more sophisticated method to assess ventilatory limitation is to place an exercise tidal flow-volume loop within a maximal flow-volume loop (Johnson et al. 1999). Using this approach, wheelchair rugby players with cervical SCI who compete at national level and above have been

shown to exhibit dynamic lung hyperinflation despite only limited evidence of expiratory flow limitation (Taylor et al. 2010; West et al. 2014a) (see also Sect. 4.2). The immediate hyperinflation in response to exercise would be expected to permit "passive" increases in expiratory flow and to decrease airway resistance. However, high lung volumes would be expected to decrease the capacity of the diaphragm to generate inspiratory pressure through an inability to operate at or near optimal length for force generation and to increase the elastic load presented to the inspiratory muscles (De Troyer and Wilson 2009). Short inspiratory muscle lengths at high lung volumes would also be expected to reduce the endurance of these muscles (Roussos et al. 1979; McKenzie and Gandevia 1987). Thus, individuals with cervical SCI may be especially prone to exercise-induced inspiratory muscle fatigue.

The first study to assess the influence of exercise on inspiratory muscle fatigue in individuals with SCI found a significant reduction in the centre frequency of the diaphragm EMG power spectrum during sustained, high-intensity exercise in the majority of patients studied with cervical SCI or prior poliomyelitis infection (Sinderby et al. 1996). However, shifts in the EMG power spectrum are related more to disturbances in action potential transmission than to a fatiguing process at the sarcomere level, and are rapidly reversed with rest even though the muscle may remain in a fatigued state (Supinski et al. 2002). A more objective index of diaphragm fatigue is the twitch transdiaphragmatic pressure response to phrenic nerve stimulation. In healthy able-bodied subjects, this technique has been used to show that the diaphragm fatigues in response to sustained high-intensity lower-limb exercise (~85–95 % $\dot{V}O_{2max}$) as demonstrated by 15–30 % reductions from baseline in twitch transdiaphragmatic pressure (Romer and Polkey 2008). In Paralympic wheelchair rugby players with cervical SCI, however, twitch transdiaphragmatic pressure was not different from baseline at any time following arm-crank exercise that was sustained to the limit of tolerance at ~90 % $\dot{V}O_{2peak}$ (Taylor et al. 2010). The absence of diaphragm fatigue, despite the presumed shorter inspiratory muscle lengths, might have been related to the absolute level of ventilation during exercise. For instance, the ventilatory requirements during arm exercise were substantially less than the maximum mechanical capability of the respiratory muscles to produce flow and volume, as demonstrated by inspiratory tidal flow reaching only 44 % of the maximum available inspiratory flow and the ventilatory response to exercise reaching only 47 % of the estimated ventilatory capacity. Importantly, the degree of ventilatory constraint did not appear to influence the adequacy of alveolar ventilation or systemic O_2 delivery. Hyperventilation occurred and there was no evidence of arterial hypoxaemia (i.e., arterial O_2 saturation was maintained at resting levels). Collectively, these findings suggest that the low active muscle mass in individuals with high SCI does not impose enough stress on the respiratory system to elicit ventilatory constraint or inspiratory muscle fatigue.

In conclusion, Paralympic wheelchair rugby players with cervical SCI do not exhibit objective evidence of exercise-induced diaphragmatic fatigue and rarely reach mechanical ventilatory constraint. Thus, the respiratory system appears to have ample capacity to cope with the demands placed on it during upper-body exercise in this population. Whether these findings in fit healthy subjects with SCI

can be extended to those who are less fit, but otherwise healthy, is not entirely clear. Also unclear is whether the respiratory system might be limiting in those with lower lesions. Notwithstanding, there is preliminary evidence from a case-study that the increased ventilatory response associated with low-lesion SCI may increase the likelihood of exercise-induced diaphragm fatigue (Romer et al. 2014). In a Paralympic and World Champion oarsman with low-thoracic SCI (T_{12}), the twitch transdiaphragmatic pressure response to phrenic nerve stimulation was reduced by 33 % immediately after a simulated 1000 m time-trial on a rowing ergometer. Despite relatively well-preserved pulmonary function, the ventilatory requirements during exercise were substantial (peak minute ventilation: 154 L/min; ~60 % MVV). Interestingly, neuromuscular activation of the diaphragm was higher during the second half of the time-trial, yet transdiaphragmatic pressure and tidal volume were lower. This uncoupling of central respiratory drive and thoracic volume displacement suggests that the diaphragm fatigue might have been attributable, at least in part, to factors other than ventilation (e.g., postural drive).

4.5 Cardiopulmonary Interactions

It is often unappreciated that the act of breathing influences venous return, cardiac filling and ultimately stroke volume. In the upright human, the skeletal muscle pump and sympathetically mediated vasoconstriction are generally considered the major determinants of venous return at rest and during exercise. Nevertheless, the location of the heart within the thoracic cavity makes it susceptible to respiratory-induced changes in intrathoracic pressure. Indeed, the reduction in intrathoracic pressure upon diaphragmatic descent at the onset of inspiration is transmitted across the heart, thereby reducing right atrial pressure and augmenting venous return. Conversely, as intrathoracic pressure narrows during expiration right atrial pressure is increased and filling is compromised. This mechanical consequence of breathing on the heart is complicated by the finding that outside of the thoracic cavity the associated intraabdominal pressure swings during inspiration compromise femoral venous outflow, presumably due to a cuffing of the inferior vena cava, which ultimately reduces venous return to the heart (Miller et al. 2005a). Moreover, the specific effect of breathing on cardiac filling appears to be critically dependent on the volume of blood within the inferior vena cava (Takata et al. 1990). When abdominal inferior vena cava volume is high, tidal increases in intra-abdominal pressure will augment venous return. Conversely, when inferior vena cava volume is low, tidal abdominal pressure swings will exert little effect. This complex within-breath modulation of cardiac function has been shown to remain present in the face of rhythmic contractions of the lower-limbs (Miller et al. 2005b). More recently, the use of double-plethysmography (i.e., combination of whole-body plethysmography for lung volumes and optoelectronic plethysmography for lung volumes plus blood shifts) has enabled the partitioning of thoracic volume shifts due to the movement of air and blood (Aliverti et al. 2009, 2010), thereby providing a unique opportunity

to investigate the within-breath modulation of cardiac function. Using this technique during moderate exercise, it has been reported that diaphragmatic breathing coupled with an 'expiratory effort' causes a relatively large redistribution of blood from the abdomen to the heart, whereas during rib-cage breathing blood is redistributed from the extremities into the trunk (Uva et al. 2015). Thus, there is now clear evidence that respiratory pressure swings mechanically modulate cardiac filling, and ultimately output, at rest and during exercise in the able-bodied population.

Whether the same respiratory modulation of cardiac filling occurs in SCI remains unknown. However, the measurement of ventricular volumes in cervical SCI implies severely reduced venous return, which likely occurs due to the absence of an effective sub-lesional skeletal muscle pump and inadequate centrally-mediated sympathetic vasomotor outflow to the peripheral vasculature (West et al. 2012b; de Groot et al. 2006; Thijssen et al. 2009; Grigorean et al. 2009). Moreover, the paralysis of accessory inspiratory and expiratory muscles results in an almost exclusive diaphragmatic contraction during inspiration. In cervical SCI, tidal esophageal pressure swings (as an index of intrathoracic pressure) are similar to those in able-bodied individuals, but abdominal pressure swings are much lower (West et al. 2012b), presumably due to an over compliant abdominal wall (Goldman et al. 1986a). Thus, on the one hand the preserved diaphragmatic contraction should enhance ventricular filling during inspiration due to the associated reduction in intrathoracic pressure, but the limited increase in abdominal pressure will likely have a negligible effect on promoting venous return from the abdominal inferior vena cava. When an abdominal binder is applied tightly to individuals with cervical SCI, the associated increase in intra-abdominal pressure promotes venous return and increases stroke volume at rest (West et al. 2012c) (see also Sect. 4.6). Little is known about cardiorespiratory interactions during exercise in SCI. In individuals with cervical SCI, exercise-induced dynamic lung hyperinflation may conceivably place a constraint on ventricular preload during inspiration by a direct compressive effect of the lung on the cardiac fossa and the inferior and superior vena cava (Marini et al. 1981; Takata and Robotham 1991; Kyhl et al. 2016). This effect may be compounded during the latter stages of exercise due to a reduction in the ratio of diaphragmatic breathing to chest wall breathing (Taylor et al. 2010), which would be expected to attenuate the tidal intra-abdominal pressure swing, thereby further compromising ventricular filling and stroke volume. Impaired venous return secondary to exercise-induced mechanical changes of the respiratory system may be particularly problematic in a population where the lack of sympathetically mediated splanchnic vasoconstriction prevents the typical exercise-induced redistribution of blood to the active musculature (Thijssen et al. 2009) (see also chapter entitled "Cardiovascular Responses to Exercise in Spinal Cord Injury").

4.6 Methods to Augment Respiratory Function

4.6.1 Exercise Training

Individuals with SCI have frequent respiratory problems (e.g., impaired cough, atelectasis) due to decreases in pulmonary function and active respiratory musculature (Brown et al. 2006). Furthermore, there is a high prevalence of physical inactivity and increased risk of cardio-metabolic disorders in this population (Warburton et al. 2007). If respiratory function can be improved with exercise training then the incidence of respiratory problems may be reduced. Furthermore, if the ventilatory response to exercise can be improved then individuals may be able to exercise at higher intensities. High intensity exercise training is more effective at improving cardio-metabolic risk compared to moderate intensity exercise training (Kemi et al. 2005; Swain and Franklin 2006).

Cross-sectional studies comparing exercise trained versus non-exercise trained individuals with SCI suggest that exercise training improves respiratory function (Crane et al. 1994; West et al. 2012b). However, cross-sectional studies suffer from selection bias. Nevertheless, there is some evidence that short-term exercise training may improve respiratory function in persons with SCI (Sheel et al. 2008). For example, a 6 week programme of arm crank exercise was shown to significantly increase vital capacity and respiratory muscle endurance in individuals with thoracic SCI (Silva et al. 1998). Significant increases in vital capacity were also noted after 8 weeks of functional electrical stimulation (FES) assisted cycle exercise training in individuals with cervical SCI (Phillips et al. 1989). Another modality that has been shown to improve selected measures of respiratory function is locomotor step training with body weight support (Terson de Paleville et al. 2013).

In healthy able-bodied subjects, upper-body exercise training has been shown to increase ventilation at peak exercise (Loftin et al. 1988) and to reduce the response at fixed sub-maximal intensities (Rasmussen et al. 1975). The increased ventilatory responses at peak exercise reflect training-induced increases in exercise intensity. The reduced ventilatory responses at fixed submaximal intensities were likely due to a reduction in one or more of the factors (neural and/or humoral) purported to cause the hyperpnea of exercise (see Sect. 4.3). Upper-body exercise training has also been shown to reduce the intensity of sensory perceptions (e.g., dyspnea) for a given level of exercise (Gigliotti et al. 2005; Romagnoli et al. 2013). A contributing factor to the reduction in sensory perceptions with training is the accompanying decrease in ventilation (Gigliotti et al. 2005; Romagnoli et al. 2013).

Relatively few studies have assessed the influence of exercise training on ventilatory responses in individuals with SCI (Sheel et al. 2008). Nevertheless, there is some evidence that ventilation, as well as tidal volume and ventilatory reserve, may be improved after wheelchair exercise training (Gass et al. 1980; Bougenot et al. 2003; Le Foll-de Moro et al. 2005). There is also evidence that the ventilatory response may be modified by FES training. Whilst the ventilatory response to submaximal and maximal FES-induced leg cycle exercise was not

significantly altered by training (Faghri et al. 1992; Barstow et al. 1996; Hooker et al. 1995), faster kinetic responses were noted during steady-state exercise and recovery (Barstow et al. 1996). Hybrid FES exercise, which describes combined voluntary upper-extremity with FES lower-extremity exercise, further increases the training stimulus (Hooker et al. 1992; Deley et al. 2015). Using this approach, FES row training was shown to produce a modest increase in peak ventilation and a reduced ventilatory response for a given level of exercise in individuals with high-lesion SCI (Qiu et al. 2016). In a single subject with incomplete cervical SCI, body weight supported treadmill training was shown to lower the ventilatory response and promote locomotor-respiratory coupling during walking (Sherman et al. 2009).

In summary, exercise training has the potential to improve respiratory function and exercise ventilation in individuals with SCI. Unfortunately, the available evidence is difficult to interpret due to small sample sizes; differences in the exercise modality; and inconsistencies in the frequency, intensity and duration of exercise training. Importantly, most of the exercise training studies have included only individuals with low-level lesions and minimal deficits in respiratory function. Since respiratory function is typically within the normal range for those with low SCI, improvements may be difficult to achieve and of limited clinical significance.

4.6.2 Respiratory Muscle Training

Evidence in healthy able-bodied individuals suggests that respiratory muscle training (RMT) can improve resting respiratory muscle strength and endurance and reduce the perceived intensity of dyspnea during exercise. Several studies have demonstrated variable, but statistically significant, RMT-induced improvements in exercise performance in able-bodied individuals for both time trials and constant-load exercise tests, as summarized in two recent meta-analyses (Illi et al. 2012; HajGhanbari et al. 2013). It should be emphasized, however, that there continues to be scientific debate on the efficacy of RMT for improving exercise performance (McConnell 2012; Patel et al. 2012). The most commonly employed methods of RMT are inspiratory pressure threshold loading and voluntary isocapnic hyperpnea. Inspiratory pressure threshold loading specifically targets the inspiratory muscles and requires the subject to produce an inspiratory pressure sufficient to overcome a negative pressure load, thereby permitting variable loading at a quantifiable intensity. Voluntary isocapnic hyperpnea requires the subject to maintain a high target level of ventilation, thereby providing a training stimulus to both the inspiratory and expiratory muscles. To ensure that the partial pressure of CO_2 does not decrease below resting levels during voluntary hyperpnea it is necessary to increase the inspired fraction of CO_2, either by partially rebreathing the expired air or by titrating CO_2 into the inspired gas.

In individuals with cervical or high-thoracic SCI, positive effects of RMT have been reported for inspiratory muscle strength (Gross et al. 1980; Rutchik et al. 1998; Silveira et al. 2010) and endurance (Mueller et al. 2008b; Verges

et al. 2009), and a recent systematic review concluded that there was "level 4" evidence to support RMT as an intervention that might decrease dyspnea and improve respiratory function (Sheel et al. 2008). The effect of RMT on exercise tolerance and/or performance in SCI is less clear. In untrained individuals with cervical SCI, a small but statistically significant increase in arm-crank derived $\dot{V}O_{2peak}$ was reported following 6-weeks of flow-resistive inspiratory muscle training (IMT) (Uijl et al. 1999). In contrast, recreational wheelchair athletes exhibited no change in $\dot{V}O_{2peak}$ in response to 10 weeks of flow-resistive inspiratory and expiratory muscle training (Litchke et al. 2008), although the inclusion of individuals with various disabilities renders these findings difficult to interpret in the context of SCI. A limitation of the abovementioned studies is that a true placebo group was not incorporated into the experimental designs. In able-bodied IMT studies, a placebo group subjected to a similar intervention but with negligible (<15 % of $P_{I,max}$) resistance imposed by the training device is typically included (Romer et al. 2002). In SCI, a placebo group undergoing such an intervention has been shown to exhibit a similar increase in $P_{I,max}$ as an experimental group undertaking IMT at 50 % of $P_{I,max}$ (Goosey-Tolfrey et al. 2010), implying that even low-dose IMT may provide a training stimulus in this population. To circumvent this challenge, West and colleagues compared 6-week of pressure threshold IMT against sham bronchodilator treatment in Paralympic wheelchair rugby players with cervical SCI (West et al. 2014b). The participants were informed that they were taking part in a study to compare the effects of IMT versus bronchodilator medication, and were therefore blinded to the true purpose of the study and the expected outcomes. Compared to placebo, IMT increased both inspiratory muscle strength at rest and the V_T to f_R ratio during maximal incremental arm-crank exercise. There was also a strong trend, with large observed effect, for a positive influence of IMT on peak work rate and $\dot{V}O_{2peak}$ (Fig. 4.5). These findings suggest that IMT may provide a useful adjunct to exercise training in wheelchair rugby players with cervical SCI.

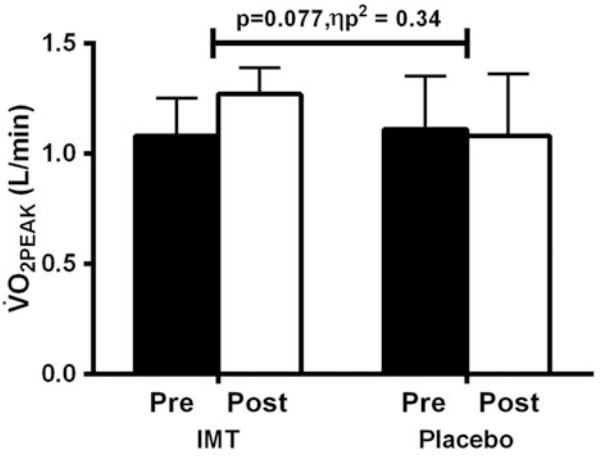

Fig. 4.5 Peak O_2 uptake before and after inspiratory muscle training or placebo (sham bronchodilator treatment). Note that there was a strong trend and large effect towards a greater change (increase) in peak O_2 uptake post-intervention in the IMT group relative to the placebo group. Data are presented as group mean ± SD. η_p^2, partial-eta squared. Based on data from West et al. (2014b)

The mechanisms by which RMT could elicit an ergogenic effect on exercise performance have yet to be clearly identified. In able-bodied individuals, RMT may reduce the severity of respiratory and/or locomotor muscle fatigue by attenuating or delaying the respiratory muscle metaboreflex (see Sheel and Romer (2012) for review). In SCI, it is unclear if exercise imposes sufficient stress to induce a respiratory muscle metaboreflex. An interesting observation in able-bodied individuals is that RMT has no appreciable effect on $\dot{V}O_{2max}$ (McConnell and Romer 2004a), yet two studies in SCI point to an increase in $\dot{V}O_{2peak}$ following RMT (West et al. 2014b; Uijl et al. 1999). Although the mechanisms underlying the increase in $\dot{V}O_{2peak}$ remain elusive, we speculate that increased aerobic capacity may be caused by an increase in diaphragm strength and/or a change in rib-cage configuration. Conceivably, both changes may result in a greater circulatory pump action of the diaphragm and/or a prevention of the transition to a predominant rib-cage contribution to inspiration during the latter stages of exercise (Taylor et al. 2010), which may have the net effect of increasing venous return, stroke volume, and O_2 delivery (see also Sect. 4.5). It is equally possible, however, that any improvements in aerobic performance may occur by way of relieving the sensation of respiratory discomfort (McConnell and Romer 2004b). Further carefully designed and randomized control trials that specifically investigate the interplay between the cardiorespiratory and perceptual responses to exercise are necessary to determine the effectiveness of RMT in people with SCI.

4.6.3 Abdominal Binding

The majority of studies that have investigated abdominal binding in individuals with SCI have shown that this strategy acutely increases VC in the seated position (Hart et al. 2005; Goldman et al. 1986b; Bodin et al. 2005; Estenne et al. 1998; Boaventura et al. 2003). In contrast, relatively few studies have assessed the influence of abdominal binding on lung volume subdivisions. Those that have tend to report that RV and FRC are reduced in individuals with cervical and high-thoracic SCI (Hart et al. 2005; Estenne et al. 1998; Bodin et al. 2005). The effect of abdominal binding on TLC in cervical SCI remains controversial, with one study reporting an increase (McCool et al. 1986), one study reporting a decrease (Bodin et al. 2005), and two studies reporting no change (Estenne et al. 1998; Hart et al. 2005). The effect of abdominal binding on pulmonary function in SCI was the focus of a recent meta-analysis (Wadsworth et al. 2009). The mean weighted score for all studies suggested that abdominal binding increases VC and RV, reduces FRC, whereas TLC remains relatively unchanged. Abdominal binding exerts beneficial pulmonary effects by enhancing expansion of the lower rib cage via an increase in diaphragmatic appositional forces (Urmey et al. 1986; Mead et al. 1984), which appears to occur secondary to binding-induced increases in abdominal pressure and therefore diaphragmatic pressure production (Goldman et al. 1986b; Hart et al. 2005). Binding may also enable the diaphragm to operate

on a more effective portion of its length-tension relationship and thereby exert greater insertional forces (De Troyer and Wilson 2015). Further to conveying a diaphragmatic mechanical advantage, binding has been show to produce small but inconsistent improvements in expiratory function in individuals with cervical SCI (Estenne et al. 1998). More recently, the improvements in diaphragmatic muscle function and absolute lung volumes with binding were also shown to be present in wheelchair rugby and tennis players with cervical SCI (West et al. 2012c). Esophageal pressure and airflow were substantially enhanced throughout a maximal expiratory VC maneuver. The larger and more consistent improvements in expiratory function in trained (West et al. 2012c) vs. untrained (Estenne et al. 1998) were likely attributable to differences in the degree of abdominal compression achieved with the binder.

Since abdominal binding increases intra-abdominal pressure, it is reasonable to assume that there will also be cardiac and/or hemodynamic benefits. In patients with acute cervical SCI, binding has been shown to attenuate the degree of orthostatic hypotension and to increase resting $\dot{V}O_2$ (Guttman 1973). In two individuals taking part in a study to investigate the effect of abdominal binding on lung volumes (McCool et al. 1986), binding induced an increase in right atrial size. In wheelchair rugby and tennis players with cervical SCI, a doubling of intra-abdominal pressure with abdominal binding was associated with improved systolic function, presumably through an increase in venous return via compression of the abdominal inferior vena cava (West et al. 2012c).

Few studies have assessed the influence of abdominal binding on exercise responses. Early studies showed that an anti-gravity suit incorporating abdominal and lower-limb inflation bladders improved submaximal hemodynamics in cervical and high-thoracic SCI (Hopman et al. 1992; Pitetti et al. 1994), but only increased $\dot{V}O_{2peak}$ in cervical SCI (Hopman et al. 1993; Pitetti et al. 1994). In Paralympic wheelchair rugby players with cervical SCI, abdominal binding enhanced performance during field-based exercise tests, likely via improvements in central hemodynamics and truncal stability (West et al. 2014c). A follow-up laboratory study in a sub-set of the wheelchair rugby players revealed that binding reduced the degree of dynamic hyperinflation during exercise without imposing mechanical ventilatory constraint or influencing expiratory flow limitation, perceived symptoms, or exercise tolerance (Fig. 4.6) (West et al. 2014a). Intriguingly, $\dot{V}O_{2peak}$ was increased with binding and peak blood lactate was reduced, yet peak work rate was unchanged. At first glance one may attribute this finding to a reduced mechanical efficiency of wheelchair propulsion with binding (i.e., greater O_2 cost for a given work rate), perhaps secondary to changes in push mechanics. However, push mechanics were unaltered with binding (West et al. 2014c). A more likely explanation is that the driving pressure for venous return and subsequently stroke volume was enhanced via a direct compressive effect of the binder on the abdomen or a reduction in the degree of dynamic hyperinflation. This has important implications for O_2 delivery in cervical SCI as the typical exercise-induced increase in cardiac output is blunted by sympathetic decentralization of the sino-atrial node, ventricular tissue, and vasculature (Krassioukov and West 2014). As such, exercise-induced

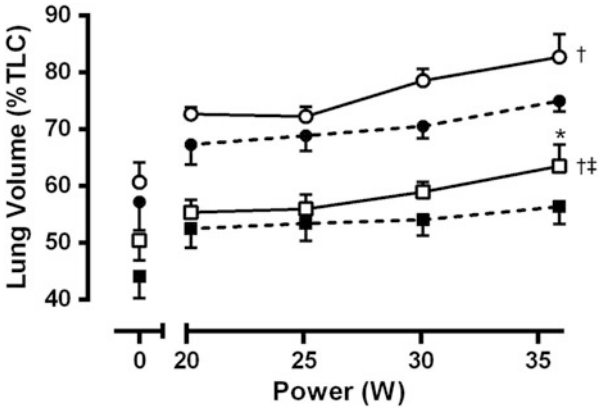

Fig. 4.6 End-expiratory (*squares*) and end-inspiratory (*circles*) lung volume at rest and in response to submaximal wheelchair propulsion in the bound (*dashed lines, closed symbols*) and unbound condition (*solid lines, open symbols*). Note the immediate and progressive increase from resting values in operating lung volumes (i.e., dynamic hyperinflation) and the downward shift in operating lung volumes in response to abdominal binding. Data are presented as group mean ± SE. †Significant main effect for condition ($P < 0.05$). ‡Significant interaction effect ($P < 0.05$). *Significant post hoc pairwise comparison ($P < 0.05$). Reproduced from West et al. (2014a)

increases in cardiac output are mediated entirely through small increases in heart rate secondary to withdrawal of vagal tone. Thus, if binding can improve stroke volume then it stands to reason that cardiac output and hence O_2 delivery can also be improved. In support of this idea is the finding of an increase in O_2 pulse at peak exercise with binding (West et al. 2014a).

In trained wheelchair road-racing/track athletes with mid-thoracic SCI (T3-T6), abdominal binding did not improve $\dot{V}O_{2peak}$ or exercise tolerance (Kerk et al. 1995). Why binding improves $\dot{V}O_{2peak}$ in highly-trained athletes with cervical (i.e., West et al. 2014a) but not mid-thoracic SCI is not entirely clear. In mid-thoracic SCI, the cardiac-projecting sympathetic preganglionic neurons remain under medullary control which allows these individuals to produce a near-normal chronotropic response to exercise and to elevate cardiac output (Krassioukov and West 2014). Conversely, those with cervical SCI typically demonstrate chronotropic incompetence and therefore may be more limited by a low exercise-induced increase in cardiac output and systemic O_2 delivery. Thus, cervical SCI may exhibit a cardiovascular limitation to exercise that can be partially circumvented with abdominal binding, whereas thoracic SCI do not exhibit this same limitation. Collectively, these findings suggest that abdominal binding has the potential to improve resting pulmonary and respiratory muscle function in individuals with high SCI. During exercise, binding may benefit aerobic performance via improvements in central circulatory function and O_2 transport capacity.

4.7 Concluding Remarks and Future Directions

The resting pulmonary, respiratory muscle, and airway changes that accompany SCI are well described, but our knowledge of how the respiratory system responds to dynamic exercise in SCI is comparatively rudimentary, especially in untrained individuals. In trained individuals (mostly Paralympic wheelchair rugby players) there is evidence of immediate and sustained hyperinflation during exercise that may permit increased expiratory flow and reduced airway resistance but impede central circulatory function. That hyperinflation occurs without any apparent ventilatory constraint or inspiratory muscle fatigue suggests that this response, although atypical, is beneficial from a respiratory perspective. Yet from a cardiovascular perspective the response may impact negatively on venous return. It is important to note, however, that the method of plotting sequential flow-volume loops within a maximal flow-volume envelope to assess ventilatory constraint assumes that the maximal flow-volume envelope does not change during exercise. It remains to be seen if this is the case in cervical SCI as many of the muscles that contribute to the expiratory portion of the maximal flow-volume envelope at rest are also prime-movers during exercise. This raises the possibility that the exercise maximal flow-volume loop may actually be smaller than is presently thought, thus providing conditions conducive to the development of ventilatory constraint. Future studies should, therefore, specifically examine the effect of various exercise perturbations on the maximal flow-volume envelope. Whilst we have a reasonable appreciation of the ventilatory responses to exercise in individuals with cervical SCI, few studies are available in those with thoracic SCI. The one case study highlighted in the current chapter suggests that future research should be directed to this area as the high ventilatory demand imposed on the respiratory system during exercise in those with thoracic injures may exceed capacity, thereby predisposing such individuals to ventilatory constraint and respiratory muscle fatigue. The most robust improvements in respiratory function in response to exercise training, RMT, or abdominal binding have been reported in individuals with high injuries. Almost all of the studies that have assessed interventions primarily targeted at the respiratory system, however, have not consider the concomitant changes in cardiovascular function. Moreover, no study has combined methods of augmenting respiratory function. For example, one may envisage that the synergistic effects of exercise training or IMT while wearing an abdominal binder may produce a more pronounced effect compared to either intervention alone.

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Chapter 5
Alterations in Cardiac Electrophysiology After Spinal Cord Injury and Implications for Exercise

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Abstract When the spinal cord is injured at or below thoracic level 5 (T_5), cardiovascular control is markedly unbalanced as the heart and blood vessels innervated by upper thoracic segments remain under brain stem control, whereas the vasculature of the lower body is affected by unregulated spinal reflexes. As a result, mid-thoracic spinal cord injury (SCI) results in chronic arterial pressure and cardiac volume unloading due to a rapid and sustained reduction in arterial pressure, venous return and end-diastolic volume, secondary to the loss of sympathetic vasoconstrictor tone below the level of the injury. The resulting hypotension and reduced cardiac filling initiates a dramatic and immediate reflex increase in sympathetic outflow and decrease in parasympathetic outflow to the heart. These high levels of sympathetic outflow and reduced parasympathetic outflow following mid-thoracic SCI have been reported to induce calcium overload, left ventricular dysfunction, cardiac injury and ST-segment elevation. The myocardial damage also promotes nerve growth factor-induced sympathetic sprouting, hyper-innervation of the heart and pathological neuroplasticity in the autonomic ganglia, spinal cord and autonomic centers within the brainstem. Pathological neuroplasticity following SCI is associated with many lingering complications such as chronic pain, spasticity, neurogenic bladder, and autonomic dysreflexia. Pathological neuroplasticity is also associated with changes in cardiac electrophysiology and an increased susceptibility to life-threatening ventricular arrhythmias. These complications are exacerbated by the sedentary lifestyle of the typical individual with SCI. Regular exercise may exert a protective effect via an increased plasma volume, increased venous return and a subsequent volume loading of the heart, which in turn maintains contractile function, arterial pressure and reduces sympathetic sprouting, hyper-innervation and pathological neuroplasticity.

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5.1 Introduction

"Spinal cord injury is a ferocious assault on the body that leaves havoc in its wake. Paralysis is certainly part of its legacy, but there are other equally devastating consequences including autonomic dysfunction, compromised cardiovascular, bowel, bladder, and sexual function. Treatments and cures for these losses would greatly improve the quality of life for all of us living with spinal cord injury" (Reeve 2005). In fact, when surveyed, individuals living with spinal cord injury (SCI) state that their quality of life is severely impacted by the consequences of impaired cardiovascular and autonomic function (Anderson 2004). However, cardiovascular and autonomic dysfunction following SCI remains an under-investigated area compared with motor and sensory dysfunction (Inskip et al. 2009). Nevertheless, understanding the mechanisms responsible for the cardiovascular and autonomic dysfunction as well as therapeutic strategies (i.e. dynamic exercise) for improving cardiovascular function, has the potential to impact the lives of millions of individuals and families living with SCI (Anderson 2004).

Prior to World War II, 80 % of individuals with SCI died within 3 years of the injury, primarily due to kidney and pulmonary infections (Stauffer 1978). However, with the advent of antibiotic drugs and advancements in acute care and rehabilitation, the life expectancy of individuals with SCI has increased to near that for able-bodied individuals. However, cardiovascular disease is now the leading cause of death and morbidity for individuals with SCI (Graitcer and Maynard 1991; DeVivo et al. 1992, 1993; Le and Price 1982; Whiteneck et al. 1992; Wicks et al. 1983; West et al. 2012b; Groah et al. 2001; Kessler et al. 1986). The risk for significant cardiovascular dysfunction is aggravated by an abnormal and unstable autonomic control of the cardiovascular system as well as the sedentary lifestyle of the typical individual with SCI (Inskip et al. 2010). In fact, individuals with SCI are placed at the lowest end of the human fitness spectrum (Jacobs and Nash 2004). Additionally, individuals with SCI have blood lipid profiles characterized by elevated total and low-density lipoprotein cholesterol as well as depressed high-density lipoprotein cholesterol, a lipid profile normally associated with, if not a direct result of, the sedentary lifestyle (Cowan and Nash 2010). Therefore, exercise with the arms is often recommended for individuals with SCI based on studies demonstrating improvements in aerobic capacity and lipoprotein profiles (DiCarlo 1982; DiCarlo et al. 1983). In fact, the Centers for Disease Control has recommended further research to evaluate the efficacy of exercise to prevent the development of cardiovascular disease in individuals with SCI (Graitcer and Maynard 1991). In this chapter we will discuss the association of an abnormal and unstable autonomic control of the cardiovascular system as well as a sedentary lifestyle on cardiac electrophysiology and susceptibility to cardiac rhythm disorders. Furthermore, we will discuss the potential of regular exercise to increase plasma volume; increase venous return and subsequently volume load the heart and thus maintain contractile function, arterial pressure and reduce pathological neuroplasticity.

5.2 Mid-Thoracic SCI

Mid-thoracic spinal cord injury markedly disrupts sympathetic outflow to the heart and blood vessels. Specifically, the cell bodies of sympathetic preganglionic neurons originate in the spinal gray matter of the thoracic (T1–T12) and upper lumbar (L1–L2) segments of the spinal cord. Axons of the sympathetic preganglionic neurons exit through the anterior roots of the spinal cord and synapse onto postganglionic sympathetic neurons in the sympathetic chain ganglia and prevertebral ganglia. Sympathetic postganglionic fibers are mainly adrenergic, releasing the neurotransmitter norepinephrine. The exception to this general rule involves the sympathetic fibers innervating sweat glands and piloerector muscles, which release acetylcholine. Sympathetic innervation of the heart and blood vessels of the upper limbs originates at segments T1–T4. Sympathetic innervation of the critical circulation to the splanchnic vasculature and lower limbs occurs at segments T6–L2. Thus, when the spinal cord is injured at or below thoracic level 5 (T5), cardiovascular control is markedly unbalanced as the heart and blood vessels innervated by upper thoracic segments remain under brain stem control, whereas the vasculature of the lower body is affected by unregulated spinal reflexes. Importantly, the regulation of heart rate and cardiac function is abnormal after mid-thoracic spinal cord injury at T5 because sympathetic outflow to the heart is increased.

Preganglionic neurons of the parasympathetic nervous system originate within four cranial nerves (III, VII, IX and X) of the brainstem and within the sacral spinal segments (S2–S4). The heart, pulmonary system and upper portion of the gastrointestinal tract are under parasympathetic control through the parasympathetic vagus nerve (cranial nerve X). Specifically, cardiac parasympathetic fibers originate in the dorsal motor nucleus of the vagus and the nucleus ambiguus in the medulla oblongata (Loewy and Spyer 1990) and travel in the vagus nerve to the heart. Subsequently, these fibers synapse with postganglionic cells on the epicardial surface or within the walls of the heart near the sinoatrial node, atrioventricular node, atria and ventricles (Coote 2013). The vagus nerve also exits the brainstem and innervates the pulmonary system and the nerve cells in the enteric nervous system of the upper gastrointestinal tract. The lower gastrointestinal tract receives parasympathetic innervation from segments S2-S4. Importantly, because the cardiac parasympathetic fibers never pass through the spinal cord, spinal cord injury does not *directly* interrupt cardiac parasympathetic activity. Regardless of this fact, spinal cord injury profoundly alters cardiac vagal structure and function (Lujan et al. 2014).

5.3 Myocardial Damage Following SCI

Mid-thoracic spinal cord injury is associated with high levels of cardiac sympathetic activity and reduced levels of cardiac parasympathetic activity that cause myocardial damage and cardiac dysfunction (Lujan et al. 2014; Morita et al. 2010). Specifically, an increased release of norepinephrine from sympathetic terminals is cardio-toxic (Goldspink et al. 2004; Reiken et al. 2003; Teerlink et al. 1994; Shizukuda et al. 1998) and causes significant myocyte death and hypertrophy (Reiken et al. 2003; Teerlink et al. 1994; Shizukuda et al. 1998). Chronic sympathetic hyper-activity and consequent activation of the beta-adrenergic receptor signaling pathway also leads to protein kinase A mediated hyper-phosphorylation of the ryanodine receptor 2 (RyR2) of the sarcoplasmic reticulum (Marx et al. 2000). Phosphorylation of the RyR2 results in continuous intracellular Ca^{2+} leakage and impaired cardiac contractility (Marx et al. 2000). In addition, reduced cardiac vagal activity is a predictor of high mortality and promotes progressive left ventricular structural remodeling (Lujan et al. 2014).

The mechanisms mediating the myocardial damage and cardiac dysfunction are high levels of sympathetic outflow and reduced parasympathetic outflow in response to chronic arterial pressure and cardiac volume unloading (Fig. 5.1).

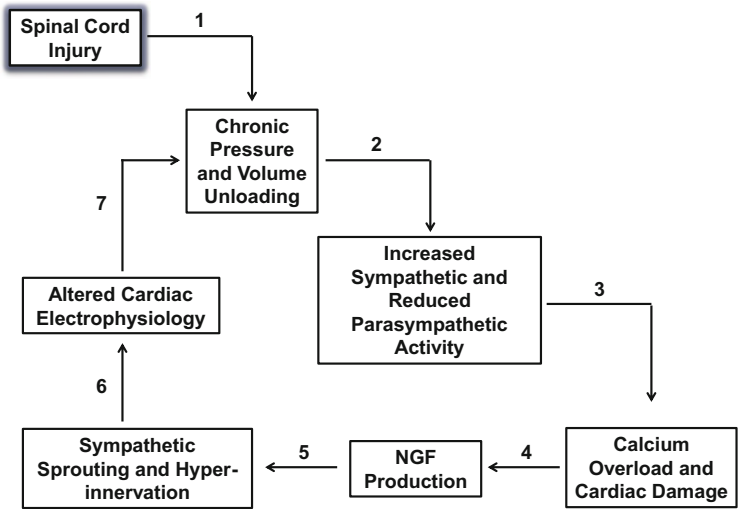

Fig. 5.1 Sequence of events by which spinal cord injury leads to myocardial damage and cardiac dysfunction. Spinal cord injury, with loss of vasoconstrictor tone below the level of the injury, results in: (1) chronic pressure and volume unloading which, (2) increases sympathetic and reduces parasympathetic activity. Together, this causes myocardial calcium overload and cardiac damage (3) and the production of nerve growth factor (NGF) (4). Nerve growth factor is responsible for the maintenance and proliferation of sympathetic nerves and causes sympathetic sprouting and hyperinnervation of the heart (5) which alters cardiac electrophysiology (6) and contributes to chronic pressure and volume unloading (7)

The chronic arterial pressure and cardiac volume unloading results from a rapid and sustained reduction in both mean arterial pressure and end-diastolic volume secondary to the loss of sympathetic vasoconstrictor tone below the level of the injury (West et al. 2014; Teasell et al. 2000). Specifically, the loss of descending sympathetic drive to the vasculature innervated below the level of the spinal cord injury results in hypotension which initiates a dramatic baroreflex-mediated increase in sympathetic outflow and decrease in parasympathetic outflow to the heart. These high levels of sympathetic outflow and reduced parasympathetic outflow following SCI have been reported to induce calcium overload (Sharov and Galakhin 1984), left ventricular dysfunction, cardiac injury and ST-segment elevation (Morita et al. 2010). In response to the cardiac injury, nerve growth factor (NGF) is produced by either the injured myocardium or lymphocytes recruited to the site of injury and induces sympathetic sprouting and hyper-innervation of the heart (Levi-Montalcini 1976).

Thus, a dynamic interaction between a target tissue and its innervation is required for optimal functioning (Purves et al. 1988; Voyvodic 1989; Lujan et al. 2012). Changes in target tissue function are associated with NGF induced neuroplasticity in autonomic pathways regulating target organ function (de Groat et al. 1990; Steers et al. 1990). For example, bladder enlargement and smooth muscle hypertrophy produced by anatomical or functional obstruction of the bladder outlet are associated with NGF-induced morphological and neuroplasticity in the pathways regulating micturition (de Groat et al. 1990; Steers et al. 1990). Similarly, SCI-induced cardiac dysfunction is associated with increased cardiac and stellate ganglion NGF content and sympathetic neuroplasticity in the heart, stellate ganglia and spinal cord (Lujan et al. 2009, 2010a, 2012). This sympathetic neuroplasticity (pathological neuroplasticity) markedly alters cardiac electrophysiology and increases the susceptibility to cardiac rhythm disorders. Exercise may exert a cardio-protective effect via an increased plasma volume, increased venous return and a subsequent volume loading of the heart, which in turn maintains contractile function, arterial pressure and reduces autonomic remodeling (Lujan and DiCarlo 2014).

5.4 Altered Autonomic Control of the Heart and Vasculature Following SCI

It is now widely accepted that sympathetic activity is elevated and parasympathetic activity is reduced above the level of the injury in individuals with mid-thoracic SCI and the regulation of heart rate and cardiac function is abnormal and unstable (Collins et al. 2006; Lujan et al. 2012). Specifically, mid-thoracic SCI is associated with an enhanced sympathetic support of heart rate and cardiac function as suggested by the observation that following blockade of the sympathetic nervous system, heart rate and cardiac function are markedly lower in rats with mid-thoracic

SCI compared with sham-operated intact rats (Lujan et al. 2009; Rodenbaugh et al. 2003a). These data document a distinct cardiac dysfunction and enhanced reliance on the sympathetic nervous system to maintain cardiac function following mid-thoracic SCI. Importantly, chronic elevations of sympathetic activity and reduced parasympathetic activity have profound long term deleterious effects on cardiac performance and electrophysiology (Billman 2009).

The altered autonomic control of cardiac electrophysiology and function appears initiated by the arterial baroreceptors. Arterial baroreceptors, located in the aortic arch and carotid sinuses, have a profound influence on cardiac rate, performance and rhythm by reflexly altering cardiac sympathetic and parasympathetic activity. The arterial baroreceptors respond to a reduction in arterial pressure by reflexly decreasing activity of the parasympathetic division and reflexly increasing activity of the sympathetic division of the autonomic nervous system. In contrast, the arterial baroreceptors respond to an increase in arterial pressure by reflexly increasing activity of the parasympathetic division and reflexly decreasing activity of the sympathetic division of the autonomic nervous system. Arterial pressure is abnormal and unstable after spinal cord injury. Hypotension occurs immediately after the injury because of loss of tonic supra-spinal excitatory drive to spinal sympathetic neurons (Calaresu and Yardley 1988). Subsequently resting arterial pressure returns towards normal, but remains low, and episodic bouts of hypertension often develop as part of the condition termed autonomic dysreflexia (AD) (Mathias and Frankel 1992; Naftchi 1990). Furthermore, activities of daily living produce large variations of blood pressure and orthostatic hypotension can become a significant problem for individuals with SCI (Stiens et al. 1995; Faghri et al. 2001). This is due, in part, to a reduced arterial baroreflex control of the autonomic nervous system. Specifically, baroreflex control of the sympathetic nervous system is lost below the level of the injury. In this setting, there is reduced buffering of changes in arterial pressure. Accordingly, individuals and animals with SCI have increased blood pressure variability (Rodenbaugh et al. 2003b). Importantly, increased blood pressure variability significantly increases the incidence of blood pressure related cardiovascular disease risk factors (Rizzoni et al. 1992; Stevenson et al. 1997; Julius and Valentini 1998). Blood pressure related cardiovascular disease risk factors include elevated systolic and diastolic blood pressure variability, increased standard deviation of individual blood pressure recordings,(Rizzoni et al. 1992; Stevenson et al. 1997) and elevated heart rate (Julius and Valentini 1998). These blood pressure related cardiovascular disease risk factors are highly correlated with end organ damage, as well as vascular structure changes and an increased incidence of myocardial infarction, stroke and cardiac arrhythmias (Frattola et al. 1993; Palatini and Julius 1997, 1999; Stamler et al. 1993). The increased blood pressure variability mediates highly erratic changes in arterial baroreceptor activity which unpredictably alters cardiac sympathetic and parasympathetic activity and profoundly affects cardiac rate, performance and rhythm. Taken together, these data suggest that enhanced tonic activity of the arterial baroreflex control of the autonomic nervous system above the level of the injury and the loss of arterial baroreflex control below the level of the injury initiates cardiac damage, increases

arterial blood pressure variability and contributes to the unstable regulation of arterial pressure and cardiac function.

5.5 Altered Cardiac Electrophysiology Following SCI

The autonomic nervous system affects cardiac electrophysiology over seconds to minutes. In particular, the sympathetic division of the autonomic nervous system affects cardiac electrophysiology by activating α- and β-adrenergic receptors. β-Adrenergic receptor stimulation, which increases intracellular cAMP levels, increases heart rate, atrial-ventricular (A-V) nodal conduction, and contractile force and shortens atrial and ventricular refractoriness. β-Adrenergic receptor stimulation enhances the plateau phase of the action potential by increasing current through L-type Ca^{2+}channels, while repolarization is accelerated due to an increase in both the delayed cardiac rectifier K^+ current and the Cl^- current. Thus β-adrenergic receptor stimulation may shorten or prolong action potential duration depending on whether effects on Ca^{2+} currents or K^+/Cl^- currents predominate. β-Adrenergic receptor stimulation also causes more rapid pacemaker activity in the sinus node by increasing the rate of the pacemaker current to positive potentials. In addition, α-adrenergic receptor stimulation enhances cardiac contractility due to Ca^{2+} influx. Furthermore, α-adrenergic stimulation enhances the development of after-depolarizations and triggered beats. In this situation, multiple ionic mechanisms are involved, and elevated intracellular Ca^{2+}concentration is a common feature. α-adrenergic stimulation also results in reduction of the electrical stimulus threshold to induce ventricular fibrillation as well as increased likelihood of spontaneous ventricular arrhythmias. β-Adrenergic receptor blockade and enhanced parasympathetic tone inhibit these effects and are known to be protective against ventricular arrhythmias and sudden death (Engel 1978; Schwartz et al. 1993; Wharton et al. 1992; Zipes 1991).

Sympathetic signals also alter cardiac electrophysiology over the time course of hours by affecting the expression and abundance of cardiac Ca^{2+}regulatory proteins. Specifically, previous reports have documented that adrenergic receptor stimulation enhances the expression of the Na^+/Ca^{2+} exchanger in vivo and in vitro (Golden et al. 2000, 2001). For example, Na^+/Ca^{2+} exchanger message and protein abundance were increased in the presence of the β-adrenergic receptor agonist isoproterenol (Golden et al. 2000). The authors also demonstrated a functional significance for the β-adrenergic receptor-mediated increase in the Na^+/Ca^{2+} exchanger. That is, the increased expression of the Na^+/Ca^{2+} exchanger was associated with an increase in the amplitude (indicating an increased activity of the L-type calcium channel) and decay rate (indicating an enhanced rate of intracellular calcium removal and/or sequestration) of the Ca^{2+} transient. Adrenergic receptor stimulation, via cAMP-dependent pathways, also regulates the function and expression of phospholamban and sarco/endoplasmic reticulum $Ca2^+$-ATPase (SERCA) (Muller et al. 2003). Specifically, cAMP response-element modulators

regulate the expression of SERCA, whereas cAMP-dependent phosphorylation of phospholamban directly affects SERCA function (Muller et al. 2003). Thus multiple adrenergic receptor-stimulated cAMP pathways may be affecting the abundance as well as the function of the Ca^{2+} regulatory proteins.

Importantly, there is substantial evidence to document increased sympathetic activity above a mid-thoracic spinal cord injury (Maiorov et al. 1997; Rodenbaugh et al. 2003a). For example, paraplegia increases cardiac sympathetic tonus in rats (Rodenbaugh et al. 2003a; Lujan et al. 2009). Furthermore, paraplegic rats (Mayorov et al. 2001; Rodenbaugh et al. 2003a, b; Lujan et al. 2009; Lujan and DiCarlo 2007) and humans (Davis and Shephard 1988; Jacobs et al. 2002; Kinzer and Convertino 1989) have elevated heart rates.

As discussed, individuals with mid-thoracic SCI have enhanced sympathetic outflow and reduced parasympathetic outflow above the level of the injury. Furthermore, mid-thoracic SCI results in the loss of arterial baroreflex control below the level of the injury. Together, these responses following SCI mediate an erratic, abnormal and unstable autonomic control of the heart and vasculature. Importantly, autonomic control of the heart has a profound influence on cardiac electrophysiology. Accordingly, Rodenbaugh et al. (2003c) examined the intrinsic excitability and conductive properties of the heart following mid-thoracic SCI. Specifically, the investigators recorded the atrio-ventricular interval, sinus cycle length, sinus node recovery time (SNRT), SNRT corrected for spontaneous sinus cycle, Wenckebach cycle length, the ventricular effective refractory period and the electrical stimulation threshold to induce sustained ventricular tachy-arrhythmias in intact and spinal cord injured rats. This was an important investigation because cardiac electrophysiological dysfunction is a major cause of death in humans and electrophysiological testing is routinely performed to evaluate arrhythmias and disorders of cardiac conduction. Mid-thoracic SCI reduced the atrio-ventricular interval (−25 %), sinus cycle length (−24 %), sinus node recovery time (−28 %), sinus node recovery time corrected for heart rate (−53 %) and Wenkebach cycle length (−18 %,). The reduced cardiac electrophysiology parameters were also associated with a reduced electrical stimulation threshold to induce ventricular arrhythmias (−48 %,). In this study, rats with mid-thoracic SCI also had significantly higher heart rates.

The altered cardiac electrophysiology parameters were also associated with alterations in the abundance of cardiac calcium regulatory proteins (Rodenbaugh et al. 2003c). Specifically, mid-thoracic SCI increased the relative protein expression of SERCA2 (45 %) and the Na^{+}/Ca^{2+} exchanger (40 %), whereas relative protein expression of phospholamban was significantly decreased (−28 %). It is well documented that reductions in phospholamban and/or increases in SERCA protein abundance result in an increased sarco(endoplasmic) reticulum calcium load (Ji et al. 2000). The sarco(endoplasmic) reticulum calcium overload may produce spontaneous calcium releases, thereby leading to ectopic activity. Accordingly, as mentioned, these changes in calcium regulatory proteins were associated with a reduced electrical stimulation threshold to induce ventricular arrhythmias (−48 %).

5.6 Autonomic Neuroplasticity Following SCI

When the spinal cord is injured at the mid-thoracic level, cardiovascular control is markedly unbalanced as the heart and blood vessels innervated by upper thoracic segments remain under brain stem control, whereas the vasculature of the lower body is affected by unregulated spinal reflexes. Accordingly, the regulation of heart rate and cardiac function is abnormal and unstable after mid-thoracic SCI because sympathetic outflow to the heart is increased while parasympathetic outflow to the heart is decreased. The increased sympathetic outflow is attributable to multiple mechanisms including an increased cardiac sympathetic innervation density, altered morphology of stellate ganglia sympathetic post-ganglionic neurons, and structural neuroplasticity of cardiac sympathetic preganglionic neurons (SPNs) in spinal cord segments T_1-T_5 (Lujan et al. 2009, 2010a, 2012). Furthermore, these neuroplastic changes associated with SCI are mediated by nerve growth factor (NGF). NGF is a neurotrophin that supports the survival and differentiation of sympathetic neurons and enhances target innervation (Levi-Montalcini 1976). Thus, stellate ganglia-projecting sympathetic pre-ganglionic neurons within spinal segments T_1-T_5 as well as cardiac projecting sympathetic post-ganglionic neurons within the stellate ganglia from rats with mid-thoracic SCI have larger dendritic trees than uninjured rats (Lujan et al. 2009, 2010a). The hearts of rats with mid-thoracic SCI are also hyper-innervated by tyrosine hydroxylase (TH)-immunoreactive sympathetic axons (Lujan et al. 2010a). These neuroplastic changes are associated with increased nerve growth factor content within the heart and stellate ganglia (Lujan et al. 2009, 2012).

Mid-thoracic SCI is also associated with reduced cardiac parasympathetic activity (Lujan et al. 2009). Reduced cardiac parasympathetic activity is a predictor of high mortality. Furthermore, parasympathetic dysregulation promotes progressive left ventricular structural remodeling (Sabbah et al. 1994, 2000). Importantly, mid-thoracic SCI is associated with structural neuroplasticity in pre-motor (pre--ganglionic parasympathetic neurons) cardio-inhibitory vagal neurons located within the nucleus ambiguus as well as left ventricular structural remodeling (Lujan et al. 2014). Specifically, following mid-thoracic SCI, there was a significant increase in cardiac parasympathetic pre-ganglionic neuron dendritic arborization, soma area, maximum dendritic length, and number of intersections/animal (Fig. 5.2) (Lujan et al. 2014). This parasympathetic structural remodeling was associated with a profound left ventricular structural remodeling. Specifically, mid-thoracic SCI increased left ventricular chamber area, reduced left ventricular wall thickness, and increased collagen content (Fig. 5.3) (Lujan et al. 2014).

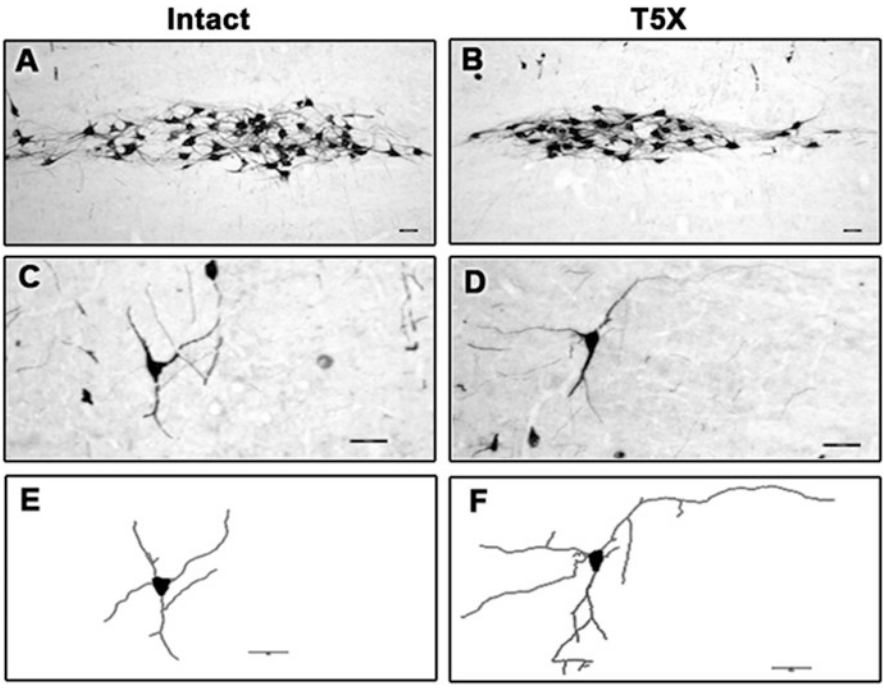

Fig. 5.2 Spinal cord injury (T5X) increased the dendritic arborization of cardioinhibitory vagal neurons located within the nucleus ambiguus projecting to the heart. Scale bar, 50 μm. From: Lujan HL, Janbaih H, DiCarlo SE. Structural remodeling of the heart and its premotor cardioinhibitory vagal neurons following T(5) spinal cord transection. *J Appl Physiol* (1985). 2014 May 1;116(9):1148–55

5.6.1 Incidence of Cardiac Arrhythmias Among Individuals with SCI

The incidence of cardiac arrhythmias among individuals with SCI remains unclear. Many reasons account for this lack of clarity including the fact that most studies did not use continuous methods to record heart rate or the electrocardiogram (Hector et al. 2013). In addition to the short duration of assessment, nearly all evaluations were conducted during resting conditions and in the absence of provocative procedures. The influence of medications, prior incidence of cardiovascular disease and the recurring and cyclic nature of autonomic dysreflexia may also contribute to the uncertainty. Accordingly, there is a potential of underestimating the incidence of arrhythmic events among individuals with SCI. Despite these limitations,

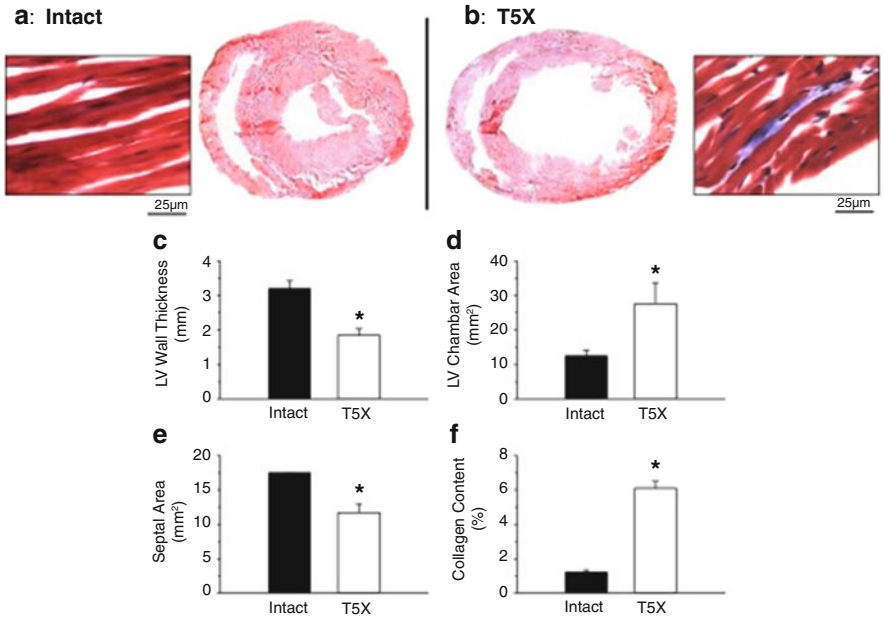

Fig. 5.3 Spinal cord injury (T5X) reduced left ventricular (LV) wall thickness and septal area and increased LV chamber area and collagen content. *$P \leq 0.05$, intact vs T5X. From: Lujan HL, Janbaih H, DiCarlo SE. Structural remodeling of the heart and its premotor cardioinhibitory vagal neurons following T(5) spinal cord transection. *J Appl Physiol* (1985). 2014 May 1;116 (9):1148–55

bradycardia and brady-arrhythmias are frequently seen in the acute period after cervical SCI and are usually self-limiting after a few weeks (Hector et al. 2013; Bartholdy et al. 2014).

During the chronic period after SCI, reports suggest that cardiac arrhythmias are not more common among individuals with SCI than among able-bodied individuals (Hector et al. 2013; Bartholdy et al. 2014). However, provocative stimuli (e.g. tracheal suction, tracheal intubation, or penile vibro-stimulation), often elicit a variety of cardiac arrhythmias. Notwithstanding these clinical reports, experimental studies in rats document an increased susceptibility to ventricular arrhythmia induced by programmed electrical stimulation (Rodenbaugh et al. 2003a, c), myocardial ischemia induced by coronary artery occlusion (Lujan et al. 2009) and reperfusion (Lujan and DiCarlo 2007).

5.7 Susceptibility to Ventricular Arrhythmias Following SCI

It is well documented that the autonomic nervous system modulates cardiac electrophysiology and that abnormalities of autonomic function can increase the risk of ventricular arrhythmias. It is also well known that autonomic control of the cardiovascular system is abnormal and unstable following spinal cord injury. For example, individuals with paraplegia have elevated heart rates, increased blood pressure variability, episodic bouts of life threatening hypertension as part of a condition termed autonomic dysreflexia, and elevated sympathetic activity and reduced parasympathetic activity above the level of the lesion. Furthermore, cardiovascular morbidity and mortality are high in individuals with spinal cord injuries due, in part, to a relatively sedentary life style and higher prevalence of other cardiovascular disease risk factors, including obesity and diabetes.

Accordingly, two early reports tested the effect of mid-thoracic SCI on the susceptibility to ventricular arrhythmias (Rodenbaugh et al. 2003a, c). In the first study, conscious female hypertensive rats with mid-thoracic SCI had a significantly lower electrical stimulation threshold to induce ventricular arrhythmias compared to intact rats. Specifically, the intensity of current required to cause a ventricular arrhythmia was 62 % lower in injured rats compared with intact rats. Associated with the increased susceptibility to ventricular arrhythmias was a significantly higher resting heart rate and cardiac sympathetic tonus. Triggered beats occur more frequently in the presence of increased heart rate (Rosen and Reder 1981). Elevated sympathetic activity also elevates intracellular calcium which closes gap junctions decreasing cell-to-cell coupling and thereby decreasing action potential conduction directly provoking arrhythmias. In a subsequent study, similar results were obtained in normotensive rats with mid-thoracic SCI (Rodenbaugh et al. 2003c).

These early studies induced ventricular arrhythmias via a non-physiological mechanism using programmed electrical stimulation. Importantly, arrhythmias induced by programmed electrical stimulation do not predict the risk of ventricular fibrillation or the effectiveness of anti-arrhythmic agents (Bourke et al. 1995; Spector 2005). Accordingly, subsequent studies demonstrated that rats with mid-thoracic SCI also have an increased susceptibility to ventricular arrhythmias induced by myocardial ischemia and reperfusion. Specifically, mid-thoracic SCI increased the susceptibility to ischemia-induced (Fig. 5.4) as well as ischemia/reperfusion-induced sustained ventricular tachycardia in rats with mid-thoracic SCI (Lujan et al. 2009; Lujan and DiCarlo 2007) (Fig. 5.5). The increased susceptibility to the life-threatening arrhythmia was prevented with cardiac β_1-adrenergic receptor blockade, documenting that increased sympathetic activity mediates, in part, the increased risk.

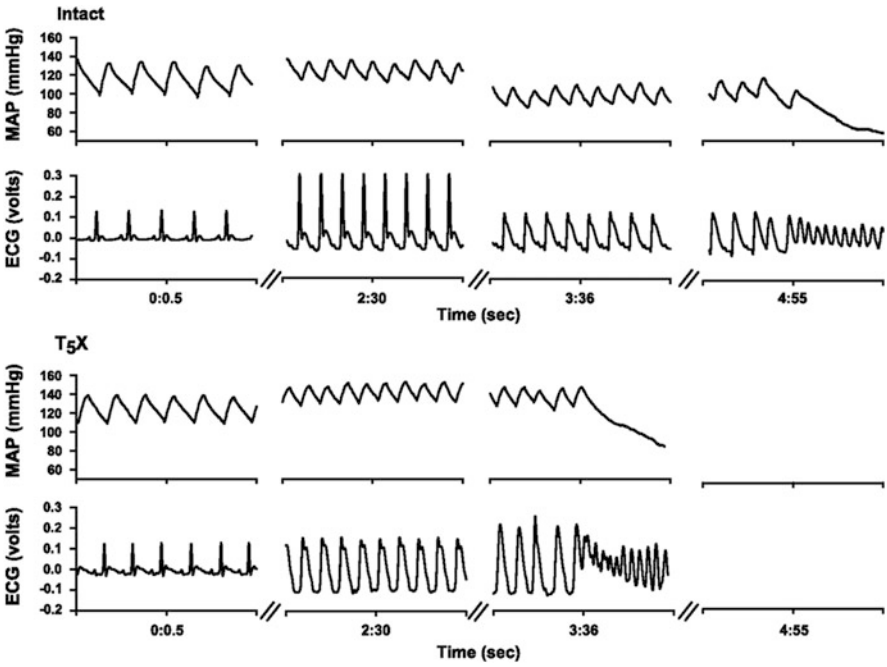

Fig. 5.4 Spinal cord injury (T5X) reduced the ventricular arrhythmia threshold induced by coronary artery occlusion. In this example, sustained ventricular tachycardia and reduction in arterial pressure occurred at 3 min 36 s in the T5X rat compared with 4 min 55 s in the intact rat. From: Lujan HL, Chen Y, DiCarlo SE. Paraplegia increased cardiac NGF content, sympathetic tonus, and the susceptibility to ischemia-induced ventricular tachycardia in conscious rats. *Am J Physiol Heart Circ Physiol*. 2009 May;296(5):H1364–72

5.8 Implications for Exercise Following SCI

Arm cycling exercise is an important therapeutic intervention to improve aerobic capacity, functional capabilities and alter the autonomic control of the heart and circulation of individuals with SCI (Huonker et al. 1998; Washburn and Figoni 1998; DiCarlo 1982, 1983, 1988). These therapeutic effects are mediated, in part, to an increase in plasma volume, venous return, and cardiac function as well as an increase in parasympathetic efferent activity and decrease in sympathetic efferent activity (Scheuer and Tipton 1977; Tipton 1991; Chen and DiCarlo 1997; Stone and Liang 1984; Stone et al. 1985; DiCarlo et al. 1989; DiCarlo and Bishop 1999). These multiple adaptations are critical for reducing the incidence of cardiovascular disorders (Goldberg 1989). This is an important consideration because cardiovascular disease is now the leading cause of death and morbidity for individuals with SCI. Furthermore, individuals with SCI have a threefold greater risk of developing cardiovascular disease than their able-bodied counterparts (Garshick et al. 2005; Cragg et al. 2013; Cowan and Nash 2010). Accordingly, regular exercise has the

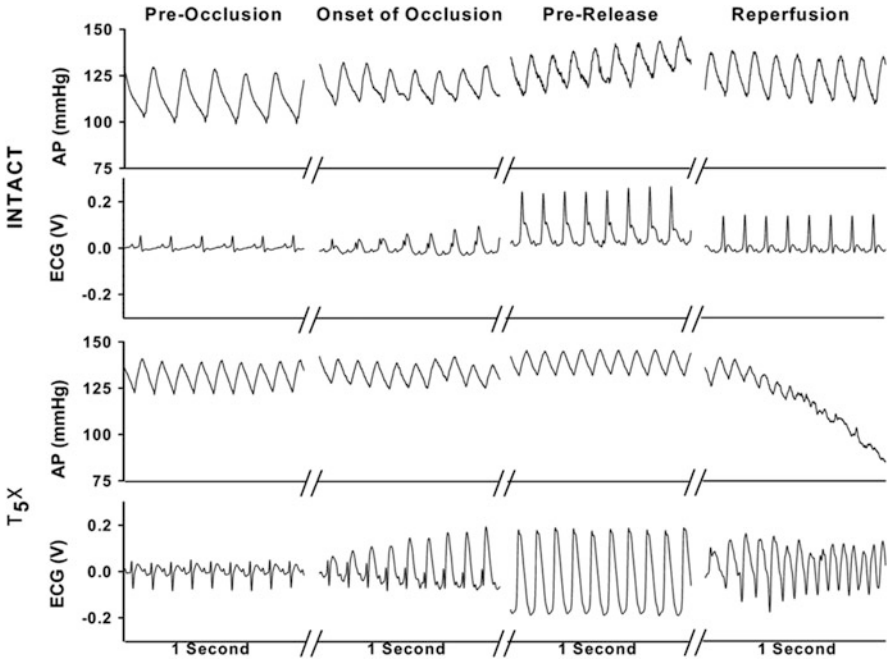

Fig. 5.5 Spinal cord injury (T5X) increased the incidence of reperfusion induced ventricular tachycardia. In this example, reperfusion failed to induce ventricular tachycardia in intact rats; however, reperfusion in the T5X rat resulted in sustained ventricular tachycardia and a reduction in arterial pressure. From: Lujan HL, DiCarlo SE. T5 spinal cord transection increases susceptibility to reperfusion-induced ventricular tachycardia by enhancing sympathetic activity in conscious rats. *Am J Physiol Heart Circ Physiol*. 2007 Dec;293(6):H3333–9

potential to positively impact the leading cause of death and morbidity while improving the quality of life for individuals living with SCI.

Individuals with mid-thoracic SCI usually lose voluntary motor function below the level of the lesion. This limitation of voluntary motor function can lead to a relatively sedentary life style and a consequent reduction in physical work capacity, unless these individuals participate in strenuous wheelchair activities (Saltin et al. 1968; Knutsson et al. 1973; Pollock et al. 1974; Gass and Camp 1979; Ekblom and Lundberg 1967; DiCarlo 1982, 1988; DiCarlo et al. 1983). Other consequences of profound inactivity are a higher body weight, a higher percentage of body fat (Oscai 1973; Edwards et al. 2008; Gupta et al. 2006), skeletal muscle dysfunction (Glynn et al. 2008; Drummond et al. 2008; Fry et al. 2012) and a lower forced vital capacity than occur in sedentary able-bodied individuals (Zwiren and Bar-Or 1975; West et al. 2012b; Gupta et al. 2006). These factors also increase their risk of stroke (Oscai 1973; Morris et al. 1966; Ressl et al. 1977; Naughton and Hellerstein 1977), coronary heart disease (National Heart Institute 1966; Bauman and Spungen 2008), diabetes (Bauman et al. 1999) and, possibly death (Morris et al. 1966; Paffenbarger et al. 1970). Importantly, exercise has been documented to positively impact these risk factors in a large

variety of populations. Thus, individuals with spinal cord injuries tend to have a need for regular physical activity that is equal to or greater than the need of able-bodied individuals (Clausen et al. 1970; DiCarlo 1988; Huonker et al. 1998; Morganroth et al. 1975; Phillips et al. 2011; Stewart et al. 2004) and stand to benefit from exercise by reducing the risk factors associated with a sedentary lifestyle.

It is important to note that some investigators have questioned if the limited muscle mass and strength following SCI would prevent the adaptations associated with regular exercise (Gates et al. 2002; Nash and Jacobs 1998; West et al. 2012b; Davis et al. 1987). Specifically, some investigators questioned if individuals with SCI could reach the optimum threshold of exercise intensity required to induce a training adaptation. However, it is well documented that individuals with SCI, notwithstanding the limited muscle mass and strength available for training, obtain significant training adaptations (DiCarlo 1982, 1983, 1988; Knutsson et al. 1973; Oscai 1973; Huonker et al. 1998; Washburn and Figoni 1998). However, the position of the body during exercise may promote the therapeutic benefits of exercise (McLean and Skinner 1995) (see below).

5.9 Exercise and the Importance of Venous Return

Reduced activity of the skeletal muscle pump combined with impaired autonomic control of the circulation below the level of the injury can severely impact venous return and restrict cardiac output during arm cycling exercise. In this case, venous pooling can lead to a hypokinetic circulation (Glaser 1985; Glaser and Davis 1988). Accordingly, it seems reasonable to suggest that performing arm cycling exercise while in a supine position may promote venous return, improve cardiac output and increase the therapeutic effects of exercise (McLean and Skinner 1995). Furthermore, supine exercise with electrical stimulation to activate the skeletal muscle pump may provide an additional advantage. Other techniques have also been used to enhance venous return and increase stroke volume and cardiac output during arm cycling exercise including abdominal binders (Kerk et al. 1995), and fighter pilot anti-G suits (Hopman et al. 1992, 1993; Pitetti et al. 1994). These interventions would be expected to increase venous return, increase left ventricular pressure, increase cardiac output and arterial pressure and maintain contractile state. This strategy may also be effective for a number of other physiologic and environmental conditions (inactivity/bed rest/spaceflight, neurological diseases, myocardial infarction) that result in similar impairments in cardiac structure and function (West et al. 2012a; Helmi et al. 2013).

5.10 Exercise and Autonomic Dysreflexia

Individuals with mid-thoracic SCI often experience episodic bouts of life-threatening hypertension as part of the condition termed autonomic dysreflexia (AD) (Collins and DiCarlo 2002a, b; Mathias and Frankel 1992; Naftchi 1990). Autonomic dysreflexia occurs in as many as 85 % of individuals with lesions above thoracic level 6 (T_6) and is characterized by severe hypertension. The paroxysmal hypertension can be caused by noxious stimulation of the skin (Lujan et al. 2010b), distension of the urinary bladder or colon, and muscle spasms (Corbett et al. 1975; Mathias and Frankel 1983; Collins and DiCarlo 2002a, b; DiCarlo et al. 1995). If not treated promptly, the hypertension may produce cerebral and subarachnoid hemorrhage, seizures, and renal failure and may lead to death (McGuire and Kumar 1986). The long-term consequence of repeated episodes of severe hypertension has yet to be fully determined (Alan et al. 2010; Ashley et al. 1993).

Importantly, individuals with SCI are prone to cardiac arrhythmias during autonomic dysreflexia (Fig. 5.6) (Claydon et al. 2006; Forrest 1991; Pine et al. 1991; Guttmann et al. 1965; Collins and DiCarlo 2002b). This appears to be due, in part, to the fact that autonomic dysreflexia presents a unique stimulus to the heart such that sympathetic drive may be extremely high, and is coupled with high vagal tone through the arterial baroreflex (Courtois et al. 2004). Thus autonomic dysreflexia presents a particularly potent arrhythmic stimulus (Fig. 5.6) as sympathetic activation increases calcium transients (Bers 2002) whereas vagal activation reduces the effective refractory period (Zipes et al. 1974). The divergence between action potential duration and intracellular calcium transient, which are normally tightly coupled, increase the forward Na/Ca exchanger current, which contributes to the generation of arrhythmias (Patterson et al. 2006).

Forelimb exercise has been shown to be a safe therapeutic approach for attenuating the severity of autonomic dysreflexia in rats with mid-thoracic SCI. Although the mechanisms responsible for this therapeutic effect of exercise on autonomic dysreflexia has yet to be fully determined, one mechanism appears to be by reducing α-adrenergic receptor responsiveness (Laird et al. 2009; Collins and DiCarlo 2002a). Several investigators have demonstrated that a single bout of mild-to-moderate dynamic exercise significantly attenuates the post-exercise response to α-adrenergic receptor agonists (Halliwill et al. 1996; Howard and DiCarlo 1992; Howard et al. 1992; Patil et al. 1993; VanNess et al. 1996). As examples, a single bout of dynamic exercise significantly attenuated the post-exercise response to α-adrenergic receptor activation in the intact conscious rabbit (Howard and DiCarlo 1992), rat (Patil et al. 1993; VanNess et al. 1996), and human (Halliwill et al. 1996). These data suggest that the ability to increase peripheral vascular resistance or activate α-adrenergic receptor after exercise is significantly reduced.

Dynamic exercise may also be a countermeasure for autonomic dysreflexia by reducing sympathetic nerve activity because a single bout of mild-to-moderate dynamic exercise often lowers post-exercise sympathetic nerve activity in individuals and animals (DiCarlo et al. 1994; Halliwill 2001). Similarly, targeted ablation

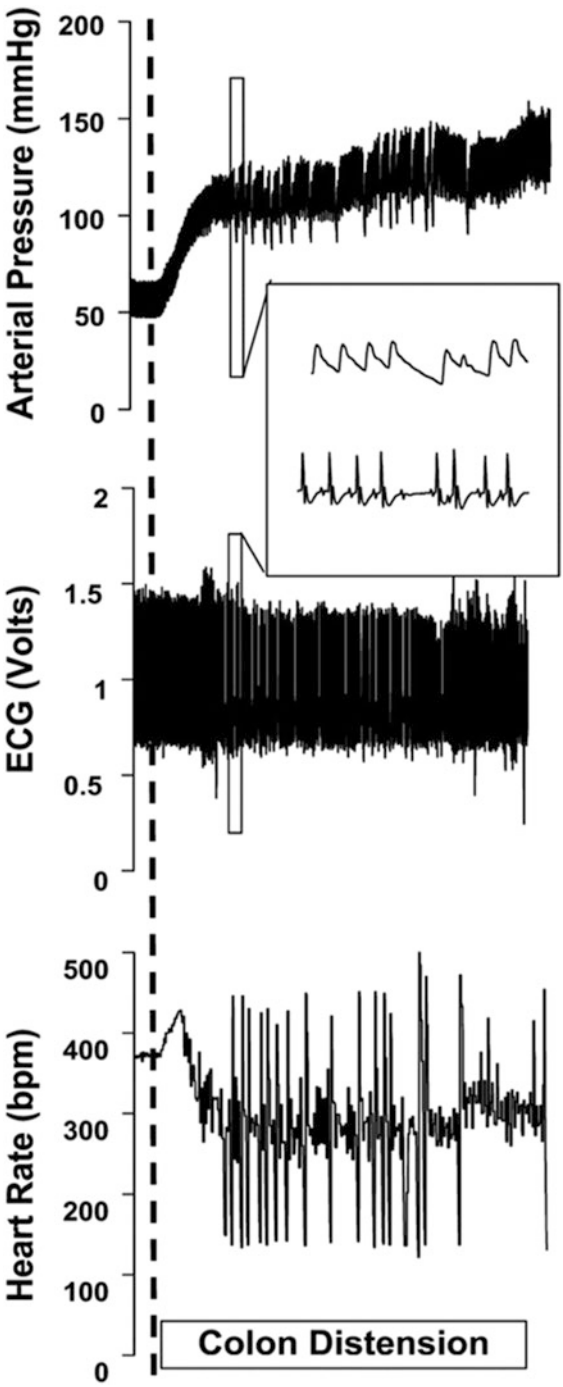

Fig. 5.6 Autonomic dysreflexia produced by colon distension induces cardiac dysrhythmias. In this example, colon distension produced pressor and bradycardic responses. Of interest are the arrhythmias produced by colon distension (shown in box). From: Collins HL, DiCarlo SE. TENS attenuates response to colon distension in paraplegic and quadriplegic rats. *Am J Physiol Heart Circ Physiol*. 2002 Oct;283(4):H1734–9

of mesenteric projecting sympathetic neurons also reduced the severity of autonomic dysreflexia by reducing sympathetic activity (Lujan et al. 2010b). A reduction in sympathetic nerve activity during autonomic dysreflexia would be expected to reduce the arterial pressure response to noxious stimuli below the level of the injury and reduce the arrhythmic environment. Furthermore, since α-adrenergic receptor stimulation enhances the development of after-depolarizations and triggered beats, reducing α-adrenergic receptor responsiveness post exercise may contribute to the anti-arrhythmic effects of exercise.

5.11 Summary and Integration

Individuals with mid-thoracic SCI have major deficits in motor, sensory and autonomic function that markedly impacts their quality of life and promotes pathological processes. The loss of volitional motor control below the level of the injury can lead to an extremely sedentary lifestyle with an increased incidence of secondary complications including diabetes, cardiovascular disease and an atherogenic lipid profile. Impairments in autonomic function, specifically the loss of descending sympathetic drive to the vasculature below the level of the spinal cord injury, results in hypotension and a dramatic baroreflex-mediated increase in sympathetic outflow and decrease in parasympathetic outflow to the heart (Moffitt 2010). This autonomic dysfunction induces myocardial damage which promotes NGF-induced sympathetic sprouting, hyper-innervation of the heart and pathological neuroplasticity in the autonomic ganglia, spinal cord and autonomic centers within the brainstem. Pathological neuroplasticity, following SCI, is associated with many lingering complications, such as chronic pain, spasticity, neurogenic bladder, and autonomic dysreflexia (Arnold et al. 1995; Brock et al. 2006; Brown and Weaver 2011; Fouad et al. 2001; Hill et al. 2001; Hou et al. 2008; Krassioukov and Weaver 1995; Krenz et al. 1999; Llewellyn-Smith and Weaver 2001; Ondarza et al. 2003; Pan et al. 2007; Seki et al. 2002; Yeoh et al. 2004; Llewellyn-Smith et al. 2007). Pathological neuroplasticity is also associated with an increased susceptibility to life-threatening ventricular arrhythmias (Figs. 5.4 and 5.5) (Lujan et al. 2009, 2010a; Lujan and DiCarlo 2007). Dynamic exercise may exert a protective effect via an increased plasma volume, venous return and a subsequent volume loading of the heart, which in turn maintains contractile function, arterial pressure and reduces autonomic pathological remodeling and neuroplasticity (Fig. 5.7) (Lujan and DiCarlo 2014; Teasell et al. 2000).

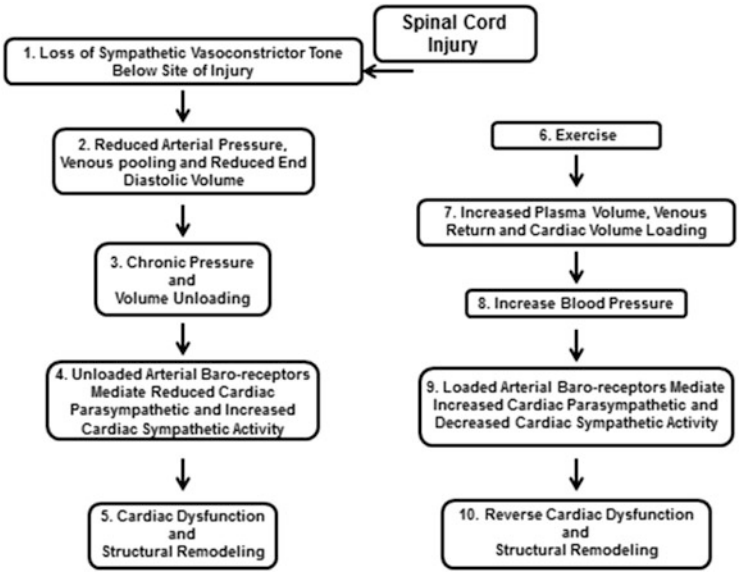

Fig. 5.7 Spinal cord injury results in: (1) Loss of sympathetic vasoconstrictor tone below the level of the injury which, (2) reduces arterial pressure, end diastolic pressure and causes venous pooling. Together, this causes chronic pressure and volume unloading (3), unloaded arterial baroreceptors with resultant reduced cardiac parasympathetic activity and enhanced cardiac sympathetic activity (4). All of which cause cardiac dysfunction and structural remodeling (5). Exercise (6), by increasing venous return, arterial pressure and cardiac volume loading (7–8) loads arterial baro-receptors and enhances cardiac parasympathetic activity and reduces cardiac sympathetic activity (9). As a result, cardiac dysfunction and structural remodeling are prevented or reversed (10). From: Lujan HL, DiCarlo SE. Increasing venous return as a strategy to prevent or reverse cardiac dysfunction following spinal cord injury. *J Physiol*. 2014 Apr 15;592(8):1727–8

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Chapter 6
Cardiovascular Responses to Exercise in Spinal Cord Injury

Thomas J. Barton, David A. Low, and Dick H.J. Thijssen

Abstract Spinal cord injury (SCI) has a significant impact on the structure and function of the cardiovascular system, typically leading to smaller sized vessels below the lesion and impairment of endothelial function throughout the body. These cardiovascular changes are primarily driven by a reduction in physical activity, supported by the ability to (at least partly) reverse these cardiovascular adaptations after (electrical stimulation-mediated) exercise training. This chapter provides an overview of the adaptations that occur in the cardiovascular system in SCI individuals, involving the heart, conduit, resistance and (skin and muscle) microvessels. These changes to the cardiovascular system have significant impact on the cardiovascular responses to exercise. For example, the inability of paralyzed muscles to pump back blood, pooling of blood in the veins and impaired blood redistribution contribute to a reduced return of blood to the heart. The ability of the heart to pump out large quantities of blood is vital when performing exercise. Therefore, an impaired return of blood will significantly affect the ability of SCI individuals to perform exercise. The ability to perform exercise is further compromised in SCI individuals who have disturbed cardiac innervation, which impairs the ability to increase heart rate during exercise. This chapter summarized the work related to the cardiovascular responses to exercise in subjects with a SCI, and how this affects the ability to perform exercise.

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6.1 Impact of a Spinal Cord Injury on the Cardiovascular System

Mortality rates after a spinal cord injury (SCI) are elevated by as much as 47 % compared to the able-bodied (AB) population, with cardiovascular disease (CVD) being a leading cause of all-cause mortality (Garshick et al. 2005). A first logical explanation for this observation relates to changes in cardiovascular risk factors. However, several studies found that those with SCI and AB individuals demonstrate no differences in the presence of traditional CVD risk factors, such as blood glucose, cholesterol and triglycerides (Bauman et al. 1999; Bauman and Spungen 1994; Jones et al. 2004; Liang et al. 2007). Therefore, increased risk for CVD in the population of individuals with SCI is unlikely explained through traditional cardiovascular risk factors. An alternative explanation resides in the concept that a SCI has a direct impact on the cardiovascular system. The (partial) loss of motor function after a SCI results in lower limb deconditioning and extreme physical inactivity below the level of the lesion. As a result, arteries show marked remodeling and changes in vascular function, both below and above the level of the lesion. These detrimental effects of lower limb physical inactivity on cardiac and vascular structure and function may contribute to the increased risk for CVD in SCI.

In this chapter, we discuss the impact of extreme lower limb physical inactivity in individuals with SCI on structural and functional changes in the heart, conduit arteries, resistance vessels, and the microcirculation. These changes are clinically relevant as they may contribute to the increased CVD risk in individuals with SCI. Furthermore, we discuss the impact of these cardiovascular adaptations on cardiac, hemodynamic and vascular responses to exercise in individuals with SCI. The altered hemodynamic responses to exercise may lead to an impaired ability of individuals with SCI to perform exercise, further contributing to a physically inactive lifestyle and increased cardiovascular risk.

6.1.1 Cardiac Function and Structure

Cardiac Structure The heart is highly adaptable and is subject to morphological changes in response to different loading conditions. Several studies have described the presence of myocardial hypertrophy in response to prolonged periods of (extensive) exercise training, both related to resistance and endurance training (Pluim et al. 2000). Opposite to these changes, prolonged physical inactivity in AB subjects, such as spaceflight (Perhonen et al. 2001) and bed rest (Levine et al. 1997; Perhonen et al. 2001), decrease myocardial size and mass. In line with these changes, individuals with SCI demonstrate smaller cavity sizes and mass compared to AB controls (de Groot et al. 2006b; Kessler et al. 1986; West et al. 2012b). More specifically, a significant reduction in left ventricle (LV) mass and chamber dimensions are found in individuals with SCI (de Groot et al. 2006b; West et al. 2012b).

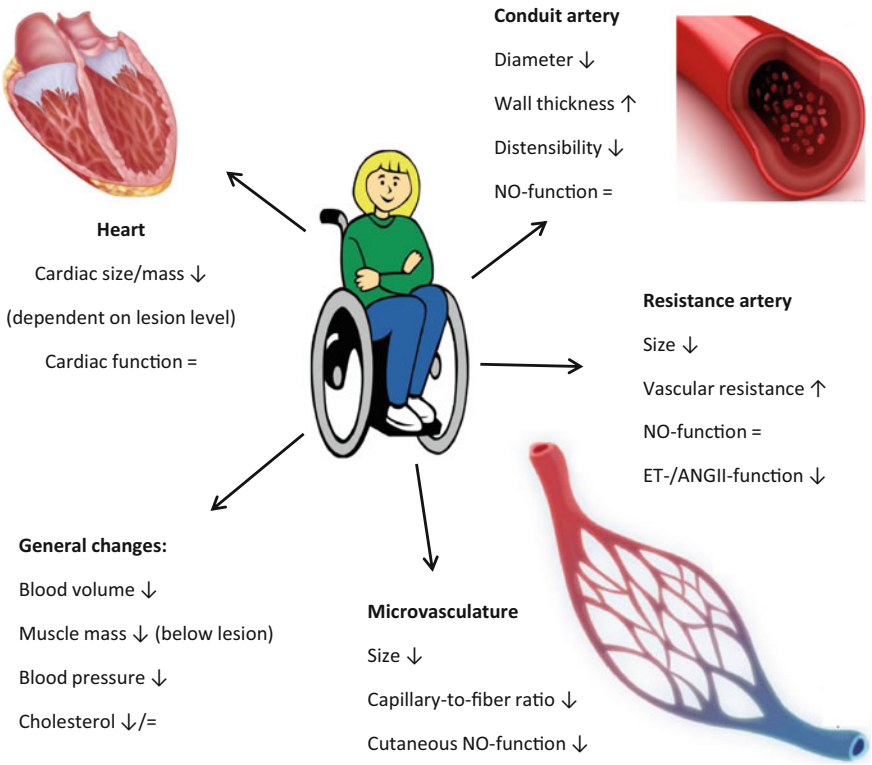

Fig. 6.1 Cardiovascular consequences of SCI

The explanation for this remodeling likely relates to changes in cardiac workload. Due to paralyses of lower limb muscles only a relatively small upper limbs muscle mass is available to perform exercise, leading to a small cardiac workload. Furthermore, those with SCI show reductions in total blood volume and hemoglobin mass, and increased venous pooling below the injury (Houtman et al. 2000). These findings, coupled with an inactive skeletal muscle pump, impair venous return and cardiac preload in SCI. These hemodynamic changes (West et al. 2012b) likely further contribute to remodeling of the heart in individuals with SCI (Fig. 6.1).

Cardiac Function In the face of chronic pressure and volume unloading, myocardial wall stress is significantly diminished in individuals with SCI. As a result, one may also expect changes in cardiac function. However, previous studies provide little evidence to support that measures of LV function, such as ejection fraction, are altered after a SCI. Doppler echocardiographic measurements of mitral inflow velocities, determined by the early LV relaxation (E-wave) and the subsequent contribution of atrial contraction (A-wave), are popular indices of diastolic function (i.e. E/A wave velocity). No difference in diastolic function is present when comparing SCI to AB controls (de Groot et al. 2006b; West et al. 2012b,

2014). Similarly, systolic function and overall ventricular performance, quantified by ejection fraction (EF), end-systolic volume (ESV) and peak systolic pressure/end-systolic volume (PSP/ESV) ratio, do not differ between those with SCI and ambulatory controls (de Groot et al. 2006b; Kessler et al. 1986; West et al. 2012b). These results of preserved cardiac function may indicate that structural remodeling of the heart after a SCI likely represent a normal physiological response to maintain myocardial function (Fig. 6.1).

6.1.2 Vascular Structure

Conduit Arteries Conduit arteries are large compliant vessels, responsible for supplying blood to the internal organs and limbs. These arteries have important distensible properties giving them the ability to expand and provide a low resistance vessel for blood. Models of extreme physical inactivity, such as bed rest (Bleeker et al. 2005b; van Duijnhoven et al. 2010a), leg casting (Sugawara et al. 2004), lower limb suspension (Bleeker et al. 2005a) and SCI (De Groot et al. 2003, 2004b, 2006a), result in a marked decrease in femoral arterial lumen diameter. Examining the impact of physical inactivity on conduit artery remodeling, changes in diameter turn out to be specific for arteries supplying the inactive areas. For example, unilateral limb suspension causes a decrease in femoral artery in the suspended leg, but not in the weight-bearing limb (Bleeker et al. 2005a). Similarly, bed rest causes a marked decline in artery diameter in the lower limbs, whilst conduit artery diameter of the upper limbs is largely unaffected (van Duijnhoven et al. 2010a). Interestingly, changes in conduit artery diameter are strongly linked to the size of the muscle mass that it supplies. Indeed, a 37 % reduction in femoral artery diameter was found in those with SCI relative to AB controls (Olive et al. 2003). However, when femoral artery diameter was expressed per unit of muscle volume, no differences were apparent between groups. Even changes in femoral artery diameter and upper limb volume seem to follow a similar path during the first 6 weeks after a SCI, since no changes were observed when arterial diameter was corrected for limb volume changes.

Conduit arterial wall thickness (WT), measured in both carotid and peripheral arteries, is commonly recognized as a surrogate marker for atherosclerosis severity and has strong predictive value for future cardiovascular events (de Groot et al. 2004a; Lorenz et al. 2007; Simon et al. 2010). Remodeling of conduit arterial WT is an apparent response to physical (in)activity and is well established in both AB subjects after prolonged periods of severe physical inactivity (i.e. bed rest) (Rowley et al. 2011, 2012) and in individuals with SCI (Bell et al. 2011; Matos-Souza et al. 2009; Paim et al. 2013; Rowley et al. 2012). For example, 60 days of bed rest in AB subjects resulted in a significant increase in carotid and superficial femoral artery wall thickness (van Duijnhoven et al. 2010a), strongly supporting the presence of a systemic impact of physical inactivity on conduit artery wall thickness. The ability to partly prevent this increase in wall thickness through (resistive)

exercise training highlights the importance of physical inactivity to mediate these changes in wall thickness. In parallel, individuals with SCI demonstrate larger carotid intima media thickness relative to controls (Matos-Souza et al. 2009). Taken together, physical inactivity is a potent stimulus for remodeling of conduit arteries, leading to a smaller artery diameter and thicker walls.

Repeated increases in blood flow represent a key stimulus for vascular adaptation. Studies in animals (Langille and O'Donnell 1986; Tuttle et al. 2001), but also in humans (Hambrecht et al. 2003; Tinken et al. 2010), show that elevations in blood flow and shear stress are required for improvement in vascular function and outward remodeling of arteries. For example, we examined the impact of bilateral handgrip exercise training (8-weeks) on vascular function and structure. Using a blood pressure cuff, we unilaterally attenuated the increase in shear stress during each handgrip exercise bout. Adopting this within-subject design, 8 weeks of bilateral handgrip exercise training resulted in significant, time-dependent changes in vascular function and structure of the brachial artery in the non-cuffed arm. In contrast, exercise training-related adaptations were non-existent in the cuffed arm. The importance for elevations in shear stress in individuals with SCI was indirectly demonstrated by a cross-sectional comparison of conduit artery size between sedentary paraplegics and athletes with paraplegia (Huonker et al. 1998). The athletes demonstrated a significantly larger subclavian artery cross-sectional area, which is most likely a direct result from the intensive wheelchair training and repeated exposure to higher shear stress (Huonker et al. 1996). Despite the large training volume, blood flow only marginally changes in the lower limbs during arm crank exercise (Thijssen et al. 2009b). Accordingly, sedentary wheelchair users and wheelchair athletes both possessed a similarly reduced femoral artery diameter relative to AB individuals, supporting the presence of local adaptations in conduit artery diameter that are most likely linked to changes in shear stress.

In contrast to changes in diameter, little evidence supports a direct role of repeated elevations in shear stress to mediate changes in conduit artery wall thickness. Subjects that underwent 60 days of bed rest were able to largely prevent changes in wall thickness through exercise training in both the femoral and carotid arteries, whilst exercise only minimally influences carotid artery blood flow and shear rate (van Duijnhoven et al. 2010a). Furthermore, a significantly smaller carotid and femoral WT was found in physically active individuals with SCI compared to their sedentary peers (Jae et al. 2008; Paim et al. 2013). These data provide indirect evidence that physical inactivity leads to systemic adaptations in conduit artery wall thickness, whilst these adaptations seem largely independent of repeated elevations in shear stress (Fig. 6.1).

Resistance Arteries Assessing changes in resistance artery structure traditionally involves measuring hyperemic blood flow responses to a maximal vasodilator stimulus, since maximal blood flow is restricted by structural aspects of the vessels. These measures also represent independent predictors for cardiovascular disease (Anderson et al. 2011; Lind et al. 2011). Individuals with a SCI demonstrate a 40–60 % lower peak reactive hyperemic response in the lower limbs than AB

controls (de Groot et al. 2006a; Olive et al. 2003). Some speculate these changes in vascular resistance and blood flow result from a loss of supraspinal sympathetic vascular tone. However, no such changes in vascular resistance are observed after long-term sympathectomy (Lepori et al. 1999). Studies using limb immobilization (Bleeker et al. 2005a) and bed rest (Bleeker et al. 2005b) have also reported a decrease in lower limb reactive hyperemic blood flow, predominantly present in the physically inactive limbs. This indicates that the extent of reactive hyperemic impairment is dose dependent. For example, 5 and 52 days of bed rest lead to a 22 and 38 % reduction in superficial femoral artery peak reactive hyperemia, respectively (Bleeker et al. 2005b; Hamburg et al. 2007), whereas chronic SCI is linked to a 40–60 % lower response. Taken together, physical inactivity leads to a marked reduction in resistance artery structure, which is likely related to local processes in the physically inactive areas (Fig. 6.1).

Microvessels The microvasculature is comprised of the smallest vessels within the vascular network and primarily serves as an exchange site to facilitate the movement of nutrients between the blood and localized tissue. The microcirculation in humans is typically examined in muscle tissue. Several studies have identified changes in the muscle microvascular bed in individuals with SCI, characterized by a reduced capillary-to-fiber ratio (Chilibeck et al. 1999; Martin et al. 1992). Similar findings have also been reported following periods of inactivity in AB subjects (Degens and Alway 2006; Edgerton et al. 1995; Qin et al. 1997). These changes in capillary-to-fiber ratio were also accompanied by a decrease in maximal perfusion of the muscle tissue, which further supports the presence of remodeling in the microvasculature in response to physical inactivity. In addition to the muscle, studies have also examined the skin microcirculation. Given the different role and regulation, the skin microcirculation represents a completely different vascular bed and cannot be simply used as a surrogate for the skeletal muscle microcirculation and vice versa. Although skin microcirculation is relevant for thermoregulatory control as well as in the development of secondary complications in those with SCI [e.g. skin ulceration, poor wound healing (Deitrick et al. 2007)], no study examined cutaneous microvascular structure following SCI.

6.1.3 Vascular Function

Conduit Arteries Flow mediated dilation (FMD) is a simple, non-invasive technique used to assess conduit artery endothelium-dependent, nitric oxide (NO) mediated vascular function following brief periods of reactive hyperemia. A lower FMD response is indicative of endothelial dysfunction and is directly associated with cardiovascular morbidity and mortality (Green et al. 2011). It is well established that exercise training reduces the risk of CVD and improves baseline NO production and FMD (Clarkson et al. 1999; Fuchsjager-Mayrl et al. 2002; Green et al. 2003). Remarkably, a higher FMD of conduit arteries in

the lower limbs of individuals with SCI is reported (de Groot et al. 2004b, 2005, 2006b), although some data is conflicting (Stoner et al. 2006) (Fig. 6.1). In AB subjects, most studies reveal that FMD is preserved or even increases after a period of physical inactivity induced by bed rest (i.e. femoral artery) (Bleeker et al. 2005b), unilateral lower limb suspension (i.e. femoral artery) (Bleeker et al. 2005a) and unilateral upper limb inactivity (i.e. brachial artery) (Birk et al. 2013). Remarkably, the increase or preserved FMD is typically observed in the inactive limbs, whilst leaving the normally active limbs largely unaffected (de Groot et al. 2004b). Therefore, based on the generalized increase in FMD after periods of lower limb or whole body exercise, the localized increase in FMD in the inactive areas after prolonged physical inactivity is somewhat counter-intuitive. At least, these observations suggest that the effects of deconditioning on conduit artery function are not simply the inverse of exercise training.

A possible explanation for a preserved or increased FMD relates to the inverse relation between baseline arterial size and FMD (Pyke and Tschakovsky 2005; Schroeder et al. 2000; Thijssen et al. 2008a). The significant inward remodeling of the femoral artery in individuals with SCI, consequently, is expected to result in an increase in FMD. As a consequence of the smaller sized vessels, arteries are exposed to an increase in reactive hyperemic shear stress stimuli during FMD testing. Correcting for differences in baseline diameter, but also potential differences in the post-occlusion reactive hyperemia, may contribute to the preserved or even increased FMD after prolonged physical inactivity (de Groot et al. 2004b; Thijssen et al. 2008b). Another potential explanation for the differences in FMD between both groups relates to differences in the wall-to-lumen ratio, especially since arteries with a larger wall-to-lumen ratio possess larger responsiveness to vasodilator stimuli (Thijssen et al. 2011). Based on the larger wall-to-lumen ratios in those with SCI relative to AB controls, such differences may further contribute to the observations between groups. Therefore, lower limb deconditioning in individuals with SCI does not lead to a decrease in FMD, an observation that may, at least partly, be related to marked remodeling of the vessel (i.e. smaller diameter, larger wall-to-lumen ratio).

The functional capacity of an artery can also be examined using the compliance and stiffness, which reflects the change in diameter across the cardiac cycle in response to an increase in blood pressure. Stiffening of conduit arteries reduces its buffering capacity and is associated with an increase in cardiovascular risk (Laurent et al. 2006). Previous studies have reported that individuals with a SCI demonstrate an increase in arterial stiffness in both central (Miyatani et al. 2009; Phillips et al. 2012) and peripheral (de Groot et al. 2005; Schmidt-Trucksass et al. 2000; Wecht et al. 2004) arteries. The decrease in femoral artery blood flow and pulse pressure in individuals with SCI, as a consequence of physical inactivity and deconditioning, may alter the elastin properties in the arterial wall. These changes may contribute to stiffening of the artery and impeding its functional ability. Differences in artery stiffness were not present when comparing physically active individuals with SCI and age matched AB individuals (Jae et al. 2008), whilst

localized electrostimulation to activate the paralyzed muscles of individuals with SCI reduces femoral artery stiffness. These observations suggest that stiffening of conduit arteries is a direct consequence of physical inactivity, whilst systemic hemodynamic stimuli are most likely responsible for these changes.

Resistance Arteries Various models of physical inactivity, such as limb casting (Green et al. 1997), bed rest (Christ et al. 2001; Pawelczyk et al. 2001) and chronic SCI (Hopman et al. 2002; Kooijman et al. 2003; Thijssen et al. 2007) have detrimental effects on resistance artery function, manifested by a characteristic increase in basal vascular resistance. Considering the importance of vasodilators for vascular health, in particular NO, increases in vascular resistance in the paralyzed limbs of individuals with SCI may be the result of impairment in the NO pathway. A number of previous studies have examined the contribution of NO dilator pathways to vascular resistance. For example, by examining blood flow responses to intra-femoral infusion of incremental doses of a NO-synthase blocker, Bleeker et al. reported no difference between individuals with SCI and AB controls in the contribution of NO to lower limb vascular tone. Furthermore, no difference in the responses to a NO-synthase blocker were found after 4-weeks of unilateral lower limb suspension (Bleeker et al. 2005c). In parallel, individuals who underwent casting-induced immobilization of the forearm had comparable forearm vascular responses during intra-arterial infusion of a NO-synthase blocker immediately and 6 weeks after cast removal (Green et al. 1997). Collectively, these studies suggest that the increased vascular resistance due to deconditioning cannot be explained by impairment in vasodilator pathways (Fig. 6.1).

Alternatively, upregulation of vasoconstrictor pathways and endothelium-derived constricting factors may better explain the increased vascular resistance observed in deconditioned muscles. In support of this hypothesis, previous studies have reported an increase in circulating vasoconstrictor substances such as endothelin-1 (ET-1) (Maeda et al. 2001; Robergs et al. 1993) and angiotensin II (ANG II) (Bestle et al. 2001; Maeda et al. 2001) using various models of deconditioning. However, circulating levels of vasoconstrictors do not simply reflect their role in the regulation of vascular tone (Thijssen et al. 2008c). Therefore, to truly understand the role of vasoconstrictors, Thijssen et al. used local intra-arterial infusion of an ET-1 receptor blockade in the deconditioned legs of individuals with SCI (Thijssen et al. 2007). They observed a larger vasodilatory response compared with age matched AB controls, indicating that ET-1 contributes to the increased vascular tone in the lower limbs of individuals with SCI. Furthermore, another study examined the role of ANG II in the regulation of vascular tone in the lower and upper limb of paraplegic subjects as well as AB controls (Groothuis et al. 2010). Whilst blockade of ANG II-receptors did not alter blood flow responses in upper or lower limbs in AB controls, a significant increase in blood flow was observed in the lower limbs of paraplegic subjects. This data provides further support that vasoconstrictors, such as ET-1 and ANG II, contribute to the increased vascular resistance in the lower limb of individuals with SCI

Microvessels Whilst no previous study examined microvascular function in the skeletal muscle vascular bed, some studies have explored skin microcirculatory function using the non-invasive laser-Doppler flowmetry. A commonly adopted technique to examine skin microvascular function relates to local heat-induced vasodilation, which leads to an initial axon-reflex mediated peak, followed by a partly NO-mediated plateau. The inactive limbs of individuals with a SCI demonstrate a diminished axon-reflex and NO-mediated plateau to local heating compared with able bodied controls (Nicotra et al. 2004; Van Duijnhoven et al. 2009). Interestingly, a similar skin microcirculatory impairment is observed above the lesion in the upper limbs (Van Duijnhoven et al. 2009), suggesting a systemic adaptation and impairment of skin microvascular NO function following SCI. Despite physical (in)activity being fundamental in modulating vascular adaptations in larger vessels, the diminished cutaneous vasodilator responses observed in the upper limbs in individuals with SCI suggests that skin microcirculatory impairment is not a direct result of physical inactivity per se. A more plausible explanation lends itself to the persistent lack of exposure to sufficient increases in core body temperature and/or changes in skin blood flow usually present during physical activity. Indeed, the attenuated vasodilator responses observed during short term physical inactivity in able bodied individuals (Crandall et al. 2003; Michikami et al. 2004) is prevented by exercise (Shibasaki et al. 2003), whilst repeated functional electrical stimulation (FES) cycling in individuals with SCI, which induces only marginal increases in core body temperature, has no effect on skin microcirculatory function (Van Duijnhoven et al. 2009). Therefore, SCI leads to a generalized and systemic impairment of skin microcirculatory function to local heating, whilst these changes are most likely mediated by mechanisms other than the direct effects of physical activity.

6.1.4 Time-Course of Adaptation

Following a SCI, a rapid inward remodeling of conduit arteries supplying the inactive limbs is present. Such adaptations occur within 1 week (de Groot et al. 2006b) after the injury and are largely accomplished within 3 weeks (Thijssen et al. 2012). These observations are supported by the impact of short-term physical inactivity induced by 25 days of bed rest in AB individuals, which resulted in a 13 % decrease in femoral artery diameter (Bleeker et al. 2005b). Interestingly, longer periods of inactivity, such as 52 days of bed rest or chronic SCI (Hopman et al. 1996), further reductions in conduit artery diameter are marginal, thus suggesting that the adaptations in vascular structure occur rapidly and within the first weeks of deconditioning. Possibly, remodeling occurs in response to absence in peak levels of shear stress (de Groot et al. 2006a; West et al. 2013). The rapid inward remodeling in individuals with SCI may, therefore, be explained by the reduction in high flow rates and peak shear stress induced by immobilization and paralysis.

The time course of conduit artery wall thickening contrasts somewhat with the localized and rapid changes in vessel diameter. Whereas much of this latter remodeling process is completed within 3 weeks of chronic inactivity, thickening of the artery wall develops according to a more gradual pattern of change and takes several months. Thijssen et al. repeatedly assessed the diameter and wall thickness of the femoral and carotid artery across the first 24 weeks after a SCI. Changes in wall thickness were only apparent between weeks 8 and 24 of assessment, despite the rapid changes in diameter (Thijssen et al. 2012). Taken together, physical inactivity leads to a slow and progressive change in wall thickness which is preceded by a rapid inward remodeling in conduit artery diameter.

Distinct time course of adaptation is also apparent between vessel beds, where a rapid decrease in femoral artery diameter in individuals with SCI is not paralleled by an equally rapid decrease in reactive hyperemic blood flow (de Groot et al. 2006b) (reflecting resistance artery structure). Similarly, 52 and 25 days of bed rest in able bodied individuals induced a large decrease in femoral artery diameter, while femoral artery reactive hyperemia remained relatively unchanged (Bleeker et al. 2005b). It is therefore conceivable that the changes in vessel beds located at the distal end of the vascular tree are mediated by alternative mechanisms than those driving conduit artery remodeling. These alternative mechanisms may potentially relate to different hemodynamic stimuli associated with deconditioning.

6.2 Exercise and Cardiac Responses

Physical activity or exercise provokes integrated, exercise-dose dependent, physiological adjustments that enhance oxygen and micronutrient delivery to the active musculature and maintain blood pressure and homeothermia within safe limits. Autonomic modulation of the heart and circulation plays a key role in determining hemodynamic adjustments. Sympathetic denervation in individuals with SCI can dramatically alter these hemodynamic responses (Krassioukov 2009; Low et al. 2012), limiting the ability to increase (maximal) heart rate. These changes potentially affect (maximal) cardiac output and, consequently, reduce physical capacity and fatigue in some individuals (Claydon et al. 2006). The hemodynamic responses to exercise in individuals with SCI (typically performed with the arms) depend mainly on the type of contraction—dynamic or static—and the level and completeness of injury (Theisen 2012). During dynamic exercise, the lack of sympathetic innervation and muscle pump below the lesion in individuals with SCI causes a diminished increase in mean systemic filling pressure and end-diastolic ventricular volume, resulting in smaller increases in SV according to the Frank-Starling mechanism. Consequently, heart rate is higher during submaximal exercise in order to maintain cardiac output (Hopman et al. 1992a, 1993c) (Fig. 6.2).

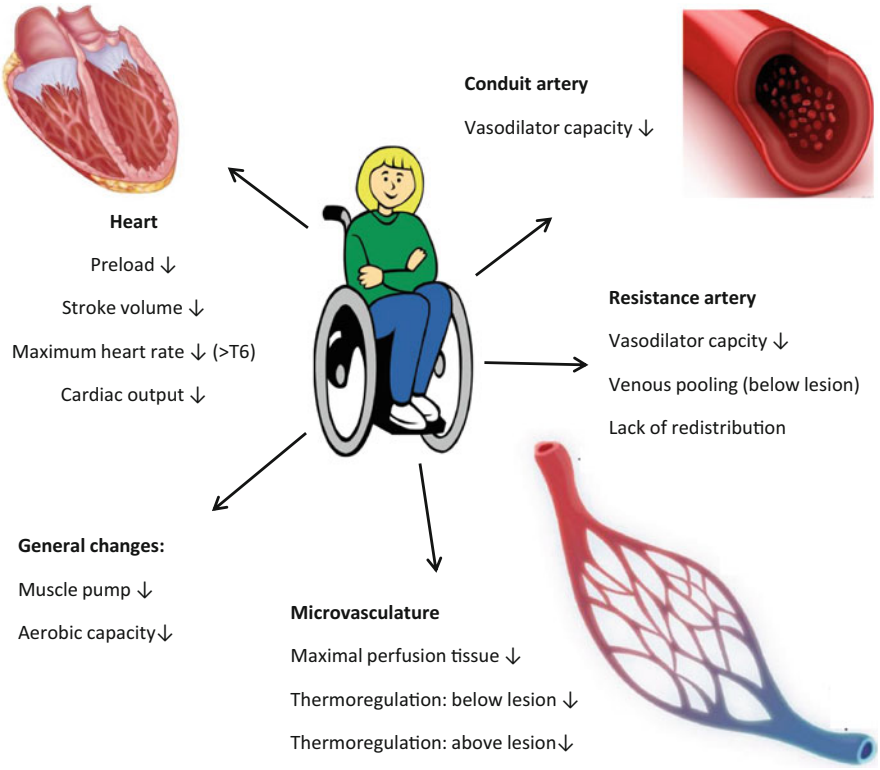

Fig. 6.2 Cardiovascular implications for exercise in SCI

A SCI with a lesion above T6 will have partly disturbed cardiac innervation, meaning that reductions in SV during exercise cannot be fully compensated by an increase in HR. Therefore, cardiac output can decline during exercise in tetraplegia, particular with prolonged exercise and/or hot environments (Fitzgerald et al. 1990; Hopman et al. 1993b). Some research has reported lower cardiac output during exercise in individuals with mid-low thoracic lesions (T4-T11) during arm-crank exercise who also displayed a lower cardiac output at rest (Jacobs et al. 2002). In maximal exercise conditions, performance can be limited by a smaller active muscle mass and a lower SV that limit maximal cardiac output and, therefore, oxygen delivery (Hopman et al. 1992a, 1993c). Studies of cardiac function during exercise in individuals with SCI are scarce, although a previous study reported septal hypokinesis and hyperkinetic hearts with no evidence of systolic dysfunction in tetraplegics (C5-C6) during electrically-stimulated lower limb exercise (Nash et al. 1995).

6.3 Exercise and Exercise-Induced Blood Flow

6.3.1 Active Areas

At the onset of exercise, blood flow markedly increases in the active regions in an exercise intensity-dependent manner, as an attempt to meet the increased metabolic demand (Green et al. 2005; Schreuder et al. 2014; Thijssen et al. 2009a). These changes in perfusion are, at least partly, mediated through local metabolites and vasodilatory pathways. For example, handgrip exercise, which is associated with minor changes in mean arterial blood pressure and cardiac output, induces large hyperemic responses. Therefore, vasodilation in downstream resistance vessels of the forearm represents an important contributor to the increase in blood flow that occurs during exercise in the active areas (Green et al. 2005). Activating a larger (upper limb) muscle mass, such as during arm crank exercise, leads to the activation of a larger muscle volume and consequently increases blood pressure and cardiac output. The consequent increases in upper limb blood flow still results from changes in downstream resistance vessel dilation, but also through increases in central driving pressure. Therefore, local vasodilator mechanisms along with increases in arterial pressure and cardiac output contribute to exercise hyperemia in the active areas. Thus, there is little support for differences between SCI and AB populations in the regulation of exercise hyperemia in the active areas in SCI individuals.

6.3.2 Non-active, Paralyzed Areas

At the start of exercise, blood flow in the inactive regions (e.g.. internal organs, muscles that are not active, (sub)cutaneous tissue) typically demonstrates a small decline (Green et al. 2002). When exercise continues, the decline in cutaneous blood flow in the non-active regions is reversed to an increase, which most likely is a direct result of thermoregulatory purposes that is required to dissipate the heat that is produced during continued exercise (Simmons et al. 2011). Since these changes in non-active areas are largely mediated through neural pathways, such adaptation in non-active, paralyzed areas do not occur in subjects with a SCI. Nonetheless, previous work has found that femoral artery blood flow goes up during upper limb arm crank exercise in subjects with a complete thoracic lesion (Thijssen et al. 2009b). However, the increase in femoral blood flow was marginal and was largely explained through elevation in mean arterial pressure, i.e. the driving pressure for blood to peripheral vessels. Upper limb exercise, therefore, unlikely leads to significant increases in perfusion of the non-active (paralyzed) areas in individuals with SCI. This is further supported by lack of differences in femoral artery diameter and wall thickness between sedentary individuals with SCI and highly active athletes with SCI (Huonker et al. 2003; Rowley et al. 2012). Taken together, only marginal increases in

blood flow and shear stress are present in the non-active, paralyzed areas during exercise in individuals with SCI.

6.3.3 Blood Redistribution

The decline in blood flow in the non-active areas in AB subjects at the start of exercise contributes to blood redistribution to facilitate a relatively larger blood volume (and cardiac output) for the active areas. To better understand cardiovascular responses during arm crank exercise in paraplegics, venous pooling of the lower limbs during arm crank exercise was examined in paraplegic subjects and AB controls. Upper limb exercise in AB subjects induced a decrease in calf volume that continued to decline throughout the exercise test (Hopman et al. 1993d). In contrast, paraplegic individuals demonstrated a lower decline in calf volume, whilst volume changes were correlated with the level of the lesion. This shows that paraplegic subjects are unable to redistribute blood from the inactive lower limbs, which is partly caused by a loss of sympathetically induced vasoconstriction.

Theoretically, external pressure on the legs could prevent venous pooling, aid venous return and, consequently, improve cardiovascular responses to arm crank exercise. To examine this hypothesis, subjects with paraplegia performed submaximal exercise with and without an anti-gravity suit, which provides 52 mmHg of positive pressure to the lower limbs (Hopman et al. 1992b). Whilst cardiac output at submaximal exercise level was comparable, the anti-gravity suit was associated with lower heart rates in the presence of elevated levels of stroke volume. Possibly, the increased pressure on the lower limbs caused elevation of venous return, consequently leading to a larger preload and stroke volume. A follow-up study further explored whether the anti-gravity suit affects maximal exercise performance (Hopman et al. 1993a). Although lower peak heart rates were achieved, no significant improvement in peak workload or peak oxygen consumption was observed, possibly because alternative limiting factors are present that affect maximal performance. Nonetheless, venous pooling is present in individuals with SCI during upper limb exercise, which significantly affect hemodynamic responses to (sub)maximal exercise and may impair the ability of individuals with SCI to perform exercise.

In addition to the lower limbs, also the splanchnic area contributes to blood redistribution during exercise (McAllister 1998). Since splanchnic perfusion is under sympathetic control, individuals with SCI may show impaired regulation of splanchnic blood flow during exercise. Therefore, we have explored splanchnic perfusion during arm crank exercise in individuals with SCI with (i.e. a low lesion, $<$T7) and without sympathetic control of the splanchnic area (i.e. a high lesion, $>$T6) (Thijssen et al. 2009c). Across a 25-min, moderate-intensity arm crank exercise bout we found a gradual decline in portal vein blood flow in AB controls and individuals with SCI who have splanchnic sympathetic control. In marked contrast, no changes were observed in portal blood flow in individuals with SCI

who lack splanchnic sympathetic control. A more recent study demonstrated that the lack of redistribution splanchnic blood volume in individuals with SCI may affect exercise performance (West et al. 2012a). Abdominal binding in individuals with SCI who have a high lesion resulted in an increase in cardiac output, which was explained through elevation in stroke volume rather than changes in heart rate. Therefore, absence of redistribution of splanchnic blood volume in individuals with SCI further contributes to impairment in venous return to the heart, consequently affecting the ability to increase cardiac output during exercise (Fig. 6.2).

6.4 Adaptations to Exercise Training

Conduit Arteries In able bodied subjects, exercise training is associated with an outward remodeling and enlargement of the conduit arteries supplying the active skeletal muscle (Dinenno et al. 2001; Thijssen et al. 2006). Data from experimental studies (Langille and O'Donnell 1986; Tinken et al. 2010; Tuttle et al. 2001) indicate that vascular enlargement is likely related to repeated increases in shear stress, with the magnitude of luminal expansion being proportionate to the level of blood flow and wall shear. This is further supported by evidence from endurance trained populations, who are chronically exposed to greater increases in blood flow and possess larger arteries than healthy controls (Schmidt-Trucksass et al. 2000). More importantly, exercising the extremely inactive limbs during bed rest (Bleeker et al. 2005b) and SCI (Thijssen et al. 2006) counteracts and partially reverses the adverse changes in artery dimeter. Using functional electrical stimulation (FES) cycling as a method of activating the paralyzed limbs of individuals with SCI, Thijssen et al. reported a 6 % increase in femoral artery diameter. Most notably, changes in diameter were observed after just 2 weeks, i.e. four 25-min sessions. Collectively, these data reinforce that structural changes in conduit artery diameter are attributable to physical inactivity, whilst exercise training represents a potent stimulus that leads to a rapid, dose-dependent increase in conduit artery lumen size.

Previous cross sectional studies support the presence of a lower conduit artery wall thickness in physically active individuals compared to sedentary controls (Dinenno et al. 2001; Rowley et al. 2011). This suggests that, in addition to artery diameter, changes in arterial wall properties are also linked to physical activity and exercise training. Indeed, a previous intervention study demonstrated that exercise training during chronic physical inactivity represents an effective countermeasure for the inactivity-induced increase in conduit artery wall thickness (van Duijnhoven et al. 2010a). More specifically, resistance exercise combined with whole body vibration during bed rest inactivity largely prevented the increase in carotid and femoral artery wall thickness. Furthermore, physically active individuals with SCI showed no difference in carotid wall thickness when compared with age-matched able bodied controls (Jae et al. 2008). Currently, little evidence exists regarding the mechanisms involved in the exercise mediated changes in carotid artery wall

thickness. Considering the increase in carotid artery blood flow during physical activity is only marginal, it is unlikely that wall thickness is influenced by the direct effect of shear stress per se, but more likely through systemic hemodynamic stimuli. Nonetheless, the systemic increase in conduit artery wall thickness with chronic physical inactivity can, at least in part, be reversed by exercise intervention.

Resistive vibration exercise during bed rest inactivity in able bodied individuals counteracts and largely prevents increases in FMD (van Duijnhoven et al. 2010b). Furthermore, unilateral electrical stimulation cycling exercise in individuals with SCI leads to a decrease in conduit artery FMD in the active limb only (de Groot et al. 2005). Collectively, these findings indicate that exercise training leads to a decrease in FMD, or conduit artery endothelial function, following extreme inactivity. This is somewhat surprising considering that vascular endothelial function has been shown to increase after exercise training in AB individuals (Clarkson et al. 1999) and is lower in sedentary subjects compared with physically active AB individuals (DeSouza et al. 2000). A possible explanation relates to the strong interaction between structure and function (as mentioned previously in this chapter in Sect. 6.1). In addition, individuals with SCI show stiffer arteries compared with AB controls (de Groot et al. 2005; Miyatani et al. 2009). These between-group differences, however, were abolished when comparing physically active individuals with SCI and age matched AB individuals (Jae et al. 2008), whilst the increased arterial stiffness in individuals with SCI is reversible with electrical stimulation cycling (de Groot et al. 2005). Therefore, strong evidence supports the role of physical activity and the potential to improve vascular function during extreme deconditioning, most notably by FMD normalization and increase arterial compliance.

Resistance Arteries A majority of exercise training studies in AB individuals who reveal an impaired a priori resistance vessel vasodilator function have documented vast improvements (Maiorana et al. 2001; Parnell et al. 2005). Although resistance vessel vasodilator function remains largely unaffected following bed rest inactivity and SCI, exercise training appears to improve resistance vessel structure and function in the lower limbs of individuals with SCI. For example, 2–8 weeks of electrically stimulated exercise training in the chronically deconditioned lower limbs is able to reverse the increase in vascular resistance towards normal values (Hopman et al. 2002; Thijssen et al. 2007). With regards to the mechanisms involved, the increase vascular resistance is most likely explained by modulation of vasoconstrictor pathways. Exercise training has been shown to have a significant role in suppressing humoral vasoconstrictors such as ET-1 and Ang II in patients with cardiovascular disease (Adams et al. 2005; Maeda et al. 2009). In further support, FES-based exercise training in individuals with SCI reverses the contribution of the ET-1 pathway to regulate baseline vascular tone. Collectively, these data provide evidence to support the role of exercise training in reversing the adaptive responses to SCI in resistance vessel structure and function.

Microvessels Capillary growth is closely linked with exercise training and has been previously shown in the paralyzed limbs of SCI individuals (Chilibeck

et al. 1999; Crameri et al. 2004). For example, a 39 % increase in capillary number is reported following 8 weeks of electrically stimulated cycling exercise in paraplegics (Chilibeck et al. 1999). In addition to the exercise induced improvements within the muscle microvasculature, a number of studies have reported an increase in cutaneous microvascular function in older (Black et al. 2008) and diabetic (Cohen et al. 2008) AB individuals. Furthermore, the decline in maximal cutaneous vasodilator responses during bed rest inactivity in able bodied subjects was prevented by cycling ergometry (Shibasaki et al. 2003). However, in Individuals with SCI, 6 weeks of FES cycling had no effect on the impaired axon-reflex and NO mediated skin blood flow responses to local heating, possibly due to an insufficient thermoregulatory stimuli during FES-exercise.

6.5 Summary

A spinal cord injury is associated with significant changes in structural remodeling of the cardiovascular system, leading to a smaller sized heart, smaller conduit artery diameters with thicker walls, a smaller resistance artery vascular bed as well as a reduction in the capillary bed (Fig. 6.1). This remodeling typically occurred below the level of the lesion, and seems to be accompanied with functional changes. Whilst these changes in vascular function occurred across all levels of the vascular tree, adaptations are largely present in the inactive areas. Importantly, for both functional and structural adaptation, physical inactivity seems to be the principle stimulus mediating these changes. Furthermore, changes in cardiovascular function and structure seemed to have important implications for exercise performance in individuals with SCI, specifically relating to the limited increase in blood flow to active regions. Also a decrease in blood volume, inability for blood redistribution and lack of muscle pump importantly impair exercise performance in this population (Fig. 6.2). Due to these impairments in the cardiovascular system, individuals with SCI are importantly restricted in the ability to perform exercise, both at recreational as well as elite level.

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Chapter 7
Thermoregulatory Considerations for the Performance of Exercise in SCI

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Abstract Spinal cord injury (SCI) results in thermoregulatory impairment related to the disruption in autonomic function. As a result, body core temperature generally increases at a greater rate during exercise in individuals with SCI compared to their able-bodied counterparts, placing them at elevated risk for heat-related illnesses. These effects are exacerbated during exercise in the heat. Conversely, body core temperature may decrease at a greater rate during exercise in cold environments. In this chapter, we first briefly describe the anatomy and physiology of normal (non-disrupted) thermoregulation. Next, we present evidence demonstrating that SCI results in impaired thermoregulation both at rest and during exercise. We then discuss the mechanisms behind why these impairments occur, particularly in terms of how disruptions in the sympathetic nervous system affect the various arms of the thermoregulatory negative feedback loop. Next, we discuss how the types of exercise available to individuals with SCI may present additional challenges to thermoregulation, and finally, we present strategies currently in use or under investigation for combatting these thermoregulatory challenges.

7.1 Introduction

It has long been recognized that spinal cord injury (SCI) results in thermoregulatory impairment. Early studies in animals with complete spinal cord transections observed dramatic and rapid reductions in body temperature during cold exposure (Sherrington 1924; Pembrey 1897). Later, investigators studying humans who had sustained SCI often referred to these patients as 'poikilotherms', those lacking the ability to maintain a constant body core temperature independent of ambient temperature (Holmes 1915; Downey et al. 1967; Attia and Engel 1983). In a lecture in 1875, Dr. Jonathan Hutchinson (1875) was the first to attribute these impairments to loss of autonomic control, stating, "The unusual combination of symptoms is

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explicable only by supposing the vasomotor completely paralysed, and at the same time the heart's vigor much depressed."

Following these early reports, subsequent investigations have attributed impaired thermoregulation following SCI to the loss of sympathetic innervation over a large portion of the body. As displayed in Fig. 7.1, body core temperature decreases as a result of the inability to constrict cutaneous blood vessels or activate shivering during exposure to cold ambient conditions. Conversely, due to an impaired ability to sweat and increase skin blood flow under conditions of heat gain, core temperature increases at a much faster rate in individuals with SCI compared to their able-bodied (AB) counterparts. These effects are exacerbated with exercise, as the cardiovascular system is not able to keep up with blood flow demands for maintaining both exercise and thermoregulation. Even under exercising conditions where AB individuals can easily maintain their core temperature, individuals with SCI will experience net heat gains, placing them at elevated risk of heat-related illness.

During exercise, the increase in metabolic rate challenges the autonomic and cardiovascular systems to raise skin blood flow to divert warm blood to the skin surface for the dissipation of heat. Although individuals with SCI have difficulty maintaining body temperature at rest in cool conditions, this is not generally a challenge during exercise as metabolic heat production is able to offset heat loss to the environment (Boot et al. 2006; Dawson et al. 1994). As such, in this chapter we will focus on impairments in heat loss mechanisms, save for a short section summarizing the literature on individuals with SCI exercising in the cold.

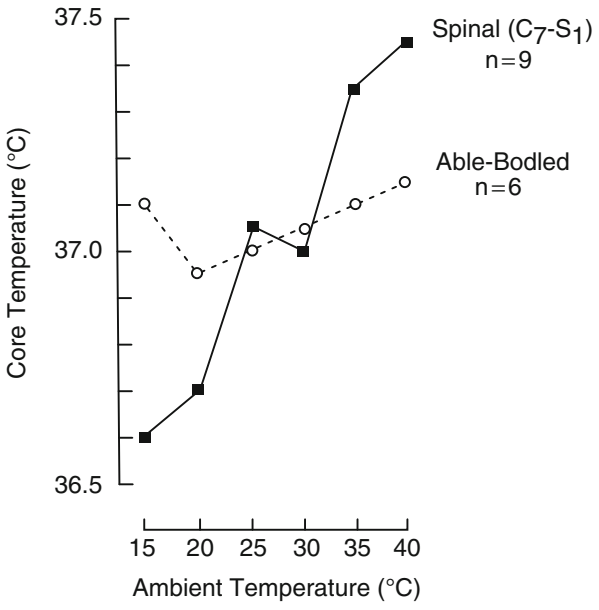

Fig. 7.1 Individuals with intact nervous systems are able to maintain core temperature across a wide range of ambient temperatures. However, body temperature in spinal cord injured individuals can vary greatly with changes in ambient temperature. Data from Attia and Engel (1984) redrawn by Sawka et al. (1989)

7.2 Anatomy and Physiology of Normal Thermoregulation

Although a typical resting body core temperature for humans is about 37 °C, human internal temperature can fluctuate by 0.2 °C to 1.0 °C due to changes in the circadian rhythm (across a 24 h period) or during hormonal changes attending the menstrual cycle. Although no area of the brain has been identified in humans where the thermoregulatory "set point" resides, data from other species have suggested that mean body temperature is a regulated variable within the hypothalamus, with thermal inputs from the pre-optic area of the anterior hypothalamus and the posterior hypothalamus. Local blood temperature and neural inputs from the spinal cord and peripheral thermoreceptors are integrated within the hypothalamus in order to activate both behavioral and neural adjustments aimed at defending the internal set-point temperature. When body core and/or skin temperatures are increased, reflex responses are activated to initiate heat loss mechanisms, and when core or skin temperatures are decreased, reflex responses are activated to increase heat conservation mechanisms. This system operates as a proportional control system. That is, the more mean body temperature deviates from the set-point temperature, the greater the appropriate heat loss or heat conservation responses are activated. In addition to central mechanisms, when heat or cold is directly applied to the skin, mechanisms including local axon reflexes and vasodilator/vasoconstrictor substances from the blood vessels will alter cutaneous vascular tone, independent of reflex responses arising from the central nervous system.

In the absence of disability or disease, humans are extremely well adapted to living and exercising in warm environments. When exposed to a hot environment or in response to a rise in body heat content during exercise, a number of thermoregulatory adjustments are set into motion. The primary thermoregulatory reflexes include increasing both sweating and skin blood flow, served by an increased cardiac output and a redistribution of our limited blood supply. Under resting thermoneutral conditions, skin blood vessels maintain a low level of tonic vasoconstrictor tone, mediated by sympathetic adrenergic nerves releasing norepinephrine to α_1 and α_2 receptors. Small fluctuations in the internal or external environments are managed by modest increases or decreases in this basal level of vascular tone, allowing slight changes in the body core to skin temperature gradient. If body temperature continues to rise, tonic vasoconstrictor tone is withdrawn until a "threshold" for active vasodilation and sweating is achieved (Fig. 7.2). Active vasodilation and sweating are mediated by sympathetic cholinergic nerves, which release acetylcholine and an unknown cotransmitter to mediate sweating and active vasodilation, respectively (Kellogg et al. 1995). Current thinking is that vasoactive intestinal peptide (VIP) is the primary co-transmitter, although there is evidence both for and against this (Bennett et al. 2003; Wilkins et al. 2004). There is a well-established role for nitric oxide (NO) in active vasodilation (Kellogg et al. 1998; Wilkins et al. 2003), and it appears to be this component that is affected in conditions in which active vasodilation is diminished (Holowatz et al. 2003; Holowatz and Kenney 2007).

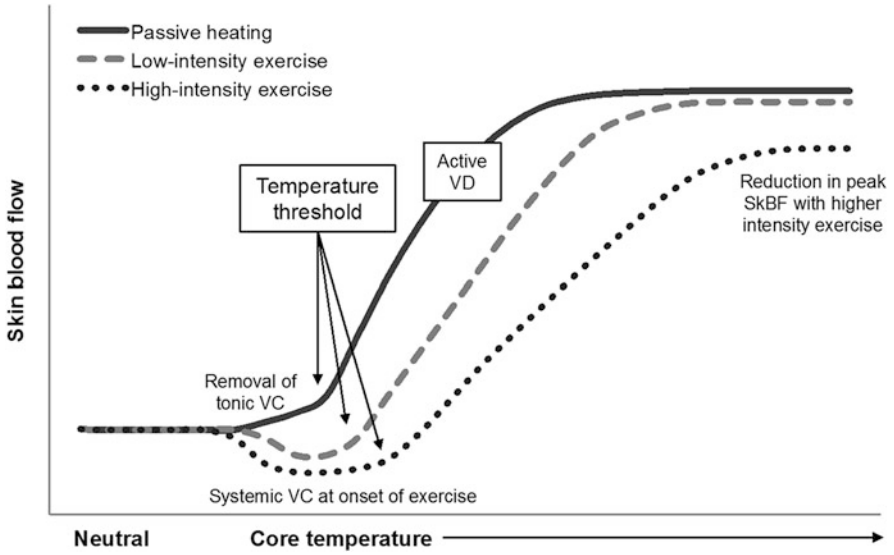

Fig. 7.2 Skin blood flow (SkBF) responses in able-bodied subjects during passive whole-body heating and during low and high intensity exercise. During passive heating, initial increases in skin blood flow occur due to withdrawal of tonic vasoconstriction (VC). After a temperature threshold is reached (~0.4 °C above resting core temperature), further increases in SkBF are the result of active vasodilation (VD). At the onset of exercise, skin blood flow will initially decrease due to systemic sympathetic VC. Threshold for active vasodilation is shifted to a higher core temperature and peak SkBF will be reduced due to competition for blood flow between the active skeletal muscle and the skin

The rise in skin blood flow in able-bodied individuals during direct passive heating in the supine position has been reported to be as high as 4.5–7 L/min, greater than or equal to resting cardiac output. This capacity for increasing blood flow is higher than any other tissue with the exception of exercising skeletal muscle. In order to achieve these very high levels of skin blood flow, cardiac output is increased via a rise in heart rate, and blood flow is redirected from the splanchnic and renal circulations and inactive skeletal muscle. During direct passive heating (such as from a high environmental temperature or in a sauna or Jacuzzi), both central and peripheral thermoreceptors provide the stimulus for thermoregulatory responses. However, central blood temperature accounts for a much greater percentage of the integrated outflow, estimated to be 80–90 % of central reflex thermoregulatory drive. Only minimal reflexively mediated increases in skin blood flow and sweating will occur if skin temperature over the entire body is rapidly elevated (i.e., before central blood temperature rises). The clearest role for skin temperature is that it affects the internal temperature theshold at which skin blood flow begins to increase. The internal threshold temperature for increasing skin blood flow and sweating are lowered when skin temperature is high. That is, with a high skin temperature, heat loss mechanisms are initiated at a lower internal body temperature. That said, in the absence of exercise, it is difficult to raise

internal temperature with neutral or cool skin temperatures. There have been attempts to independently control these variables by warming the insensate areas of skin in persons with SCI, which confirmed the affects of skin temperature on the heat loss thresholds described above (Freund et al. 1984; Tam et al. 1978a). Thus, the total integrated thermoregulatory efferent outflow is affected by the total surface area of sensate skin.

During exercise, much of the energy created by the high metabolic rate is in the form of heat that must be dissipated. This sets up a difficult cardiovascular challenge between the skeletal muscles and the skin to compete for a limited blood supply. At the onset of exercise there is a rapid vasoconstrictor response in skin, which is dependent on an intact adrenergic vasoconstrictor system (Fig. 7.2). As body core temperature continues to rise, a threshold is reached to activate active vasodilation and sweating. However, during exercise this threshold is shifted to a higher mean internal temperature than during passive heating. The influence of exercise on the internal threshold is dependent on the intensity of exercise, such that it is shifted to higher temperatures with increasing exercise intensity. This results in a lower absolute skin blood flow and sweat rate for a given body core temperature at higher exercise intensities, to the point where, at maximal exercise, skin blood flow will not increase much above baseline, despite elevations in core temperature. Under these conditions, exercise cannot be maintained for very long due to the very rapid rise in core temperature.

Skin temperature during exercise is dependent on the environmental conditions. Typically in a warm, dry environment, skin temperature *decreases* during exercise as heat is lost from the skin surface with the evaporation of sweat, despite the warmer blood perfusing the skin. However, skin temperature may increase along with blood temperature during exercise in a hot, humid environment in which evaporative cooling is no longer effective. Thermoregulation in this environment is extremely challenging and can prove to be quite dangerous.

Humans have more limited capacity to tolerate cold temperatures, with behavioral responses and prevention allowing survival in most cold environments. However, in all but the most extreme environmental conditions, body core temperature increases during exercise, even when performed in cold environments. The initial physiologic response to cold stress involves increasing cutaneous sympathetic adrenergic tone to reduce skin blood flow and minimize heat loss. This decreases the convective transfer of heat from the body core to the skin surface, affectively increasing the insulation of the body shell. With increased heat loss, body core temperature decreases further until a threshold for shivering, a form of cold induced thermogenesis, is achieved. Shivering is mediated through the alpha motor neurons and involves involuntary rhythmic contractions of skeletal muscle during which most of the metabolic activity is liberated as heat, as little external work is performed. Shivering typically starts in the torso then moves to the limbs (Bell, JAP, 1992). The extent and intensity of shivering depends on the severity of cold stress. Basal metabolic rate can also be increased in cold temperatures through increases in thyroid hormones. However, in general, both shivering and increased

metabolic rate are of limited benefit, and our ability to tolerate cold is not as robust as it is to tolerate heat.

7.3 Evidence for Impaired Thermoregulation Following SCI

7.3.1 Importance of Level of SCI

Before beginning this section, we want to comment on the importance of considering injury level, as an individual's magnitude of thermoregulatory impairment greatly depends on the level and completeness of injury (Price and Campbell 2003; Hopman et al. 1993a; Petrofsky 1992; Guttmann et al. 1958). For example, tetraplegia is associated with much greater thermal strain during both rest and exercise due to the absence of sweating over the entire body surface (Randall et al. 1966; Totel et al. 1971). By contrast, in paraplegics much of the upper body may have intact cutaneous and sudomotor systems allowing a relatively large body surface area for heat dissipation.

The sympathetic nerves exit the spinal cord at T1-L3. Therefore, tetraplegics (>C7) with complete SCI have loss of all sympathetic innervation, resulting in the largest impairments in thermoregulation. The heart is innervated by T1-T5, thus injuries above T6 result in impaired ability to increase heart rate and actively increase contractility. All increases in heart rate in individuals with complete lesions above T1 will be the result of vagal withdrawal, drastically reducing maximal heart rate during exercise (Van Loan et al. 1987; Coutts et al. 1983). Injuries above T5 result in loss of innervation to the splanchnic region (innervated by T5-L2), impairing ability to redistribute blood flow effectively (Rothe 1983). Additionally, loss of innervation to the kidneys and adrenals (innervated by T4-T11) may impact hormonal control of the circulation during exercise (Christensen and Galbo 1983) and passive heat stress (Minson et al. 1999).

Normell (1974) determined the regions of loss of cutaneous vasomotor and sweating function for a given lesion level. The skin of the face and neck are innervated by T1-T4. Therefore, tetraplegics may have little or no control of sympathetically-mediated vasodilation to the face despite having sensory control of these regions. The skin of the upper extremity is innervated by T5-T7 and the lower extremity by T10-L3.

Accordingly, grouping SCI into the following levels has been recommended when performing studies on thermoregulation (Hopman et al. 1993a; Guttmann 1976):

1. Tetraplegic >C7
2. High paraplegic: T1-T6
3. Low paraplegic: T7-T12

Additionally, for the purposes of more fully presenting available data in individuals with SCI, we have added a "very low paraplegia" category, including individuals with lesions <T12. Thermoregulation in these individuals would be expected to be near-normal as nearly all sympathetic innervation is retained.

The majority of investigations on thermoregulation have studied individuals with complete injury in order to minimize variability. Accordingly, the majority of literature presented in this chapter refers to complete SCI. However, those with complete injuries only represent approximately 35 % of the SCI community (NSCISC 2015). Those with incomplete injuries may retain some sympathetic control and thus may be better able to thermoregulate. However, this should not be assumed since complete loss of autonomic innervation can occur even when sensory innervation is partially preserved (e.g., ASIA B or C) (Cariga et al. 2002).

Lastly, level of injury will have a significant impact on exercise intensities that can be achieved. Although paraplegics are able to thermoregulate better than tetraplegics, they typically can achieve higher exercise intensities, resulting in greater metabolic heat production. Thus, it is important to ensure thermal conditions are safe for all individuals with SCI, regardless of level or completeness of injury.

7.3.2 Evidence of Thermoregulatory Impairment

In the 1960s and 1970s, a series of studies were performed in paraplegic subjects in efforts to tease out the contributions of central and skin thermoreceptor inputs to thermoregulatory drive. These studies utilized passive heating or cooling of sensate and insensate skin in order to alter core temperature with or without sensory input from the skin thermoreceptors. As a result, these studies provided key insight into the impairments in thermoregulation experienced following SCI.

Under conditions of high ambient temperature, core temperature at rest is elevated in paraplegics (Petrofsky 1992; Yamasaki et al. 2001; Huckaba et al. 1976), and even more so in tetraplegics (Petrofsky 1992; Pollock et al. 1951) (Fig. 7.3, left panel). For a given core temperature, mean whole-body sweat rate is lower in paraplegics compared to AB subjects (Hopman et al. 1993a; Huckaba et al. 1976), and even lower in tetraplegics (Downey et al. 1976), generally as a function of surface area of insensate skin (Petrofsky 1992). Even in sensate skin, local sweat rates (Tam et al. 1978a, b) and skin blood flow (Freund et al. 1984; Tam et al. 1978b) are also lower for a given core temperature. Furthermore, the onset of sweating and increased skin blood flow is delayed to a higher core temperature (Tam et al. 1978a; Downey et al. 1976).

In cold ambient conditions, core temperature decreases at a considerably greater rate in individuals with SCI compared to AB individuals, in whom body core temperature is generally well preserved (Pollock et al. 1951) (Fig. 7.3, right panel). SCI results in an impaired ability to vasoconstrict the skin microvessels or shiver below the level of the lesion, resulting in significant loss of heat to the

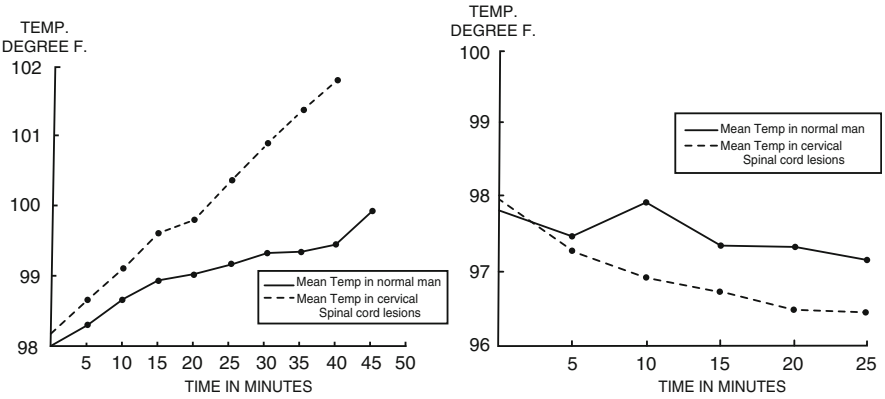

Fig. 7.3 Core temperature responses in able-bodied and tetraplegic subjects during water immersion in 102.5 °F (*left*) or 66 °F (*right*) water. From Pollock et al. (1951)

environment and limited capability to offset that loss through metabolic heat production.

With the increased use of exercise as a rehabilitation tool for individuals with SCI through the 1970s to 1980s, studies began investigating thermoregulatory impairment during exercise. Similarly to passive heat stress, individuals with SCI generally experience a greater increase in core temperature during exercise relative to that of AB individuals (Table 7.1). Mean whole-body sweat rate and local sweat rate in sensate skin are both lower (Downey et al. 1976; Yaggie et al. 2002), and skin blood flow in sensate skin is lower (Freund et al. 1984). Typically in temperate environmental conditions, skin temperature in insensate skin increases (Gass and Camp 1984; Griggs et al. 2015), as they lack evaporative heat loss mechanisms. Skin temperature in sensate skin either remains unchanged or decreases (Gass et al. 1988), reflecting abilities to sweat, albeit to a lesser extent than in AB individuals. In higher ambient temperatures, the effects on skin temperature in insensate skin will be exacerbated (Price and Campbell 2003) and skin temperature in sensate skin will increase as a function of environmental temperature.

Table 7.1 summarizes the studies that have reported core temperature and/or skin temperature changes during exercise in SCI subjects, as compared to AB subjects. The left panel displays the level of lesion by environmental condition. As environmental temperature increases, the ability to maintain a thermoneutral body temperature diminishes. Similarly, the skin temperature more closely reflects the ambient temperature. Severity of the lesion is related to the severity of the thermoregulatory dysfunction, as represented by the number of arrows. The greatest variability in what has been reported in the literature is in low-level paraplegics exercising in temperate conditions. These individuals have been studied more commonly and generally have greater exercise capacities than their counterparts with higher level SCI. Thus, there has been greater variability in the duration and intensity of exercise studied, which will greatly affect heat production, and therefore thermoregulation.

Table 7.1 Comparison of changes in core and skin temperature from rest to exercise in individuals with spinal cord injury (SCI) versus able-bodied subjects

	Core temp	Skin temp	References
Cool (<15 °C)			
Very low level paraplegic (≤T12)	↔	↔	Dawson et al. (1994)[a]
Low level paraplegic (T7-T12)	↔	↓	Boot et al. (2006)[a]
High level paraplegic (T1-T6)	↔	↓↓	Boot et al. (2006)[a]
Tetraplegic (≥C6)			
Temperate (20–25 °C)			
Very low level paraplegic (≤T12)	↑	↑	Fitzgerald et al. (1990)
Low level paraplegic (T7-T12)	↔, ↑, ↑↑	↓, ↔, ↑, ↑↑	Trbovich et al. (2014)[a], Price and Campbell (1999a, 1997)[a], Muraki et al. (1996a), Theisen et al. (2001)
High level paraplegic (T1-T6)	↑↑	↑↑	Theisen et al. (2001)
Tetraplegic (≥C6)	↑, ↑↑	↑↑	Trbovich et al. (2014)[a], Griggs et al. (2015)[a] (vs. T4-S1 paraplegics)
Warm (30–35 °C)			
Very low level paraplegic (≤T12)			
Low level paraplegic (T7-T12)	↑		Petrofsky (1992)
High level paraplegic (T1-T6)	↑↑	↑↑	Hagobian et al. (2004)
Tetraplegic (≥C6)	↑↑	↑↑	Petrofsky (1992), Price and Campbell (2003)[a]
Hot (>35 °C)			
Very low level paraplegic (≤T12)		↑	Dawson et al. (1994)[a]
Low level paraplegic (T7-T12)	↑	↑	Boot et al. (2006)[a], Petrofksy (1992)
High level paraplegic (T1-T6)	↑	↑	Boot et al. (2006)[a], Hopman et al. (1993a)[a]
Tetraplegic (≥C6)	↑↑↑		Petrofsky (1992)

All studies must have had N ≥ 3 in each group and have done at least 30 min of moderate to high intensity exercise. SCI level groups were chosen based on what has commonly been studied in the literature and based on key cutoff points for autonomic function. If groups studied crossed two categories (most commonly low and high level paraplegic), the range in which the majority of subjects fell into was used. Data from multiple conditions that fell within the same ambient temperature range were averaged

[a]Denotes trained subjects

↑ = significantly higher or lower. ↑↑ denotes >1.0 °C higher for core temperature and >2.0 °C higher or lower for skin temperature. ↑↑↑ denotes >2.0 °C higher

7.4 Autonomic Mechanisms Underlying Thermoregulatory Impairment

As discussed previously, thermoregulation is a negative feedback system that relies on intact afferent and efferent pathways for proper function. Both of these branches are disrupted following SCI (Fig. 7.4). Therefore, while sensory afferent signals from regions innervated by nerves above the level of injury may function appropriately, the overall magnitude of sensory information entering the thermoregulatory centers in the hypothalamus will be greatly attenuated. Similarly, while the efferent signals leaving the hypothalamus may be appropriate, only a subset of these signals will reach the effector organs. Impairments may also exist in the transduction of these signals to the effector organs, namely the skin microvessels and sweat glands. As such, there are multiple places in the feedback system where problems may occur. The following section will present evidence for how SCI impairs each segment of the thermoregulatory pathway.

7.4.1 Set-Point Theory

We will begin by discussing potential alterations in the thermoregulatory set point (in the hypothalamus), as from a historical perspective, this was the earliest theory to explain impaired thermoregulation. Early investigations observed that core temperature had to increase to a greater extent in individuals with SCI prior to the onset of sweating (compared to AB) (Pollock et al. 1951). This led to the theory that central thermoregulatory set-point must be increased to a higher core temperature (Downey et al. 1967; Attia and Engel 1983). Observations that sweating in sensate skin could be affected by altering skin temperatures also resulted in the suggestion that set-point could be reset to suit ambient temperature. Tam et al. (1978a) also proposed that the gain of the response may be reduced. However, these hypotheses were not able to be adequately explored as the technology did not yet exist to determine whether neural output for a given stimulus was decreased or whether the sensitivity of the effector organs was decreased (e.g., actually no change in central gain, but reduced peripheral sensitivity for a given neural outflow).

7.4.2 Reduced Afferent Input

A more likely explanation to why onset of sweating is shifted to a higher core temperature is that afferent input is reduced. As discussed previously, the thermoregulatory centers in the hypothalamus receive afferent input from both the central thermoreceptors (located in the brain and spinal cord) and skin thermoreceptors,

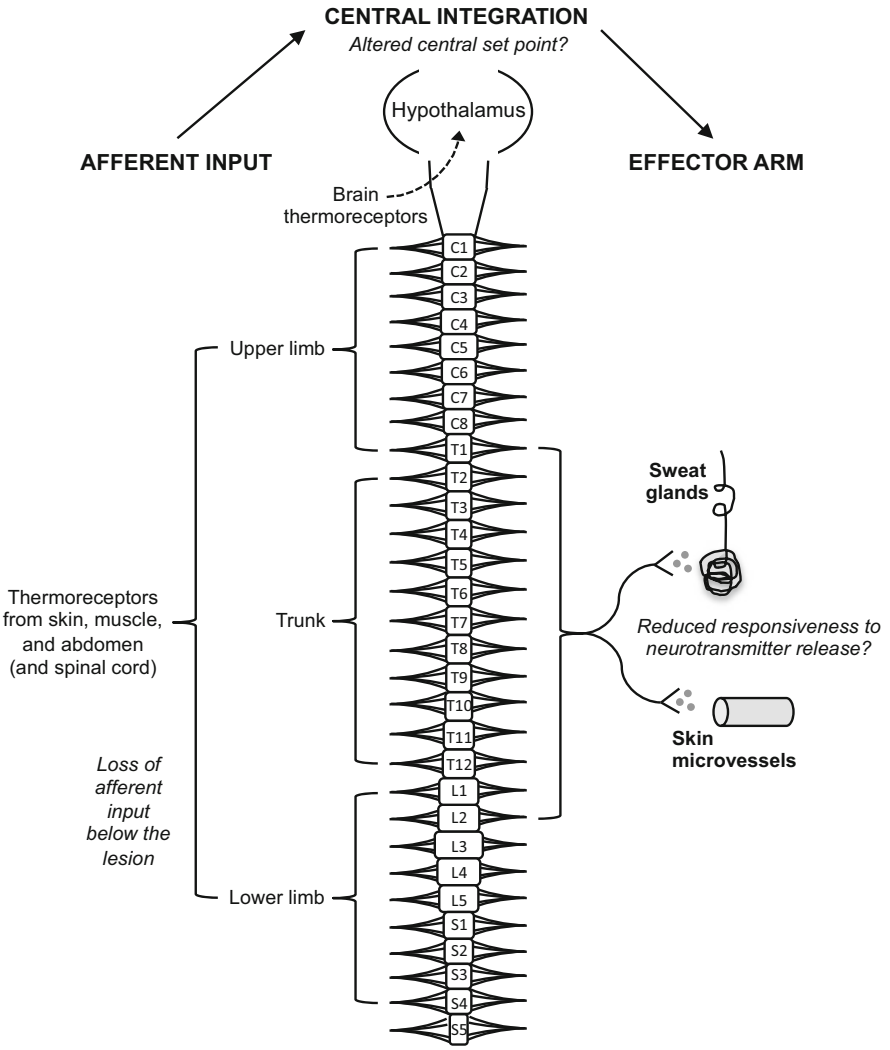

Fig. 7.4 The thermoregulation reflex arc. Afferent input from central thermoreceptors in the brain and peripheral thermoreceptors in the skin, muscle, abdomen, and spinal cord is integrated in the thermoregulatory centers of the hypothalamus. Efferent output is then sent to the sweat glands and skin microvessels. Spinal cord injury causes disruptions in neural signaling of both the afferent and efferent arms of the reflex arc below the level of the injury. Additionally, there may be some alterations in how afferent input is integrated in the hypothalamus, and the sweat glands and skin microvessels may become abundant and/or less responsive to neurotransmitter release

and both impact thermoregulatory drive. With SCI, there is a loss of afferent input from spinal thermoreceptors below the lesion and from all skin thermoreceptors located in the dermatomes innervated by spinal nerves below the lesion, representing a sizable reduction in the input coming into the hypothalamus.

The concept of mean body temperature was developed in order to better quantify the afferent input that results in a given thermoeffector output. Commonly, it is considered that core temperature contributes ~80–90 % and skin temperature contributes ~10–20 % to determine the output (e.g., sympathetic neural activity to the cholinergic nerves innervating the skin). SCI results in a significant loss of skin afferent input (up to 90 % loss in a high-level tetraplegia), and a loss of the central thermoreceptors located in the isolated spinal cord. Furthermore, thermoreceptors in the skeletal muscle and abdomen can also contribute a portion to central drive. Therefore, total afferent input received by the hypothalamus (when including input signaled by local hypothalamic temperature) could be reduced by as much as ~30 %. Accordingly, the thermoregulatory centers will respond with equally reduced sympathetic output. For example, Petrofsky (1992) found that mean whole-body sweat rate during exercise was inversely correlated with surface area of insensate skin across AB, paraplegic, and tetraplegic subjects.

In support of this, reductions in sensate skin temperature have a much greater effect on modulating thermoregulatory drive (e.g., shivering) in subjects with SCI compared to AB subjects (Downey et al. 1967, 1971, 1973; Attia and Engel 1983) since the same surface area of skin will contribute a larger overall percentage to the total afferent input.

7.4.3 Reduced Efferent Output and Target Sensitivity

While much of the thermoregulatory impairment can be explained by reduced afferent input, SCI also results in impairments in the effector arm, that is, reduced sweating and skin blood flow for a given sympathetic output. Of course, sweating and skin blood flow will be largely absent in areas below the level of the lesion due to loss of sympathetic innervation. However, SCI is also associated with impairments in these mechanisms in sensate skin. These impairments may be explained by decrements in the neural signal as it travels down the peripheral nerves due to degeneration, differences in the neural-vascular transduction of output to the target areas, or diminished responses of the skin microvessels and sweat glands to a given level of stimulation. The lowered responses could be an aspect of the injury itself, secondary to cardiovascular adaptations attempting to maintain blood pressure (e.g. elevated circulating vasoconstrictors), or as a result of detraining and/or overall health (Johnson et al. 2014).

7.4.3.1 Insensate Skin

Following complete SCI, there is no transmission of signals from the brain to the isolated spinal cord. Even in individuals who have retained some sensory innervation (e.g., ASIA B or C), the autonomic neurons may still be damaged. By this theory, no centrally-mediated increases in sweating or skin blood flow should occur

in response to elevations in core temperature. The majority of studies have supported this, detecting no sweating below the level of the lesion in response to elevations in core temperature, either as a result of high ambient temperature (Tam et al. 1978a; Guttmann et al. 1958; Pollock et al. 1951; Wyndham 1955), exercise (Petrofsky 1992), or a combination of both (Petrofsky 1992). Similarly, increases in skin blood flow below the level of the lesion are minimal (Normell 1974; Yamasaki et al. 2000, 2001; Theisen et al. 2001; Muraki et al. 1995, 1996a, b). However, in some individuals, sweating has been reported in insensate skin. Typically, it is sparse and not synchronous with sensate skin (Huckaba et al. 1976), but some individuals experience profuse sweating below the level of lesion. There are several potential explanations for these observations, as noted below.

Spinal Mass Reflex Profuse sweating can be caused in insensate skin due to a spinal mass reflex. These occurrences are not related to thermoregulation, but instead induced by other noxious stimuli, such as bladder distension, muscle spasms, intestinal conditions, painful stimuli to the skin, or emotional stress (Head and Riddoch 1917; Guttmann and Whitteridge 1947). It is believed that the reflex occurs due to remapping of the sensory and cutaneous sympathetic neurons, much like autonomic dysreflexia, a condition in which noxious sensory stimuli will trigger sympathetic vasomotor nerves, resulting in marked and sudden increases in blood pressure (Erickson 1980; Silver 2000). The spinal mass reflex typically occurs more frequently in the first few months post-injury as, over time, there may be some degeneration of the peripheral nerves. Regardless, this reflex does not originate due to thermoregulatory challenges, and would contribute only modestly to the maintenance of core body temperature.

Peripheral Thermoreceptors Some studies have reported detectable sweating below the level of the lesion in response to high ambient temperature (Randall et al. 1966; Silver et al. 1991). A few theories exist for why this may occur, in support of a local thermoregulatory reflex arc. One explanation for this is that sympathetic sudomotor neurons exiting the spinal cord above the lesion can travel via the paravertebral ganglia and innervate regions of insensate skin. Seckendorf and Randall (1961) were the first to come to this conclusion. They studied subjects with lesions between T3-T8 and so reasonably concluded that sweating in insensate skin must have originated from sudomotor nerves from T1 down to the level of the lesion. However, Randall et al. (1966), in order to ensure complete isolation of the sympathetic nerves, repeated this study in patients who all had complete transections above T1. Even in these subjects, there was some minimal, albeit sparse, sweating in response to high ambient temperatures. These results were confirmed in a later study by Silver et al. (1991). In all three of these studies, sweating ceased once patients were removed from the high ambient temperature despite core temperature remaining elevated (Silver et al. 1991). These authors concluded that there must be an intact thermoregulatory reflex arc below the lesion. Specifically, they suggested that the isolated spinal cord must be able to reflexively respond to input from skin thermoreceptors by stimulating the sympathetic sudomotor nerves, thereby inducing sweating. However, contrary to this hypothesis is the observation

that there is no sudomotor response when the peroneal sympathetic nerves are electrically stimulated (Cariga et al. 2002; Reitz et al. 2002). Together, these observations argue in favor of a local thermoregulatory reflex arc that exists between the sensory nerves and sweat glands, independent of the spinal cord.

Skin Blood Flow and Local Skin Temperature Under conditions of high ambient heat, small increases in skin blood flow in insensate skin may be observed, most likely due to a local thermal hyperemic response. Increases in local skin temperature results in vasodilation due to synthesis and release of nitric oxide (Kellogg et al. 1999; Minson et al. 2001) and endothelial-derived hyperpolarizing factors (Brunt and Minson 2012). However, although present, this response is greatly attenuated in insensate skin compared to sensate skin in both subjects with SCI and AB subjects (Nicotra et al. 2004; Van Duijnhoven et al. 2009). The magnitude of the response is also highly dependent on skin temperature (Choi et al. 2014; Houghton et al. 2006). Thus, little vasodilation will occur during exercise in temperate environments as skin temperature does not increase substantially under these conditions (and may decrease some in individuals with SCI) (Price and Campbell 1997, 1999a). In hot conditions, although a local thermal hyperemia response may occur, this will aid in thermoregulation only minimally due to the lack of temperature gradient between the skin and the environment.

7.4.3.2 Sensate Skin

Despite normally functioning neural pathways, impairments in sudomotor and vasomotor function may exist in sensate skin. Part of this is due to the anatomy of the sympathetic system—e.g., the sympathetic nerves innervating the face and neck exit the spinal cord at T1-T4, thus individuals with a high level of injury may have little to no sweating or increased skin blood flow in seemingly sensate regions of skin. However, sudomotor and vasomotor function is impaired even in sensate skin innervated by intact sympathetic nerves.

Sudomotor Function SCI is associated with reduced sensitivity of the sweat glands to cholinergic agonists (Yaggie et al. 2002). Furthermore, these authors also showed a reduction in sweat gland density and drastically reduced sweat output per gland. These observations were even more dramatic in insensate skin. Interestingly, these effects in sensate areas were partially reversed in athletes with SCI, although chronic exercise was unable to return sweat gland characteristics back to that of AB individuals. It has been demonstrated that sweat gland function is improved following repeated exposures to heat stress, independent of changes in central thermoregulatory drive (Lorenzo and Minson 2010). Similarly, repeated injections of methacholine in the skin of paraplegics resulted in improved sweating in both sensate and insensate areas (Johnson and Johnson 1970). As such, individuals with SCI may experience a peripheral “detraining” of the sweat glands, which may precede changes in central thermoregulation (Ogawa and Asayama 1978).

Vasomotor Function Sympathetically-mediated dilation in response to heat stress (known as 'active vasodilation') is primarily dependent on endothelial-derived vasodilators, such as nitric oxide (Kellogg et al. 1998; Wilkins et al. 2003; Shastry et al. 1998) and prostanoids (McCord et al. 2006). However, vascular tone is reflective of the balance between vasodilator and vasoconstrictor influences, thus vasodilation can be limited by the presence of vasoconstrictors. SCI is associated with widespread declines in vascular function and an increase in circulating vasoconstrictors, such as angiotensin-II (Groothuis et al. 2010) and endothelin-I (Thijssen et al. 2007). Accordingly, active vasodilation is attenuated even in the sensate skin of individuals with SCI (Freund et al. 1984; Muraki et al. 1996a). Although not yet shown experimentally, it is likely that active vasodilation is attenuated due to a combination of limitations imparted by increased circulating vasoconstrictors and impaired nitric oxide bioavailability. Many disease states/conditions, including SCI, are characterized by increased oxidative stress. Under these conditions, free radicals, such as superoxide, can combine with nitric oxide, thus reducing bioavailable nitric oxide and vasodilation. Importantly, exercise training improves nitric oxide bioavailability and NO-dependent vasodilation (Green et al. 2004; Hambrecht et al. 2003). As such, training status will impact active vasodilation in individuals with SCI and thus their ability to thermoregulate (as discussed in more depth below).

7.4.4 Cardiovascular Impairments that Affect Thermoregulation

Other cardiovascular autonomic impairments may also play a role in limiting thermoregulation. During exercise, these limitations become even more apparent due to competition for blood flow between the active skeletal muscles and the skin for thermoregulation. At high exercise intensities, this competition results in reduced skin blood flow and sweating in AB individuals, which is exaggerated in individuals with SCI.

As reviewed in Chap. 6 (Circulatory Responses during Submaximal and Maximal Exercise in SCI), SCI results in loss of sympathetic innervation to the heart and vasculature (depending on the level of injury), resulting in an impaired ability to increase cardiac output (Hopman et al. 1993a, b; Van Loan et al. 1987) and redistribute blood flow (Davis 1993; Hopman et al. 1992a, 1998; Kinzer and Convertino 1989; Hopman 1994). Loss of sympathetic innervation to the heart limits the relative increase in heart rate and contractility that can be achieved with exercise and/or systemic stress. Furthermore, in individuals with SCI, the ability to divert any additional blood flow away from inactive regions, such as the inactive skeletal muscle, towards active regions is impaired due to loss of sympathetically mediated vasoconstriction and loss of the muscle pump. Subsequently, blood may pool in these inactive regions, limiting venous return to the heart and further

limiting cardiac output. In addition to this, individuals with SCI generally have reduced blood volume (Knutsson et al. 1973). As an overall result, the skin is supplied with insufficient blood flow to meet thermoregulatory demands.

Additionally, the splanchnic circulation, which is a highly compliant vascular bed with a large vasoconstrictor capacity, is integral in redistributing blood flow during exercise and heat stress, and is sympathetically innervated by T5-T12. Therefore, individuals with lesions above this range will have the hardest time redistributing blood flow and will likely be the most prone to heat-related illness. Individuals with loss of sympathetic innervation to the heart (above T4-T6), will also have additional challenges, as they lack the ability to (partially) compensate for reduced venous return by increasing heart rate and/or cardiac contractility (Hopman et al. 1993a; Mathias and Frankel 1988).

Another consideration when exercising in the heat is cardiac drift. During exercise in the heat, heart rate 'drifts' up over time as core temperature increases due to direct effects of heat on the sinoatrial node (Fritzsche et al. 1999; Coyle and González-Alonso 2001) and in order to compensate for loss of plasma volume (due to sweating) and the additional blood flow demands of the skin (Rowell 1986). In individuals with SCI, this effect can be seen during exercise even in temperate environmental conditions (Dawson et al. 1994; Fitzgerald et al. 1990; Theisen et al. 2001). For example, paraplegics typically experience higher heart rate compared to AB individuals while exercising in order to compensate for lower stroke volume (Hopman et al. 1992a, 1993a; Christensen and Galbo 1983; Theisen et al. 2001). If cardiac drift occurs, these individuals may reach maximal heart rate much sooner. At this point, they either reach exhaustion and will be forced to stop exercising early, or if they continue as some may be inclined to do in competition, they will greatly predispose themselves to heat-related illness. Individuals with lesions above T4 will be even worse off as their maximal heart rate is determined by vagal withdrawal and is therefore considerably lower than lower-level paraplegics or AB individuals (Van Loan et al. 1987; Coutts et al. 1983).

7.4.5 Medications

Individuals with SCI typically benefit from ongoing medical care to manage the loss of function and prevent more serious complications. As a result, the prevalence of chronic therapeutic medication use is high in the SCI population. The most common types of medications used include those for bladder control, antispasmodics, and pain relievers. Antibiotics and anti-inflammatory medications are often used intermittently. Additionally, anti-hypertensive medications are commonly utilized by people with paraplegia. Many of these can interfere with thermoregulation, and thus should be considered on an individual basis when making exercise and environmental recommendations.

Individuals with SCI can experience either spastic/overactive or flaccid/underactive bladders, depending on the injury. Anticholinergic medications (e.g.,

oxybutynin) are commonly prescribed for spastic/overactive bladders to promote smooth muscle relaxation, whereas flaccid/underactive bladders are commonly treated with cholinergic agonists (e.g., bethanochol) to promote bladder contraction and/or alpha adrenergic blockers (e.g., dibenyline, Flomax) to help relax the sphincter. All of these medications affect the sympathetic nervous system and thermoregulation, often in a competing manner. For example, there have been case studies of patients developing sudden hypotension and hypothermia ($T_c < 36.0$ °C) secondary to the massive sweat induction experienced from concomitant use of cholinergic agonists and alpha blockers (Berard et al. 1989). In opposition, anticholinergics will inhibit sweat production, which could be dangerous for someone exercising in the heat who already has impaired sweating capabilities. Consideration of what medications athletes utilize should be of primary importance given the opposing effects of these medications.

7.4.6 Compensatory Mechanisms

Although humans primarily rely on sweating and increases in skin blood flow for heat loss, respiratory heat loss can be significant under some circumstances, particularly during exercise (Mitchell et al. 1972). In individuals with SCI, respiratory heat loss may serve to compensate for the impaired ability to sweat and redistribute blood flow to the skin. In tetraplegics (C5-C8) with low sweating capacity, minute ventilation increased substantially while resting in the heat (38 °C, 20 %rh for up to 150 min); whereas no increases were observed in AB subjects (Totel 1974). In fact, linear increases of 2.4 L/min for each 1.0 °C increase in oral temperature were observed. These increases were due to increased respiratory rate with no changes in tidal volume, thus it was essentially a 'panting' mechanism. Observations of 'panting' have been reported in other studies in subjects with SCI, although increases in ventilation were not quantified (Guttmann et al. 1958).

7.5 Considerations Based on Exercise Modalities

The aforementioned impairments in thermoregulation mean that individuals with SCI will experience considerably higher core temperatures for a given metabolic rate compared to AB individuals. These differences are greatly exacerbated for exercise in the heat. The types of exercise modalities and sports that individuals with SCI participate in may also present some additional challenges to thermoregulation. As of 2016, there are now 22 sports included in the Summer Paralympic Games and another 5 included in the Winter Paralympic Games. These range from court sports, such as wheelchair basketball, tennis, and rugby, to power lifting, and to continuous-effort sports, such as road racing and triathlon. The specific thermoregulatory factors present in each sport should be considered. For example,

wheelchair road racing requires athletes to be positioned in very compact racing chairs that are low to the ground. Their proximity to the ground while racing outside means that they will be exposed to higher radiant heat from the road surface.

The majority of the older studies on thermoregulation in individuals with SCI used continuous arm-cranking exercise; however, this may not be as applicable to field sports (Price and Campbell 1999b). Arm-crank ergometers require less force to maintain a given speed than wheelchair ergometers, although thermal strain may be higher, perhaps due to differences in propulsion biomechanics (Price and Campbell 1999b). Newer thermoregulatory studies have thus utilized wheelchair ergometers.

Many sports, including wheelchair basketball, rugby, and tennis require intermittent bouts of high-intensity exercise. Intermittent exercise results in increased thermal load compared to continuous exercise at matched overall intensities (Ekblom et al. 1971). Several of the studies presented in other sections attempted to be more applicable to wheelchair sports by utilizing intermittent sprint exercise (e.g., Griggs et al. 2015; Webborn et al. 2005; Goosey-Tolfrey et al. 2008a).

7.5.1 Upper vs. Lower Body Exercise

Even in able-bodied individuals, there are differences in the thermoregulatory responses to upper vs. lower body exercise (Sawka et al. 1989; Asmussen and Nielsen 1947; Nielsen 1968). Typically, upper body exercise results in greater heat production for a given absolute workrate or metabolic rate/VO_2 compared to lower body exercise (Sawka et al. 1984). Due to lower overall muscle mass, the arm muscles must work at a higher percent of maximal intensity in order sustain similar workrates. Efficiency is also reduced at higher intensities (Zoladz et al. 1995), meaning a higher percentage of energy expended is given off as heat rather than used for external work, resulting in greater heat production. Furthermore, due to the reduced muscle mass of the arms compared to the legs, for a given metabolic rate, less afferent input from metaboreceptors and thermoreceptors in the skeletal muscle and venous system will be sent to the brain. This may require more metabolic heat production prior to initiation of heat loss mechanisms. Accordingly, some have suggested that the thermoregulatory set point in the hypothalamus is shifted to a higher core temperature with upper body exercise (Tam et al. 1978a; Asmussen and Nielsen 1947); however, (Sawka et al. 1984) found no difference in threshold or slope of the sweat response.

The cardiovascular system may also limit thermoregulation in upper body exercise. In individuals with SCI, the lack of the skeletal muscle pump limits cardiac output, in turn limiting blood flow that can be routed to the exercising muscles and to the skin for thermoregulation. Due to the smaller muscle mass of the arms, there is less of a need to redistribute blood flow to these muscles during exercise than with leg or whole-body exercise. In individuals with SCI who already have impaired abilities to redistribute blood flow due to loss of sympathetic

vasoconstriction, loss of muscle pump does limit the rise in cardiac output. In fact, studies in which the muscle pump has been artificially created using functional electrical stimulation to the legs (Davis et al. 1990) or by wearing an anti-gravity suit (Hopman et al. 1992b) have shown increases in cardiac output and stroke volume in individuals with SCI during submaximal arm-crank exercise. Interestingly, no effects of the interventions were observed in AB subjects in either of these studies. AB individuals also experience greater plasma volume loss and hemoconcentration with upper body exercise for a given VO_2 (Miles et al. 1983; Pimental et al. 1984), which will limit sweat loss.

One advantage of upper body exercise is that the arms have a higher surface area-to-mass ratio which should facilitate convective heat transfer. However, this does not make much difference when exercise is performed in air. It may, however, make a difference in water since conduction of heat is so much greater (~24× greater). Toner et al. (1984) demonstrated that subjects exercising in 26 °C and 33 °C water had lower core temperature during upper body exercise compared to lower body exercise at a matched VO_2. However, this may not lead to substantial differences in thermoregulation in individuals with SCI, as convective heat loss is already reduced.

7.5.2 Training Status

Trained athletes with SCI are considerably better able to thermoregulate than non-trained individuals. In fact, some studies have shown that trained low-level paraplegics maintain core temperature during exercise in varied temperate conditions on par with AB athletes and have similar mean whole-body sweat loss (Price and Campbell 1999a) (although they still typically experience impaired thermoregulation in warm to hot environmental conditions). As it is almost impossible to exercise without a rise in core temperature, it is likely that much of this adaptation is secondary to an exercise heat-acclimation response.

Endurance exercise training results in earlier activation (shifted threshold to a lower body core temperature) of sweating and active vasodilation (Thomas et al. 1999) and thus elevated sweat rate and skin blood flow for any given body core temperature during exercise (Roberts et al. 1977). However, exercise training also results in functional adaptations to the cutaneous vasculature, namely, the cutaneous vasculature undergoes functional adaptations, such as increased endothelium-dependent dilation (Lenasi and Strucl 2004; Kvernmo et al. 1998; Vassalle et al. 2003). Collectively, these studies demonstrate that improved cardiovascular fitness is associated with a greater skin blood flow response to a given thermal stimuli. That said, there is also evidence that repeated exposure to heat stress, whether through passive heating or exercise heat stress, results in improved sensitivity of the skin and sweat glands to a given neural or chemical input (Lorenzo and Minson 2010).

SCI represents a massive "detraining" stimulus and many of the peripheral adaptations (e.g. sweat gland atrophy and vascular remodeling) may be largely in response to the sudden reduction in physical activity. The higher temperature thresholds required for sweating and active vasodilation are consistent with lower overall fitness following SCI. In paraplegics, long-term exercise training results in increased sweat gland density, increased sweat output per gland, and increased upper body overall sweat rates (Yaggie et al. 2002). Although not shown yet in individuals with SCI, in AB individuals, exercise training shifts the threshold for sweating and skin blood flow to lower temperatures and both are elevated at a given body core temperature. Under conditions of minimal external heat stress, this means paraplegic athletes should be generally able to thermoregulate sufficiently to remove metabolic heat within the "prescriptive zone", that is, the range of ambient conditions that core temperature increases in proportion to the metabolic rate, independent of the environment (Lind 1963). It is not until the environmental temperatures are greater that trained paraplegics experience cardiovascular limitations to thermoregulation. Of course, complete tetraplegic athletes are unable to gain training thermoregulatory adaptations as intact sweating and vasodilator systems are required to achieve these adaptations.

7.6 Strategies for Mitigating Thermoregulatory Dysfunction

As discussed in previous sections, the thermoregulatory limitations of individuals with SCI presents a great challenge to exercise, particularly in warm environments. Individuals with SCI are at elevated risk of heat-related illness in competitive sports compared to the AB population (Price 2006, 2016). In addition to compromised thermoregulation, the impaired ability to sense elevated core temperature means that athletes with SCI are less likely to discontinue exercise at high core temperatures, increasing the propensity toward thermal injury. In addition, the majority of Paralympic competitions are held in hot environments, making it imperative to investigate strategies for combatting heat gain in this population. A variety of strategies have been investigated in the AB population. Evidence of their effectiveness in individuals with SCI is limited, but promising avenues have emerged in recent years.

We have focused this section on strategies for preventing heat-related illness in warm environments, but it is also important to consider strategies for improving thermoregulation during exercise in cold environments, particularly given the rising popularity of adaptive winter sports, such as skiing. Unfortunately, there have been no scientific studies to date to investigate strategies in cold environments. However, we propose some potential options in the last sub-section below.

7.6.1 Cooling

A variety of cooling methods have been investigated in the AB population to improve performance in hot environments. These include cooling vests (Duffield et al. 2003; Hasegawa et al. 2005), whole-body pre-cooling (Kay et al. 1999; White et al. 2003), and hand/foot cooling (Grahn et al. 2005; Livingstone et al. 1995; House et al. 1997; Giesbrecht et al. 2007). The idea behind all of these methods is that, by lowering skin temperature, the skin-to-core temperature gradient will be increased, allowing for greater heat dissipation while requiring less blood to be directed to the skin for that purpose. Blood can instead be routed to the exercising muscles and higher workrates can be maintained, thereby improving exercise performance. Lower skin and core temperature also delays the onset of sweating, preserving plasma volume (Marino 2002).

It has been postulated that cooling before or during exercise may even be more effective in the SCI population due to reduced sympathetically-mediated vasoconstriction, which would normally serve to route blood away from cooler areas of skin, limiting the benefit of cooling. However, despite a wealth of knowledge on the effects of cooling strategies in AB athletes, very few studies have been performed in athletes with SCI (see Griggs et al. (2014) for a recent review of all *nine* studies). Strategies in athletes with SCI are also limited by their biomechanics. Although many devices have been developed for AB athletes, many of them are bulky and impractical for wheelchair athletes utilizing adaptive equipment.

7.6.1.1 Microclimate Cooling Vests

A variety of microclimate cooling garments have been developed and tested for their efficacy in reducing heat strain and improving performance in the heat (Bennett et al. 1995). In individuals with SCI, the two primary types of garments that have been tested are vests containing either ice (e.g. Arctic Heat, Hillsdale, NJ) or renewable phase change material (e.g. Glacier Tek, Inc., West Melbourne, FL). Ice vests have the advantage of being slightly colder (0 °C vs. ~15 °C) and so have greater capacity to remove heat; however, phase change materials may maintain lower temperatures for longer and therefore be better able to attenuate rises in core temperature during long durations of exercise (Chou et al. 2008). Phase change materials tend to be more comfortable against the skin and they may be safer for individuals with SCI when covering insensate skin since they are less likely to cause skin breakdown secondary to local cutaneous vasoconstriction when compared to ice vests (House et al. 2013).

Data on the effectiveness of ice vests in the SCI population are mixed. In endurance-trained athletes with SCI, the ice vest tended to attenuate the rise in core temperature and to reduce heat strain over a 30 min wheelchair time trial in the heat (32.9 °C, 75 %rh), but these differences were minimal (rectal temperature reduced by only 0.3 °C) and non-significant (Armstrong et al. 1995). However,

during intermittent high-intensity exercise in the heat (32 °C, 50 %rh), ice vests successfully reduced the rate at which core temperature increased (Webborn et al. 2005, 2010) and extended the volitional time to fatigue. Additionally, the authors noted that the self-selected workrates were slightly lower initially in the ice vest condition, but were better maintained throughout the exercise protocol, suggesting that cooling during exercise may allow athletes with SCI to better pace their efforts. This observation is important to consider in the SCI population, as their ability to pace may be impaired under normal conditions due to reduced afferent feedback.

Only one study has investigated the cooling abilities of renewable phase change vests in SCI individuals (Trbovich et al. 2014). These authors observed no effect of the vest on attenuating the rise in core temperature during 60 min of indoor team sport play (wheelchair basketball or rugby) in tetraplegic, paraplegic, or AB athletes. Therefore, despite studies demonstrating benefits in laboratory settings (Chou et al. 2008), the renewable phase change vest seems to be less effective in field settings and its utility remains questionable.

7.6.1.2 Refrigerated Headpieces

Refrigerated headpieces have also been designed. Transfer of heat from the head is the highest per surface area compared to other regions of the body, making it an ideal target. Additionally, the scalp lacks vasoconstrictor innervation (Nunneley et al. 1971), enhancing the cooling capacity of these devices. In AB subjects, cooling the head has been shown to be more effective at reducing core temperature than cooling 60 % of the rest of the body (Kissen et al. 1971). In athletes with SCI, cooling the head tended to attenuate the rise in core temperature during a 30-min wheelchair time trial in the heat (32.9 °C, 75 %rh), however these differences were non-significant (Armstrong et al. 1995). It may be the case that the cooling capacity of the headpiece was not able to keep up with the accelerated heat gain of the SCI subjects compared to AB subjects in previous head-cooling studies.

7.6.1.3 Hand/Foot Cooling

The hands and feet have a high abundance of arteriovenous anastomoses (AVAs), pathways that bypass the high resistance arterioles and capillaries of the papillary loops found in the superficial layer of skin. AVA's are structurally linked arterioles and venules and are connected without a capillary, and thus do not contribute to nutritive blood flow. They often form a net-like structure that facilitates the transfer of heat. These pathways open under warm conditions, supplying blood to the venous plexus and facilitating heat loss through a countercurrent mechanism. Cooling of the hands and/or feet targets AVAs and has been shown to be effective at promoting heat loss in AB subjects during rest, exercise, and exercise recovery in the heat (Grahn et al. 2005; Livingstone et al. 1995; House et al. 1997). Devices that

additionally utilize negative pressure to increase blood flow through AVAs have also been developed (e.g. Rapid Thermal Exchange; AVAcore, Inc., Palo Alto, CA), as the cold stimulus would generally cause vasoconstriction and closure of AVA pathways. However, these have not yet been employed in studies on athletes with SCI.

In SCI subjects, continuous cooling of the feet in a 32 °C 26 %rh environment reduced tympanic temperature at rest and attenuated the rise in tympanic temperature during exercise (1.0 °C increase vs. 1.6 °C increase with no cooling) (Hagobian et al. 2004). Foot cooling also had a slight effect in a comparator AB group, however core temperature under non-cooling conditions increased only minimally in this group. Another study utilized hand cooling in 10 °C water during a 10-min recovery period after 60 min of moderate-intensity intermittent wheelchair exercise in 30.8 °C 61 %rh heat (Goosey-Tolfrey et al. 2008b). In just 10 min, the reduction in core temperature was almost 0.5 °C greater in the hand cooling condition compared to no cooling. Additionally, this intervention improved subsequent performance on a 1k time trial. However, the authors noted that some subjects reported numbness and loss of dexterity, particularly when gripping the wheelchair, and in some case blisters, suggesting hand cooling may not be practical for sports where a high level of dexterity is required.

7.6.1.4 Pre-cooling

For sports in which cooling garments are either not allowed by regulations or would impede the biomechanics of wheelchair propulsion, pre-cooling may be a viable option. Whole-body pre-cooling (immediately before exercise) reduces core temperature and improves exercise performance in AB individuals, but these effects are typically brief (Bolster et al. 1999; Booth et al. 1997). In subjects with SCI, 20 min of pre-cooling using an ice vest reduced core temperature at rest by 0.3 °C and attenuated the rise in core temperature during 30-min of intermittent high-intensity exercise in 32 °C 50 %rh heat to a greater extent than cooling by the same method during exercise (Webborn et al. 2005, 2010). However, pre-cooling had no effect on exercise performance, measured by time to volitional fatigue.

7.6.2 Artificial Sweating/Water Spray

Water spray bottles are a much more commonly used and more cost-effective method of cooling compared to the devices previously described. Athletes with SCI commonly use water spray bottles in both practice and competition to mimic the sweating response that AB athletes experience.

To investigate whether water spray bottles actually affect core temperature and heat strain, Pritchett et al. (2010) studied seven paraplegic individuals during two matched trials involving incremental stages of arm-ergometer exercise with 1-min

recovery periods between stages in 22 °C, designed to mimic wheelchair basketball games which typically take place in climate-controlled gymnasiums. In one trial, subjects sprayed themselves ad libitum with a water spray bottle during the 1-min recovery periods. Unfortunately, this resulted in no significant differences in core temperature (esophageal or rectal), mean skin temperature, or thermal sensation, although the authors did observe a slightly lower heart rate by the fourth stage of the water spray trial. Given the limitations of the study, their results do not rule out an advantage of using this strategy. For example, water spraying may be more effective in warmer or drier conditions. Given the large number of athletes with SCI who utilize this strategy and anecdotally notice a difference, it certainly warrants further study.

7.6.3 Heat Acclimation

In able-bodied individuals, heat acclimation is highly effective for reducing heat strain and improving exercise performance in hot environments. Heat acclimation, which typically consists of prolonged low-to-moderate intensity exercise in a hot environment (35–50 °C) for 7–14 consecutive days, has been extensively studied and shown to induce a number of "classical" adaptations. These include reductions in resting core temperature, improved thermoregulation (e.g. higher sweat rate and skin blood flow for a given core temperature secondary to a lowered threshold), and increased plasma volume (Taylor 2014; Périard et al. 2015; Sawka et al. 2000).

Despite the extensive benefits that have been shown in able-bodied individuals, only two studies have investigated whether heat acclimation could also be a viable strategy for improving thermoregulation and performance in individuals with SCI. Price et al. (2011) observed no effects of 7 days of exercise heat acclimation (30 min of moderate intensity exercise followed by 30 min of rest in the heat) in either paraplegics or tetraplegics, although perceived thermal strain was lower in the paraplegics. Conversely, Castle et al. (2013) demonstrated that 7 days of exercise heat acclimation (20 min of low-intensity arm crank exercise followed by 40 min of rest or target shooting practice) reduced core temperature both at rest (aural temperature from 36.3 to 36.0 °C) and during exercise in the heat (average aural temperature over 60 min of exercise: 37.2–36.7 °C) (Fig. 7.5). Estimated plasma volume increased by 1.5 %; however, increases of 5–7 % are common in able-bodied individuals undergoing 7+ days of heat acclimation (Sawka et al. 2000; Nielsen et al. 1993). No changes in sweat rate, either whole-body or by patch placed on T12 vertebra, or heart rate during exercise were observed. These results indicate that heat acclimation may be advantageous in individuals with SCI; however, further studies are required. For example, the authors suggested only partial heat acclimation may have occurred since they were limited in the duration and intensity of heat exposure sessions as all subjects were Paralympic target-shooting athletes

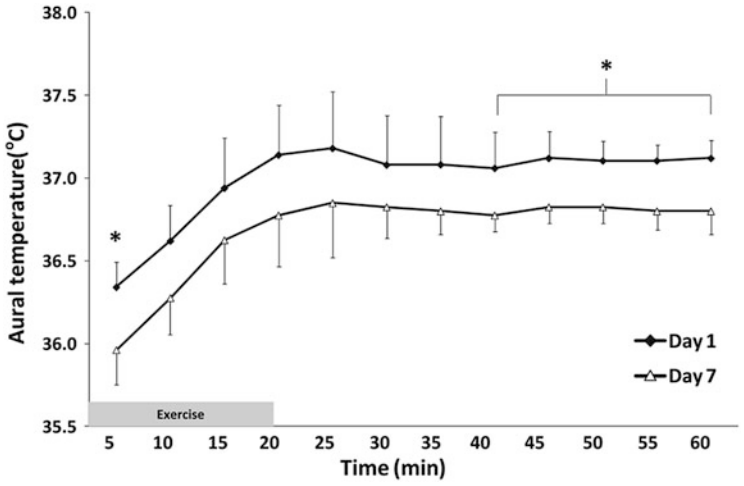

Fig. 7.5 From Castle et al. (2013). Mean ± SD aural temperature during 60 min heat acclimation sessions on day 1 and day 7 in five paralympic wheelchair-dependent target-shooting athletes. Following heat acclimation, subjects experienced a reduction in aural temperature both at rest (prior to entering the hot chamber) and during exercise in the heat

who were competing soon after participating in the study. Longer durations and/or higher target core temperatures would likely induce greater adaptation.

It may also be possible to gain the same benefits of exercise heat acclimation passively, e.g., using hot water immersion or sauna. One such study investigated the effects of 5 days of repeated hot water immersion in paraplegics (Gass and Gass 2001). The only significant change observed in paraplegic subjects was an expansion of plasma volume, estimated using the Dill and Costill (1974) method; however, there were also few significant changes observed in AB subjects (Gass and Gass 2001), suggesting that longer periods of heat exposure are required to elicit adaptation, particularly in response to passive heating.

Two recent studies describe the use of passive heating to improve macrovascular (Brunt et al. 2016a) and microvascular (Brunt et al. 2016b) function in sedentary individuals following 8 weeks of heat therapy. This strategy, utilizing hot water immersion, may prove to be useful for the improvement of vascular health in patients with SCI, but this remains to be studied.

It is also important to note the high degree of variability in responses in this population. The range of injuries and therefore disparate sweat rates and skin blood flow distribution across individuals needs to be considered. As such, extent of acclimation should be determined on an individual basis [for example, by hematocrit after a heat stress test as proposed by Racinais et al. (2012)] rather than applying the same protocols and ambient temperature regulations across entire teams.

7.6.4 Body-Weight-Supported Treadmill Training

Body-weight-supported treadmill (BWST) training is a form of rehabilitation in which patients participate in upright treadmill ambulation with the assistance of a harness and pulley system that is supporting the majority of the patient's weight. It has previously been shown to improve ambulation (Hicks et al. 2005), partially reverse muscle atrophy (Giangregorio et al. 2006), and improve heart rate and blood pressure variability (Ditor et al. 2005) following SCI, among other advantages. Cotie et al. (2010) demonstrated that 4 weeks of BWST training lowers resting leg skin temperatures. The authors approached this question from the standpoint of utilizing BWST training to reduce the incidence of pressure ulcers, as these have been associated with higher skin temperatures (Bergstrom and Braden 1992; Fisher et al. 1978). Higher skin temperatures increase the metabolic demand of the tissue, increasing ischemic tissue damage; however, lower resting skin temperature could also prove advantageous for facilitating heat loss during exercise. Of course, future studies are required to determine whether BWST actually provides any thermoregulatory benefit during exercise and/or during heat exposure.

7.6.5 Strategies for Thermoregulation During Exercise in Cool Environments

Studies investigating strategies for thermoregulation in individuals with SCI have focused on preventing heat-related illness in warm environments. However, it is important to also consider how thermoregulatory impairment can be mitigated during exercise in cold environments. This issue is particularly timely given the rise in participation in winter sports like skiing by individuals with SCI.

The two main dangers during exposure to cold environments include the risk of hypothermia and frostbite. In terms of hypothermia, there are two main types: primary and secondary hypothermia. Primary hypothermia occurs when a person is subjected to extreme cold, whereas secondary refers to hypothermia in relatively mild or modest environmental conditions caused by an inability to adequately regulate body core temperature, as can occur with certain medications. Thus, the likely causes of hypothermia in an individual with SCI include inappropriate vasodilation (possibly medication induced), inappropriate sweating, or inadequate heat production through metabolism (Menard and Hahn 1991). In the latter case, this can be due to the lack of shivering below the lesion or due to reduced thyroid function, which has been reported in SCI (Bloch 1986). In both cases, the best practice is avoidance of extremely cold temperatures for those individuals with impaired thermoregulatory responses. In extreme cold conditions, frostbite can be a significant risk to the SCI athlete, especially in insensate areas of the skin. Direct contact with the metal on wheelchairs can increase this risk in both sensate and insensate areas. For athletes with SCI, it is important to customize clothing based on

their personal thermoregulatory impairment, the intensity and duration of exercise they will be performing, and of course the environmental conditions. The transitions between exercise and recovery can pose risks for hypothermia as well, with rapid cooling and a drop in body core temperature if the individual was sweating or clothing became saturated. Thus, proper clothing is important to the individual with SCI as much as able-bodied athletes.

7.7 Conclusions

With the possible exception of very low level SCI in temperate conditions, overall thermoregulatory function is diminished in individuals with SCI during exposure to hot or cold environments. While a reduced capacity for vasoconstriction and shivering places these individuals at greater risk of hypothermia, a greater risk centers on the dangers of hyperthermia. The reduced ability to thermoregulate in hot environments places these individuals at much higher risk of heat-related illness and death during environmental extremes such as climatic heat waves and during exercise in a hot environment. The thermoregulatory challenge for this population is primarily due to the limited ability to adequately raise skin blood flow and actively sweat in order to match heat loss to heat gain from the environment or the metabolic heat produced during exercise. The total area of sensate to insensate skin is a strong predictor of their ability to tolerate a given thermal stress; however, thermoregulatory responses are diminished in sensate area of skin as well, although the exact reasons for this are not clear and likely vary between individuals. There seems to be increasing interest in finding novel approaches to protect SCI athletes from heat-related disorders during training and competition, however more research is needed to better determine ideal approaches. There is also a need to better understand the limits to how much adaptation is possible in people with SCI, so that exercise programs and heat acclimation paradigms could be designed to limit the risk in this vulnerable population.

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Chapter 8
Increased Bone Fracture After SCI: Can Exercise Reduce Risk?

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Abstract Bone density decreases rapidly in spinal cord injured (SCI) individuals to approximately 60 % of normal bone mass within the first 3 years after injury. The loss of bone mass, called *disuse osteoporosis*, results in low energy fractures, which are prevalent and extremely debilitating in this population. Bones are sensitive to their mechanical environment, promoting formation under high loads and resorption under low loads. In the SCI population, bone becomes osteoporotic solely due to the lack of mechanical stimulus. The bone loss after injury is site specific, occurring particularly at sites rich in trabecular bone, such as proximal tibia and distal femur. Harnessing the mechanosensitivity of human bone has been the central idea of therapeutic interventions to maintain bone mass and ensure bone strength in the SCI population. Numerous studies have investigated activities based training exercises such as passive weight bearing, gait training, isometric functional electrical stimulation (FES), cycling loading, FES-cycling, and FES-rowing. Only a few of these interventions have been effective in maintaining bone health and none of them have led to promoting bone formation. The most promising results in mechanical loading therapies for maintaining bone health are in acute patients. Mechanical interventions in the early stages post-injury might take advantage of the bone's ability in young, acute SCI individuals to adapt to mechanical load.

8.1 Bone Adaptations After Spinal Cord Injury

The pathogenesis of osteoporosis after a spinal cord injury (SCI) is considered to be multifactorial, resulting from hormonal changes, neuronal mechanisms (Jiang et al. 2006a), and a lack of mechanical loading (Amin 2010; Judex and Carlson 2009). Because bones adapt to their mechanical environment by adding more bone under high loads and resorbing bone that is unloaded [Wolff's law (Wolff 1986)], the loss of mechanical loads in spinal cord injured patients results in bone

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resorption in the paralyzed limbs (Lanyon 1996; Schultheis 1991). The absence of mechanical loading is the primary contributor to *disuse osteoporosis* that occurs in the SCI population. The loss of muscle contraction and weight bearing result in a lack of mechanical stimulus to the bone. An imbalance between osteoclastic (bone resorption) and osteoblastic (bone formation) activity develops as bone resorption takes over bone formation, resulting in SCI-induced bone loss.

Bone density decreases rapidly in those with SCI, especially in the initial post-injury phase (Fig. 8.1). Within the first few months, bone mineral density (BMD) begins to decline 2–4.7 % per month (Edwards et al. 2014a; Wilmet et al. 1995), with BMD losses exceeding 34 % by the end of the first year and 52 % by the end of 4 years (Dudley-Javoroski and Shields 2012; Jiang et al. 2006b). This decline in BMD continues up to 7 years post-injury (Eser et al. 2004; Hangartner et al. 1994), reaching steady state values of approximately 60 % of normal bone mass (Jiang et al. 2006b; Eser et al. 2004). In addition, the bone loss has been associated with the bone type, with an initial loss of 51.5 % in trabecular bone and only 32.7 % loss in cortical bone in the first 2 years post-injury (Hangartner et al. 1994).

Bone loss after injury is site specific, with severe bone loss in the sublesional regions. Studies that have investigated BMD loss in supralesional regions have shown that lumbar spine BMD is not different than that of the control groups (Dauty et al. 2000; Kaya et al. 2006). The bone loss occurs particularly at sites rich in trabecular bone, such as proximal tibia and distal femur (Wilmet et al. 1995; Dauty et al. 2000; Frey-Rindova et al. 2000). In addition to the overall loss of bone mass, there are also bone structural changes that occur post-injury, such as alterations in bone area and bone geometry (de Bruin et al. 2000a; Kiratli et al. 2000). With trabecular bone being more susceptible to demineralization, the SCI patient has fewer and thinner trabeculae, resulting in an extensive irreversible destruction of trabecular bone microarchitecture (Modlesky et al. 2004; Slade et al. 2005). The bone loss occurs in a smaller amount in the diaphyseal cortical bone (Frey-Rindova et al. 2000).

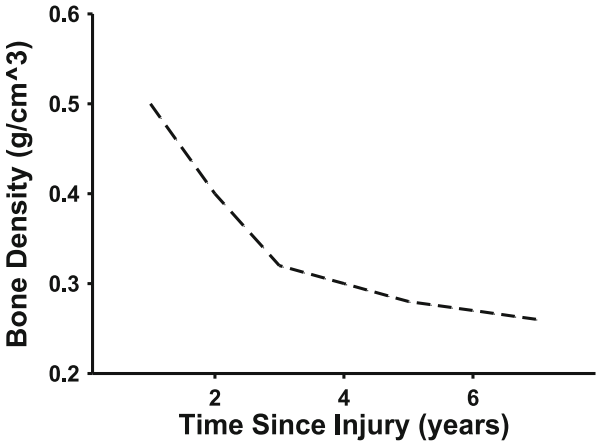

Fig. 8.1 Trabecular bone mineral density as a function of time after spinal cord injury. Adapted from Dudley-Javoroski and Shields (2012), Hangartner et al. (1994)

8.2 Risk for Fractures

The clinical consequence of bone loss and bone structural changes post-injury is an increased fracture risk. These fractures are typically low-energy fractures caused by minimal to no trauma. The reported causes of fracture by those with SCI are daily activities such as bathing, dressing, transfer activities from wheelchair to bed, non-traumatic events such as stretching in bed (Comarr et al. 1962; Lala et al. 2014; Vestergaard et al. 1998), and even due to rehabilitation protocols for muscle strengthening (Fournier et al. 1984; Hartkopp et al. 1998). These fractures generally heal poorly, leading to pressure ulcers from bracing and bed rest. More than 50 % of the fractures that require hospitalization lead to further medical complications, such as fracture non-union, delaying the healing process (Comarr et al. 1962; Frotzler et al. 2008; Gifre et al. 2014; Nottage 1981).

The prevalence and exact incidence rate of fracture post-injury is not yet well established. An estimate of 50 % of those with SCI will sustain a low-energy or osteoporotic fracture post-injury (Szollar et al. 1998), with a lower extremity fracture risk rate of 1.2–3.5 per 100 patients-years (Gifre et al. 2014; Carbone et al. 2014; Lazo et al. 2001; Morse et al. 2009a). Individuals with SCI have twice the risk of experiencing a lower extremity fracture when compared to age and gender matched controls (Vestergaard et al. 1998; Lazo et al. 2001). Fragility fractures post-injury occur around regions of the knee, the proximal tibia and the distal femur, which are the primary sites of bone resorption (Szollar et al. 1998; Eser et al. 2005; Uebelhart et al. 1995). Time since injury and severity of injury are the main determinates of fracture in the SCI population (Gifre et al. 2014; Carbone et al. 2014). Femur areal bone mineral density and suboptimal bone geometry have been significantly associated with fractures post-injury (Lala et al. 2014; Lazo et al. 2001). Coincidently with the observed bone mineral loss, fracture risk is higher in those with motor complete injuries compared to those with motor incomplete injuries (Lala et al. 2014; Gifre et al. 2014; Morse et al. 2009a; Logan et al. 2008), and paraplegics have an increased risk of fracture compared to quadriplegics, likely due to their increased mobility (Eser et al. 2005; Wang et al. 2001).

8.3 Bone Imaging After Spinal Cord Injury

Dual energy X-ray absorptiometry (DXA) is the ‘gold standard’ modality employed to assess bone mass (Dauty et al. 2000). In the SCI population, DXA is used to assess specific segments, including lumbar spine (L1-L4), distal femur, proximal tibia, and radius. However, the assessment of BMD through DXA is limited to a two-dimensional (2D) projection and thus cannot offer information regarding volumetric changes in bone mineral content. Also, DXA measurements do not allow assessing changes in trabecular and cortical bone, which make unique

contributions to bone strength (Bousson et al. 2006; Manske et al. 2009) and respond differently to bone loss therapies (Keaveny et al. 2008, 2012). Moreover, DXA is misleading when comparing bones of different sizes (Carter et al. 1992) and it is prone to positioning errors of the imaged limb (Messina et al. 2015).

Clinical quantitative computed tomography (QCT) is a three-dimensional imaging modality that decreases the projection effects seen with two-dimensional DXA. Even though QCT allows imaging of the main fracture sites in the SCI population, distal tibia and proximal femur, at an in plane-resolution of approximately 200–500 μm (Burghardt et al. 2011), this resolution is insufficient to isolate trabecular parameters and cortical porosity (Engelke et al. 2015). Additionally, QCT is associated with high doses of radiation.

Peripheral quantitative computed tomography (pQCT) allows for a non-invasive, low-radiation method of assessing three-dimensional bone architecture and volumetric bone mineral density in the cortical and trabecular compartments (Edwards et al. 2014b, c), but is limited to peripheral sites such as the distal tibia or radius. High resolution pQCT (HR-pQCT) has sufficient resolution to resolve trabecular micro-architecture, producing images with a voxel size of up to 61 μm (Manske et al. 2009; Cheung et al. 2013), but is currently not used as a standard clinical diagnostic.

8.4 Fracture Risk Assessment After Spinal Cord Injury

The successful development of bone loss therapies require a clinical fracture risk assessment specific to the SCI population (Morse et al. 2009b). Low femoral neck BMD, low distal femur and proximal tibia BMD, and suboptimal bone geometry have been used to quantify fracture risk in individuals with SCI (Lala et al. 2014; Lazo et al. 2001). However, the current modalities employed to diagnose osteoporosis using BMD measurements are inadequate for the SCI population. The majority of DXA scans used to assess areal bone mineral density (aBMD) are performed at the spine and hip. In the SCI population, the relevant sites for assessing BMD are the distal femoral metaphysis or proximal tibial metaphysis, as they are the sites with the highest demineralization rate and fracture risk (Eser et al. 2004; Szollar et al. 1998; Uebelhart et al. 1995). However, to date, there are no established clinical protocols for scanning these sites. Additionally, a bone fracture threshold has not been clearly established; the aBMD scale to diagnose osteoporosis and quantify fracture risk is representative of postmenopausal women and men over the age of 50 (Kanis 1994). Garland et al. (2005) reported a fracture threshold of 0.78 g/cm^2 at the knee in males with SCI. Peripheral QCT might offer new ways of assessing fracture risk, Eser et al. (2005) reporting a trabecular volume BMD (vBMD) fracture threshold of 114 mg/cm^3 in the distal femur and 72 mg/cm^3 in the proximal tibia in motor complete SCI individuals. Measurements of cortical thickness via pQCT are also associated with fracture fragility in those with SCI (Lala et al. 2014; de Bruin et al. 2000b).

Even though radiographic modalities can be used to assess fracture risk, significant amounts of bone must be lost before radiographic changes are evident. Thus, various biomarkers have been identified to assess bone response to exercise interventions and to predict fracture risk. Human serum collagen type I N propeptide (PINP) and the serum C-terminal telopeptide of type I collagen (CTX) are reference standards for assessing bone resorption (Vasikaran et al. 2011). The use of biomarkers to address bone turnover in the SCI population is recent. Sabour et al. (2014) confirmed that CTX is a bone resorption marker by identifying a negative correlation between CTX level and BMD in femoral and spinal bone sites in chronic SCI individuals. Six months of gait training in chronic SCI individuals showed no change in PINP and CTX levels, correlated with no change in spine, hip or femoral neck BMD (Gordon et al. 2013). However, using micro magnetic resonance imagining, the same study showed an anabolic effect on trabecular thickness after the first three months of training that was not maintained with future training. Also, Astorino et al. (2013) showed no effect on PINP and CTX with 6 months of activity based training in chronic SCI individuals. The training demonstrated only an increase in spine BMD, but no significant change in the distal femur or proximal tibia BMD.

From the few studies that used bone biomarkers to assess bone remodeling in response to exercise, it is unclear if these biomarkers are sensitive enough to capture small changes in bone resorption or bone building, or if the intervention therapies are simply not effective. Only Astriono et al. (2013) investigated BMD changes in the primary sites of interest in the SCI population using both BMD measurements and PINP and CTX levels. However, neither of them were able to detect changes in bone loss, which suggests that actually the training therapies investigated might not be effective in preventing bone loss in those with chronic SCI. Thus, the effectiveness of bone biomarkers requires further investigations, which would include activity based therapies with greater potential in bone remolding.

8.5 Pharmaceutical Interventions

Although the pathogenesis of bone loss after SCI has been well established, the current pharmaceutical and non-pharmaceutical interventions have not been proven highly effective in reducing or mitigating bone loss. Pharmaceutical interventions (usually bisphosphonates) can slow the resorption of bone immediately after injury (Bauman et al. 2005a; Bubbear et al. 2011), but have shown to have little effect in overall amount of bone loss (Moran de Brito et al. 2005), and no effect on increasing bone mass after it has been lost.

In individuals with chronic SCI, low levels of vitamin D have been associated with poor physical function (Barbonetti et al. 2016). Due to the role of vitamin D on bone metabolism, clinical interventions have tapped into the potential of vitamin D analogs to increase bone mass and treat various forms of osteoporosis. In the acute phase of SCI, pharmaceutical interventions with vitamin D have been

associated with better functional recovery (Aminmansour et al. 2015). Even though vitamin D has been shown to reduce bone loss rate on the hemiplegic side of patients with a long-standing stroke (Sato et al. 1997), in the SCI population vitamin D has been used successfully mostly as a bone mass biomarker (Benlidayi et al. 2016). In chronic tetraplegia, Bauman et al. (2005b) showed that 12-months treatment with vitamin D analogues can maintain leg BMD, but the long-term effect should be further investigated. However, in the chronic stages post-injury, the bone loss has been shown to reach a steady level, and thus the effect of vitamin D might be minimal.

Even though there are pharmaceutical interventions that slow down bone resorption in the acute phase or maintain bone loss in the chronic stages, there is a need for interventions that that promote bone formation once it has been lost.

8.6 Bone Response to Training

Non-pharmaceutical interventions have taken advantage of the importance of mechanical loading on bone metabolism. According to Wolff's law (Wolff 1986), bones are sensitive to their mechanical environment; the external shape and the internal trabecular architecture adapt in response to the stresses applied. Bone continually remodels in response to the stresses and strains applied. High stresses, resulting in high strains, promote bone modeling achieved by the recruitment of the osteoblasts, leading to enhanced cortical thickness and trabecular BMD. Under low loads, the low strain levels will induce bone loss via remodeling through osteoclasts activity. Thus, there are numerous exercise therapies that employ different forms of mechanical stimulation to improve bone health in paraplegics.

The main activities that provide weight bearing in the able-bodied population are standing and walking. Since therapeutic standing is usually incorporated in the rehabilitation programs post-injury, numerous studies have investigated the effectiveness of passive weight bearing in a standing frame for preventing osteoporosis in the SCI population. However, the use of body weight-supported training has shown only modest benefits. A regular standing (with a standing frame) intervention with an average duration of 6 months did not show any changes in femoral BMD in chronic SCI individuals (Kunkel et al. 1993) and did not prevent bone loss in either tibia or femur BMD in acute SCI individuals (Giangregorio et al. 2005). Even a longer standing intervention of 4.2 years in chronic SCI individuals showed no changes in femoral BMD, with only a slight increase in proximal femur BMD in the group with the longer daily standing time (Goktepe et al. 2008). A cross-sectional study indicated that early standing intervention might attenuate normal bone loss. Standing with long leg braces, standing frame, or standing wheelchair in the acute phase post-injury in complete SCI individuals showed a slight preventive effect on bone loss in the femoral shaft and tibial trabecular bone (de Bruin et al. 1999), but not at the proximal femur (Goemaere et al. 1994). Thus, even though therapeutic standing might be effective in reducing immobilization, it

appears to have limited effects on bone health and it might be limited to early interventions post-injury. Static loading achieved through body weight passive standing seems to be insufficient in preventing bone loss.

Low-magnitude whole body vibration has been another form investigated for delivering mechanical stimuli to benefit bone health. In the able-bodied population, low-intensity vibrations loads characterize the daily bone strain history (Fritton et al. 2000). Thus, in the absence of muscle contractions due to walking, the lack of low-magnitude strains might also be one of the potential reasons for osteoporosis after SCI. The low-magnitude vibrations provide a mechanical stimuli to the bone as a vertical oscillation. The mechanical signal is transmitted to the bone cells either through the changes in intermedullary pressure in the lacuna-canalicular network or through changes in fluid flow or sheer forces (Burger and Klein-Nulend 1999). Numerous animal studies provide strong evidence that low-magnitude vibratory loads are sufficient to stimulate anabolic activity (Bramlett et al. 2014; Garman et al. 2007; Rubin et al. 2001, 2002). A few studies have tried to replicate in individuals with SCI the mechanical loading conditions that have been successful in animal studies (Asselin et al. 2011; Davis et al. 2010; Dudley-Javoroski et al. 2015; Wuermser et al. 2015). However, whole-body low magnitude vibration or constrained lower limb vibration (Dudley-Javoroski et al. 2015) for extended periods of time (6–12 months) did not yield adaptations in BMD or trabecular micro-structure for the distal tibia or the distal femur. A single individual case study reported significant positive changes in BMD for trunk and spine from a combination of standing with simultaneous whole-body vibration (Davis et al. 2010). However, the lack of effectiveness of low-magnitude vibrations in improving bone density and structure in these studies might be due to the selected population; almost all of the participants had a chronic SCI. Vibration might inhibit resorption rather than induce formation (Vanleene and Shefelbine 2013), which would make it ineffective in the chronic population.

Exercise interventions have used functional electrical stimulation to generate isometric contractions to facilitate gait or to produce contractions against resistance during leg extensions. High-magnitude compressive loads generated by electrical muscle stimulation of different groups of muscles has been investigated as a potential intervention for reducing bone loss. Functional neuromuscular stimulation (FNS)-induced knee extension (KE) resistance exercise applied three times a week for 12 weeks appeared to decrease the rate of tibial bone loss in a group of complete and incomplete acute and chronic SCI individuals, with eight out of nine individuals experiencing a bone loss rate lower than predicted (Rodgers et al. 1991). High volume of electrically induced plantar flexor muscle contractions, resulting in a high dose of 1–1.5 body weight (BW) across the tibia, for an average of 2 years of training (5 days/week) decreased the rate of trabecula BMD in the tibia in acute complete SCI individuals (Shields et al. 2006; Shields and Dudley-Javoroski 2006). There was no effect on cortical bone. This suggests that because trabecular bone is more metabolically active than cortical bone, it responds more readily to stresses induced by isometric loading even after extensive neurological compromise. Moreover, in acute complete SCI individuals, high dose compressive load (1.5 BW)

administered via quadriceps activation in supported stance training for over 3 years resulted in an attenuation in distal femur BMD decline and in an attenuation of trabecular architecture deterioration in the tibia when compared to passive standing (low dose loading 0.4 BW) or no standing (no loading) in individuals with SCI (Dudley-Javoroski et al. 2012). Even though electrically induced muscle contractions appear to decrease the rate of tibial and femoral bone loss in SCI subjects, there are also studies that present contradictory results. Clark et al. (2007) showed no changes in total body BMD or hip BMD in acute SCI with quadriceps and plantar flexion muscle stimulation training exercises. However, the stimulation used represented a low-intensity dose, which is actually similar to the passive standing group (low dose loading 0.45 BW) in the Dudley-Javoroski et al. study. Moreover, quadriceps electromyostimulation for a period of 14-weeks in acute SCI individuals showed no changes in lumbar spine, hip and femoral neck BMD between pre and post-intervention (Arija-Blázquez et al. 2014). However, the measured sites are not the same in all studies and since bone mineral adaptations are limited to the bone area under mechanical stress, this might be a possible reason for the conflicting results. Additionally, the duration of the training protocols of the studies that showed bone adaptations to electrical stimulation was at least 2 years, compared to only 5–6 months of training that resulted in no significant effect on bone metabolism.

Applying compressive loads through a combination of standing, walking using treadmill or different ambulation devices and electrical stimulation did not yield more promising results than standing alone. Even though these interventions allow for gait restoration, no femoral bone density changes have been measured in chronic and acute SCI (Needham-Shropshire et al. 1997; Thoumie et al. 1995).

Functional electrical stimulation (FES) assisted exercise therapies use coordinated muscle contractions for more complex movements, such as FES-cycling and FES-rowing. In chronic SCI individuals, FES-cycling results in negligible changes in bone metabolism. Training protocols of 6 months (3x/week) of FES-cycling led to no significant bone adaptations in the lumbar spine, tibia or femur (Hangartner et al. 1994; BeDell et al. 1996) for both low cadence and high cadence cycling (Johnston et al. 2016). In the acute SCI individuals there might be a small beneficial effect in attenuating bone loss. FES-cycling seems to have site specific effects with increased trabecular BMD in the distal femur but no effect in the cortical bone or tibia (Frotzler et al. 2008; Lai et al. 2010). Lai et al. 2010 showed also that even though FES-cycling could partially attenuate bone loss in the distal femur in the acute stages, these benefits are lost after 3 months without FES-cycling. On the other hand, Eser et al. (2003) showed that 3 days per week for 6 months of low intensity FES-cycling in the acute period post-injury leads to no significant attenuation of tibial diaphysis bone loss. Since the studies investigated different sites for bone adaptation, a comparison is not possible.

A single case study of FES-rowing showed that high intensity FES-row training could reduce bone loss in chronic SCI (Gibbons et al. 2014). High intensity, long term FES-rowing (8 years) resulted in an increase in proximal tibial trabecular

BMD, suggesting that FES-rowing could have positive results in attenuating bone loss post-injury.

8.7 Conclusions

The impact of training based interventions on bone health varies on several factors such as exercise protocol, timing (acute vs. chronic), frequency and duration of exercise, and type (static loading vs. dynamic loading enabled by FES). Though it is widely accepted that bones respond to mechanical loading, there have been surprisingly few effective mechanical loading exercise therapies for maintaining bone health in paraplegics. The ineffectiveness of these bone loading therapies in improving bone health in the SCI population might derive from a variety of reasons.

The load applied might have insufficient intensity (magnitude, number of cycles) for promoting bone growth. Very few studies quantify the magnitude of the load applied and the number of loading cycles. In one of the few studies that did quantify load, it was shown that FES quadriceps stimulation resulting in loads of 150 % BW increased BMD, while loads of 50 % BW were ineffective (Shields et al. 2006). An exact quantification of these parameters would help understand the relationship between the mechanical stimulus and the bone response, which would lead to developing more effective mechanical therapies for inducing bone growth and slowing down bone resorption post SCI. Different types of bone (trabecular vs. cortical) respond differently to loading. The studies in FES-cycling showed site specific response with increased trabecular BMD in the distal femur but no effects in the cortical bone or tibia (Frotzler et al. 2008). However, the current investigation methods may not always be examining the right bone or the right region of the bone. Additionally, the existent imaging modalities might not have sufficient resolution to detect small changes in bone remodeling that might occur with the current exercise interventions. Thus, improved imaging modalities are necessary to better measure the response in the appropriate locations.

Another reason might be that bones of those with chronic SCI are insensitive to mechanical loading. The most promising results in mechanical loading therapies for maintaining bone health are in the acute stages, where therapies act to reduce the amount of bone lost. The bones of acute SCI individuals likely possess the ability to adapt to mechanical load, if the load is applied at sufficient magnitude and frequency. Taking advantage of the bone sensitivity to load in the acute stage post-injury might provide a non-pharmaceutical therapy to prevent bone loss and open new avenues to treat disuse osteoporosis in the SCI population.

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Chapter 9
Alterations in Body Composition After SCI and the Mitigating Role of Exercise

David R. Gater and Gary J. Farkas

Abstract Spinal cord injury (SCI) profoundly influences human body composition due to an obligatory sarcopenia, drastically reduced basal metabolism and subsequent development of neurogenic obesity. This chapter will review the pathophysiology of SCI and adipose tissue, report on the current state of the science for body composition assessment in this vulnerable population and reflect upon the literature demonstrating body composition changes through exercise for persons with SCI. Recommendations for future investigations will also be provided.

9.1 Overview

Spinal cord injury profoundly impacts almost all aspects of a person's life, including their anatomy, physiology, psychosocial interactions, spirituality and self-esteem, all of which contributes to an individual's body composition. Spinal cord disruption influences sensory and motor pathways in both central (CNS) and peripheral nervous systems (PNS), affecting perceived and unperceived afferent signals from the body, as well as voluntary and involuntary activation of smooth, cardiac and skeletal muscle. Upper motor neuron injuries result in spastic paralysis, i.e., involuntary, velocity-dependent hyperreflexia which may attenuate obligatory sarcopenia and bone loss, whereas lower motor neuron damage results in flaccid muscle paralysis with even more pronounced muscle atrophy and bone resorption. Additionally, autonomic nervous system (ANS) disruption, especially blunting and abnormal reflex activity of the sympathetic nervous system (SNS) can mitigate exercise responses in a way that can be detrimental to body composition. The combination of somatic and ANS disruption after SCI can render even an elite athlete subject to acute comorbidities including spastic or flaccid paralysis, neurogenic hypotension, neurogenic bradycardia, neurogenic adaptive cardiomyopathy,

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circulatory hypokinesis, autonomic dysreflexia, neurogenic restrictive and obstructive pulmonary dysfunction, neurogenic bowel, neurogenic bladder, neurogenic skin, immobilization hypercalcemia, osteopenia/osteoporosis, heterotopic ossification, musculoskeletal contractures, rapid and profound muscular atrophy, blunted anabolic hormonal responsiveness and poikilothermia. Each of these comorbidities contributes to a markedly reduced energy metabolism which can seldom be countered with a sufficient reduction in energy intake to achieve energy balance, resulting in a net increase in adipose accumulation, referred to from this point forward as neurogenic obesity.

9.2 Adipose Tissue Pathophysiology

Adipose tissue is a specialized connective tissue comprised of lipid-filled cells within a collagen fiber framework that represents stored energy in the human body, i.e., the excess energy accumulated as the result of energy intake exceeding energy expenditure over time. While adipose tissue also serves as a mechanical cushion and insulator to conserve heat, its main purpose is to serve as a reservoir for stored energy. Triglycerides make up more than 90 % of the adipocyte, with small amounts of free fatty acids, diglycerides, cholesterol, phospholipids and monoglycerides contributing the rest, as well as minimal amounts of water and protein. Adipose (fat) density is only 0.901 g/ml and with an energy density of 9 kcal/g, it represents a remarkably efficient way to store energy relative to other foodstuffs such as carbohydrates (4 kcal/g) and protein (4 kcal/g) (Gater 2007). Alternatively, fat-free mass density in the human body is 1.100 g/dl and is metabolically active tissue, such that the body only retains the minimal amount of fat-free mass to sustain usual activities. Hence, metabolically active tissues within the body are resynthesized according to the law of supply and demand (use it or lose it), whereas non-metabolic, energy-dense adipose tissue is generated (lipogenesis) and spared for times of need.

Once thought to be benign stored energy, adipose tissue has been demonstrated in recent years to be the primary mediator of metabolic syndrome, contributing to dyslipidemia, hypertension and insulin resistance while spewing proinflammatory cytokines, prothrombotic and vasoactive substances that further contribute to arteriosclerosis (Grundy 2008). As adipose tissue accumulates, particularly around visceral organs, circulatory non-esterified free-fatty acids (NEFA) and triglycerides overwhelm the portal circulation of the liver, increasing the production of very-low-density (VLDL) and low-density (LDL) lipoproteins, as well as apolipoprotein B which has been highly correlated with premature coronary artery disease (Kolovou et al. 2005; Kwiterovich et al. 1993). Conversely, synthesis of apolipoprotein A, the primary protein associated with “good” high-density lipoprotein (HDL) cholesterol is inhibited and catabolism is increased in the presence of elevated NEFA and triglycerides, rendering the vascular tree subject to accelerated arteriosclerosis. Arteriosclerosis reduces capacitance and worsens compliance of the vascular tree,

contributing to elevated blood pressure. Visceral fat accumulation compresses the kidneys, activating the renin-angiotensin-aldosterone system (RAAS) and increasing intrarenal pressures and sodium retention, but also secretes leptin which directly increases sympathetic nervous system activity and vascular tone (Wofford and Hall 2004). Adipocytes also secrete angiotensinogen, a potent vasoconstrictor, further contributing to adipose-induced hypertension. Within muscle, liver and adipocytes, fatty acid metabolites such as ceramides and diacylglycerol directly inhibit the PI-3 kinase cascade, subsequently blocking the translocation of glucose receptors (GLUT-1, GLUT-4 and GLUT-6) within the cell to the cell membrane, rendering the cells insensitive to insulin (Shulman 2000; Summers et al. 1998). The proximal insulin signaling cascade is further inhibited by interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) secreted directly by adipocytes (Hotamisligil et al. 1994). These proinflammatory cytokines have also been demonstrated to cause low-grade vascular inflammation and stimulate the synthesis of acute-phase reactants, C-reactive protein (CRP) and fibrinogen which have been directly and indirectly implicated in vascular endothelial cell injury and apoptosis (Blake and Ridker 2001). In recent years, adipose tissue has been shown to secrete plasminogen-activator inhibitor (PAI-1) and to increase the secretion of thrombin-activatable fibrinolysis inhibitor (TAFI) from the liver, both of which impair fibrinolysis and increase the risk for thromboembolism (Aso et al. 2005; Aubert et al. 2003).

In addition to the metabolic syndrome of obesity, diabetes, hypertension, dyslipidemia and arteriosclerosis, adipose tissue accumulation has been implicated as a significant contributor to breast cancer, carpal tunnel syndrome, cerebrovascular accidents, cholecystitis, cholelithiasis, colon cancer, depression, gout, nephrolithiasis, obstructive sleep apnea, osteoarthritis, peripheral arterial disease, pressure ulcer development, reproductive dysfunction and social isolation (Gater 2007). When factored in with the physiological, metabolic, mobility, functional and psychosocial deficits associated with SCI, adiposity (obesity) may be the greatest overall contributor to morbidity and mortality in this vulnerable population. It is essential, therefore, that neurogenic obesity is appropriately characterized and assessed in persons with SCI.

9.3 Obesity Definitions

In recent population health studies, obesity and overweight have been defined by the World Health Organization (WHO) as body mass index (BMI) $\geq$30.0 kg/m^2 and 25 kg/m^2, respectively (WHO 2000). BMI has been widely used in epidemiological studies of large populations where height and weight are readily obtained and associated with diagnostic codes for determining population health. While BMI can serve as surrogate marker for obesity in most populations, it grossly underestimates obesity in populations with low bone mass and sarcopenia and overestimates obesity in athletic populations with high muscle and bone mass, since it doesn't take into account the relative densities of fat (FM) and fat-free mass (FFM)

in these populations. Subsequently, a person with SCI who has a BMI of 22 kg/m^2 may have more than twice the body fat of an athlete whose BMI is 32 kg/m^2, with significantly greater risk of heart disease, cancer and the morbidities associated with obesity. In these special populations, therefore, it becomes essential to determine body composition, i.e., how much of the body weight is comprised of fat mass, since it is actually adipose tissue that mediates most of the risk associated with BMI.

9.4 Body Composition Assessment

Body composition assessment can be traced back to the 1950s when Brozek and associates first performed cadaveric analysis on one Caucasian female and four Caucasian male cadavers to arrive at specific tissue densities for fat and fat-free tissues, using hydrodensitometry as the "gold standard" (Brozek and Keys 1951). Interestingly, the term "gold standard" dates back to Archimedes who first described object density using water versus air displacement to distinguish gold from a gold-alloy counterfeit crown for King Hiero II in the first century BC. These determinations were used for decades in more precisely defining obesity as >22 % body fat for men and >35 % body fat in women (Heyward and Wagner 2004). Initial methods for determining body composition focused on separating fat from FFM, and were subsequently named a two-compartment (2C) model. Wang et al further organized and described up to 5 compartment models, most of which discriminate additional components of the FFM mass (Wang et al. 1992). For example, FFM can be further discriminated into protein, mineral and water compartments in the 3-compartment water molecular model, or differentiated into bone, mineral and bone-free lean tissue in the 3-compartment tissue model. The 4-compartment model, currently accepted as the gold-standard for body composition assessment in most exercise physiology laboratories, is comprised of fat, mineral, protein and water, and is especially appropriate for populations such as those with SCI because it measures the actual components of FFM mass which are otherwise erroneously assumed in the other models (Heyward 2001).

A person's body composition will undoubtedly change after SCI, significantly impacting the FFM compartments of mineral, water and protein, depending upon the level and completeness of the injury. Significant reductions in bone (mineral) mass rapidly occur within the first 18–24 months after SCI and continue at a slower rate thereafter (Garland et al. 1992). Lower extremity bone mineral content plateaus at ~2/3 normal, while upper limb bone mineral content is preserved or even increased due to wheelchair propulsion and transfers, depending upon the level of SCI (Clasey et al. 2004; de Bruin et al. 2005; Frey-Rindova et al. 2000; Modlesky et al. 2004). Total body water is most often reduced in SCI due to reduced muscle mass, even though the extracellular body water (especially interstitial) is relatively increased. Somatic nervous system disruption results in muscle paralysis and subsequent neurogenic muscular atrophy (Buchholz et al. 2003a; Cardus and

McTaggart 1984; Nuhlicek et al. 1988). If the paralysis is flaccid due to a lower motor neuron injury (e.g., conus medullaris or cauda equina syndrome), muscles will maximally atrophy due to loss of reflex and neurotrophic influences. An upper motor neuron injury, on the other hand, will usually cause spastic paralysis, and muscular atrophy will be somewhat attenuated, depending upon the degree of supraspinal disinhibition, the hormonal milieu, and therapeutic interventions such as antispasticity medications or surgical ablation. In both cases, relative sarcopenia results in significantly reduced metabolic energy expenditure at rest and during activity, ultimately putting the individual at high risk for positive energy balance, i.e., obesity (Bauman et al. 2004; Buchholz et al. 2003b; Cox et al. 1985; Mollinger et al. 1985; Sedlock and Laventure 1990). Sympathetic blunting in SCI above T3-T6 further decreases metabolic activity of the cardiovascular, ventilatory and thermoregulatory systems. Additionally, the hormonal milieu changes to a relatively-impaired anabolic state after SCI due to diminished growth hormone, IGF-1, and testosterone production. Body composition techniques that fail to take these changes in FFM compartments into account following SCI will likely underestimate %BF and neurogenic obesity for the reasons listed below. Representative examples for each method are provided in Table 9.1 and expanded upon in the text below.

9.5 Two Compartment Models

9.5.1 Hydrodensitometry

The earliest 2C model was reported by Behnke et al in 1942 and was based on total body density (Db), i.e., body mass relative to body volume (Behnke 1942). Using this technique over the next decade, Behnke's group developed the concept of a reference man that was comprised of fat mass (FM) and lean body mass (LBM) (Behnke et al. 1953). Brozek et al (1963) later determined Db of "the reference man" to be 1.064 g/ml, with its constituent parts including fat at 0.901 g/ml and fat-free mass (FFM) at 1.100 g/ml. Fat-free mass was further characterized for "the reference man" as being 73.8 % water, 19.4 % protein and 6.8 % mineral. They felt that variation in fat tissue relative to the reference body would best be characterized by the following equation (Brozek et al. 1963):

$$\%\text{Body Fat} = [(4.570/\text{Db}) - 4/142] \times 100$$

About the same time, Siri proposed an equation that suggested variations in FFM were more responsible for change in fat tissue, such that (Siri 1956):

$$\%\text{Body Fat} = [(4.95/\text{Db}) - 4.50] \times 100$$

Table 9.1 Body composition assessment for persons with SCI by method and compartment model. Para=Paraplegia, Tetra=Tetraplegia, ABT=Activity Based Therapy, NMES=Neuromuscular Electrical Stimulation, M=Male, F=Female, BMI=Body Mass Index, %BF= Per cent Body Fat, AB=Able Body, ADP=Air Displacement Plethysmography, BIA=Bioelectrical Impedance Analysis, DXA=Dual Energy X-ray Absorptiometry, 2-C=Two-Compartment Model, 3-C=Three-Compartment Model, 4-C=Four-Compartment Model using DXA, Hydrostatic Weighing and Total Body Water Determination

Authors	Number	SCI	Activity	Gender	Age (Yrs)	BMI (kg/m^2)	% BF	AB %BF	Method	Compartments
Bulbulian et al. (1987)	22	Para	Active	M	27.5	22.3	22.4	11.3	Hydrodensitometry	2-C
George et al. (1988)	15	Para/Tetra	NA	M/F	30.8	22.3	25.5	20.2	Hydrodensitometry	2-C
Lussier et al. (1983)	2	Para	Active	F	30.5	17.9	30.5	NA	Hydrodensitometry	2-C
Clasey and Gater (2005)	20	Para	Sedentary	M/F	36.1	24.8	28.3	NA	Hydrodensitometry	2-C
Clasey and Gater (2005)	20	Para	Sedentary	M/F	36.1	24.8	31.9	NA	ADP	2-C
Buchholz et al. (2003)	28	Para	Sedentary	M/F	29.1	23.5	30.8	22.8	Deuterium dilution	2-C
Tanhoffer et al. (2014)	6	Para/Tetra	Active	M	40	24	28	NA	Doubly labeled water	2-C
	7	Para/Tetra	Sedentary	M	39	27	38	NA	Doubly labeled water	2-C
Buchholz et al. (2003)	31	Para	Sedentary	M/F	34.2	24.6	30.8	24	BIA	2-C
Gibson et al. (2008)	69	Para/Tetra	Sedentary	M/F	42.4	25.8	39.2	NA	BIA	2-C
	37	Para	Sedentary	M/F	41.2	25.5	36.6	NA	BIA	2-C
	32	Tetra	Sedentary	M/F	43.8	26.2	42.4	NA	BIA	2-C
Han et al. (2015)	96	Tetra	Sedentary	M	45.2	21.3	35.2	NA	BIA	2-C
	85	Para	Sedentary	M		23.4	33.6	NA	BIA	2-C
	35	Tetra	Sedentary	F		19.4	39.4	NA	BIA	2-C
	50	Para	Sedentary	F		20.8	37.6	NA	BIA	2-C

Neto and Lopes (2011)	53	Para/Tetra	Various physical activity	M	27	21.9	20.6	NA	Anthropometry	2-C
	18	Para, Low	Various physical activity	M	30	21.9	19.9	NA	Anthropometry	2-C
	15	Para, High	Various physical activity	M	27.3	22.7	19.9	NA	Anthropometry	2-C
	20	Tetra	Various physical activity	M	24	21.2	21.7	NA	Anthropometry	2-C
Astorino et al. (2014)	17	Para/Tetra	Activity based therapy	M/F	36.1	NA	32.2	NA	DXA	3-C
Beck et al. (2014)	7	Para	Sedentary	M	41.4	23.5	35.9	27.4	DXA	3-C
Cirnigliaro et al. (2015)	40	Para/Tetra	Sedentary	M	40	26.1	35.6	29.4	DXA	3-C
Doherty et al. (2014)	95	NA	Sedentary	M	51.3	26.1	37	NA	DXA	3-C
Gorgey and Gater (2011) (Regional & Relative)	32	Para/Tetra	Sedentary	M	36	23.5	29.5	NA	DXA	3-C
Gorgey et al. (2011) (Influence of MC SAT and VAT	13	Para/Tetra	Sedentary	M	35	23	31	NA	DXA	3-C
Gorgey et al. (2012) (RT)	5	Para/Tetra	NMES + ankle weights	M	36	21	29	NA	DXA	3-C
Griffin et al. (2009)	18	Para/Tetra	FES-cycling	M/F	40	NA	32.8	NA	DXA	3-C
Jeon et al. (2010)	6	Para	Active	M	48.6	23.7	24.4	NA	DXA	3-C
Jones et al. (2003)	20	Para/Tetra	Sedentary	M	34	23.1	27.5	18.1	DXA	3-C
Jones et al. (2004)	20	Para/Tetra	Active	M	32	NA	27.5	17.8	DXA	3-C
Maggioni et al. (2003)	13	Para	Sedentary	M	33.8	25.7	31.1	20.8	DXA	3-C
Maimoun et al. (2004)	7	Para/Tetra	Sedentary	M	31.3	22.3	24.9	17.3	DXA	3-C
Manns et al. (2004)	22	Para	Sedentary	M	39	25.8	26.7	NA	DXA	3-C
Maruyama et al. (2008)	44	Para/Tetra	Sedentary	M/F	57	24.1	34	23	DXA	3-C
Mojtahedi et al. (2009)	8	Para	Active	M	22	22.5	20.6	NA	DXA	3-C
Spungen et al. (2000)	8	Para	Sedentary	M	40	22.3	33.5	26.3	DXA	3-C

(continued)

Table 9.1 (continued)

Authors	Number	SCI	Activity	Gender	Age (Yrs)	BMI (kg/m^2)	% BF	AB %BF	Method	Compartments
Spungen et al. (2003)	66	Tetra	Sedentary	M	40	25.4	36.3	24.2	DXA	3-C
Willems et al. (2015)	7	Tetra	Active	M	32	21	26.2	NA	DXA	3-C
Yarar-Fisher et al. (2013)	24	Para	Sedentary	F	42.4	26.1	37.8	35.9	DXA	3-C
	6	Para	Sedentary	F	41.5	22.6	45.5	38.3	DXA	3-C
	25	Para	Sedentary	M	NA	NA	30	NA	DXA	3-C
	7	Tetra	Sedentary	M	NA	NA	28	NA	DXA	3-C
	4	Para/Tetra	Sedentary	M	33	23	28	NA	DXA	3-C
	8	Para	Active	F	21.9	20.8	31.9	NA	DXA	3-C
	67	Para	Sedentary	M	37	25.8	34.2	24.2	DXA	3-C
		Tetra	Sedentary	F	42.4	26.1	44.4	35.9	DXA	3-C
Clasey and Gater (2005)	13	Para	Sedentary	M/F	37.1	24.3	27.7	NA	4-Compartment model	4-C

The two equations are highly correlated between body densities of 1.03 and 1.09 g/ml, but Brozek's equation appears more accurate for very lean and very obese individuals.

Both equations require the accurate determination of Db. To derive Db, dry weight, underwater weight and residual lung volume must be accurately determined, and the volume of gas present in the gastrointestinal tract is assumed to be a constant 100 ml. Because water density changes with temperature, water temperature is also taken into account in order to make appropriate corrections. Residual lung volume is determined through a close-circuit oxygen dilution technique described by Wilmore et al (1980) accuracy is thought to be improved if determined while underwater, provided tubing dead space is not excessive, as it negates the necessity to match maximal exhalations underwater with those previously determined on land. Hence, the subject must maximally exhale to reduce buoyancy while underwater in order to accurately determine body weight by force transducers. Up to ten repeated trials may be necessary in order to ensure an accurate and reliable weight determination. Once weight in air ($Wt_{air)}$, Weight in water (Wt_{water}), water density corrected for temperature (D_{water}) and residual lung volume (RV) have been collected, body density is determined, such that:

$$Db = Wt_{air} / \left\{ \left[Wt_{air} - Wt_{water} \right) / D_{water} \right] - (RV + 100) \right\}$$

When utilizing hydrodensitometry or any of its derivations, it is assumed that FFM tissue densities (water, protein and mineral) are constant, proportionally constant between individuals, i.e., individuals only differ from the reference body on in the amount of fat present, and that residual lung volume is accurately determined.

For years, hydrodensitometry was considered the gold-standard for determining body density and subsequently, per cent body fat, such that multiple alternative methods for determining body fat were validated against it. Unfortunately, several limitations prevent its routine use for persons with SCI. It is very labor intensive for persons with paralysis and for the investigator attempting to employ it. The paralyzed individual must be weighed in air and underwater, requiring multiple assisted transfers and in-water assistance to ensure safety. Fear of the water may limit participation, particularly for those whose SCI occurred while swimming and/or diving. Most individuals with SCI are less dense than water due to high body fat and restrictive lung disease, requiring that they be fitted with weighted belts and/vests in order to be fully submerged. Special adaptations must be provided for determining RV, particularly for those with limited hand function. Because most are poikiolothermic, their core temperature can rapidly drop while in the water, causing hypothermia. Despite best practices, neurogenic bowel and bladder occasionally results in incontinence during testing, and for those with external bowel /bladder appliances, every effort must be made to minimize the impact of those devices on Db determination, while optimizing hygiene. Ostomy appliances can be tightly taped and urinary catheters replaced with a condom for the short period of testing required. Open wounds may be contaminated or contaminate the water during the

procedure and it is recommended they be healed before testing. Wet swim suits must be changed and individual toweled dry before transfer back to their wheelchair; full body robes can minimize hypothermia in the interim. Even when accurate weights and residual volumes are determined, the assumptions tied to hydrodensitometry are seldom met, since FFM after SCI seldom has the proportionally constant constituents of water, protein and mineral determined for the reference body.

Three notable studies from the 1980s have reported body composition by hydrodensitometry in persons with SCI (Bulbulian et al. 1987; George et al. 1988; Lussier et al. 1983). Bulbulian et al compared 22 men with complete paraplegia (BMI 22.3 kg/m^2;[1] 22.3 ± 8.8 %BF) to n = 25 "ectomorphic" (BMI 19.4 kg/m^2 (see footnote 1); 8.3 ± 3.4 %BF) and "mesomorphic" (BMI 26.1 kg/m^2 (see footnote 1); 11.3 ± 3.8 %BF) men of slightly younger age (Bulbulian et al. 1987). Similarly, George et al compared n = 10 ♂ and n = 5 ♀ with mixed cervical/thoracic, complete and incomplete SCI (BMI 22.3 kg/m^2 (see footnote 1); 25.54 ± 13.9 %BF) against age-matched n = 6 men and n = 5 women without SCI (BMI 21.8 kg/m^2 (see footnote 1); 20.21 ± 6.77 %BF) (George et al. 1988). When matching for age, male gender and weight in that same cohort, the men with SCI had significantly higher RV (2.04 ± 0.54 L vs. 1.21 ± 0.27 L) and body fat (24.47 ± 5.95 vs. 17.0 ± 4.90 %BF) than the able bodied (AB) men. Finally, Lussier et al assessed body composition by hydrodensitometry for 2 elite women athletes with thoracic paraplegia. BMI was 16.5 and 19.2 kg/m^2 for athletes 1 and 2, respectively, while body fat was 28.9 and 32.1 %, respectively.

9.5.2 Air Displacement Plethysmography

For persons with fear of water, air displacement plethysmography (ADP) can be used in some circumstances to determine body volume (BV), with the subsequent derivation of Db. One commercial device (Bod Pod Body Composition System, Life Measurement Instruments, Concord, CA) has been developed that uses air displacement and pressure-volume relationships to derive BV, as determined under adiabatic conditions, i.e., air temperature will compress or expand as temperature fluctuates within the chamber. When the raw BV (BV_{raw}) has been determined, it can be corrected for surface area artifact (SAA) that could alter isothermal effects at the body's surface, and thoracic gas volume (TGV), which is related to but different from residual lung volume. The final equation for body volume is:

[1]Of note, the author has calculated BMI for each of the three studies above, since it was not routinely determined in the 1980's. One study from 2005 reported body composition assessment by hydrodensitometry in n = 20 persons (n = 14 ♂, n = 6 ♀) with paraplegia, noting BMI 24.8 ± 6.0 with corresponding body fat of 28.3 ± 5.2 %BF (Clasey and Gater 2005).

$$BV = BV_{raw} - SAA + 40\%TGV$$

Knowing BV, Db can be calculated by dividing Body Mass by BV. Per cent fat can be estimated using the Siri equation discussed above (software default), or through other equations, including the Brozek equation discussed previously, with similar limitations and assumptions in effect for both. Excellent validity for ADP compared to hydrodensitometry has been reported in the non-SCI population, and if validated for SCI, the technique could provide tremendous benefits over other techniques in terms of accessibility, cost, time, maintenance, and ease of use. In fact, comparison of ADP and hydrodensitometry determinations for BV and Db was made in 20 individuals with paraplegia below T3, with fairly good concordance. One important caveat must be recognized, however, in that the early work using ADP demonstrated limitations in assessing TGV for persons with SCI above the mid-thoracic region. Individuals with intercostal and abdominal muscle paralysis not only have difficulty performing the TGV, but almost certainly have greater true TGV than predicted, due to restrictive lung disease and reduced diaphragmatic excursion. These limitations can lead to spurious reductions in Db, and over-estimates of % Body Fat. Further population specific refinement of the predicted TGV equation would be necessary to ensure accuracy of ADP use in this select population. Only one study from 2005 reported body composition assessment by ADP in n = 20 persons (n = 14 ♂, n = 6 ♀) with paraplegia, noting BMI 24.8 ± 6.0 with corresponding body fat of 31.9 ± 5.2 %BF (Clasey and Gater 2005).

9.5.3 Hydrometry

Water counts for ~60 % of total body mass and roughly 73 % of the FFB mass in the human body. Total body water is comprised of intracellular water (cytosol) and extracellular fluid (plasma, interstitial fluid, bone, dense connective tissue and transcellular water) components. Hydrometry, body water measurement, is based on the dilution principle that a specific quantity of compound (isotopic tracer) in a known concentration will distribute throughout a given space in similar solvent (water), allowing the determination of water volume within that space. Hydrometry relies upon 4 basic assumptions. The tracer is assumed to distribute only in body water. The tracer is assumed to distribute evenly throughout all water components. The tracer equilibrium is assumed to be rapidly achieved. Finally, it is assumed that neither tracer nor body water is metabolized during the equilibration period. With these assumptions in mind, the following equation is used to calculate isotope dilution space:

$$N = [(WA/a)(Sa - St)f]/(Ss - Sp)$$

where N is H_2O (grams or ml), W is the water mass used to dilute the tracer dose, A is the tracer dose given, a is the amount of the dose diluted for analysis, Sa is the

measured value for the diluted dose, St is the value for tap water used in the dilution, f is the fractionation factor for body fluid sample, Ss is the post-dose sample, and Sp is the pre-dose sample. When the dilution space is determined, it should be corrected for the exchange of hydrogen or oxygen into the nonaqueous compartment, i.e., divided by 1.01 if using $H_2{}^{18}O$ or divided by a factor of 1.04 if using ^3H_2O or D_20. With TBW determined, equations have been developed to determine FFB mass, with the subsequent derivation of %BF. Per cent Body Fat determination from hydrometry also makes the assumption that the relative hydration of the FFB mass is 73.2 % water. Of note, this method appears inappropriate to estimate body composition for populations with disorders that cause edema and other significant fluid shifts within the body, such as persons with SCI or those undergoing hemodialysis.

Of note, only a few studies have been reported using hydrometry to assess body composition in SCI (Buchholz et al. 2003b; Tanhoffer et al. 2014). Buchholz et al used deuterium and corrected bromide space to determine total body water and extracellular water, respectively, in 28 people with paraplegia (n = 17 ♂, n = 11 ♀) and 34 AB individuals. BMI was similar between paraplegia and AB groups (24.3 ± 6.0 vs. 23.5 ± 1.8 kg/m^2), but body fat was significantly higher in those with paraplegia (30.8 ± 8.7 vs. 22.8 ± 7.2 %BF) (Buchholz et al. 2003b). Similarly, Tanhoffer et al used doubly labeled water to assess body composition in 6 active vs. 7 sedentary men with paraplegia, finding similar BMI (24 ± 4 vs. 27 ± 2 kg/m^2) but statistically lower body fat (28 ± 9 vs. 38 ± 6 %BF) in those who were active (Tanhoffer et al. 2014).

9.5.4 Bioelectrical Impedance Analyses

Bioelectrical impedance analysis (BIA) is a rapid, non-invasive and inexpensive method for estimating body composition in field and clinical settings for AB adults. Based on work in the early 1960s, BIA takes advantage of the fact that electrolytes in body water are excellent conductors, so that electrical current flow can be used to estimate total body water, and subsequently FFB mass. A low level of electrical current is passed through the body and the impedance (Z) of current flow is measured with a BIA analyzer. The body is assumed to be a perfect cylinder with uniform length and cross sectional area, such that the impedance of electrical current is directly related to the length of the conductor (height=length=L) and inversely proportional to the cross-sectional area of the body (A):

$$Z = \rho(L/A)$$

where ρ is a presumed constant of specific resistivity. The equation is then multiplied by L/L, such that:

$$Z = \rho\left(L^2/AL\right)$$

in order to derive volumetric information. Substituting Volume (V) for Area (A) X Length (L), $Z = \rho(L^2/V)$ and rearranging, $V = \rho(L^2/Z)$ which represents FFB mass and therefore extracellular water (ECW), from which total body water (TBW) can be derived. In point of fact, the body is not a single cylinder, but several segments of cylinders, so that the equation is modified to sum cylindrical segments of the two legs, two arms and trunk:

$$V = 2\left(\rho L^2/Z\right)_{leg} + 2\left(\rho L^2/Z\right)_{arm} + \left(\rho L^2/Z\right)_{trunk}$$

Serial impedance (Z) is actually a function of resistance (R) and reactance (Xc). Reactance represents the opposition to current flow caused by capacitance (voltage storage) produced by cell membranes in the body, such that $Z^2 = R^2 + Xc^2$. During the measurement of whole-body impedance, R is much larger than Xc, making it a much better predictor of FFB mass (and therefore ECW) than Z. Because of this, most BIA models use the resistance index (HT^2/R), where HT=height=L instead of (HT^2/Z). Further investigations have indicated that since human body segments are actually arranged in parallel rather than in series, the reciprocal of the serial equation ($Z^{-2} = R^{-2} + Xc^{-2}$) should be employed, as it is more consistent with human physiology. Multifrequency BIA has additionally been utilized in order to more accurately reflect TBW and ICW, since single-frequency (50 kHz) reflects only ECW. Multifrequency tetrapolar BIA using parallel modeling has been recommended to more accurately determine ECW, ICW and TBW for clinical populations with abnormal fluid distributions, such as SCI. Per cent body fat is derived by subtracting the calculated FFB mass derived from ECW from body weight, dividing the result by total body weight and multiplying by 100.

In order to ensure valid BIA results, several standard recommendations should be adhered to prior to testing in order to reduce hydration fluctuations. No eating or drinking should be permitted within 4 h of testing. Exercise should not be allowed within 12 h of testing. Bladder drainage should be performed within 30 min of the test. Alcohol consumption is not permitted within 48 h of the test, and diuretic medications should not be provided within seven days of testing. Females should not be tested during the water retention stage of their menstrual cycle.

Although relatively simple to complete and cost-efficient, most BIA equations have been validated against hydrodensitometry, so that the techniques are hydration dependent and are subject to similar assumptions applied to hydrodensitometry, ADP and hydrometry. BIA techniques have not been fully validated against the gold standard 4-compartment model in individuals with SCI. Nonetheless, several studies have reported body composition assessment using BIA because of its ease of use (Buchholz et al. 2003a; Gibson et al. 2008; Han et al. 2015). One group compared 31 adults with paraplegia (n = 19 ♂, n = 12 ♀) to BMI-matched AB Controls (n = 30 ♂, n = 32 ♀) and found significantly higher body fat in those with paraplegia (30.8 ± 9.2 vs. 24.0 ± 7.0 %BF) for similar BMI (24.6 ± 6.4

vs. 22.9 ± 2.0 kg/m^2) (Buchholz et al. 2003a). This group suggested reducing BMI threshold for obesity to 25 kg/m based on BIA findings. The multicenter Study of Health and Activity in People with SCI (SHAPE-SCI) study examined 69 individuals (n = 56 ♂, n = 13 ♀) with SCI (n = 37 with paraplegia, n = 32 with tetraplegia and reported BMI of 25.5 ± 4.8 vs. 26.2 ± 5.6 kg/m^2 and body fat of 36.6 ± 9.9 vs. 42.4 ± 9.4 %BF, respectively, using BIA (Gibson et al. 2008). Finally, a Korean group recently reported on body composition by BIA for 181 men and 85 women with motor complete spinal cord injury, distinguishing those with tetraplegia from paraplegia (Han et al. 2015). Men with tetraplegia had BMI of 21.3 ± 3.9 kg/m^2 and body fat of 35.2 ± 9.9 %BF, whereas those with paraplegia had BMI of 23.4 ± 3.6 kg/m^2 and body fat of 33.6 ± 9.7 % BF. Similarly, women with tetraplegia had BMI of 19.1 ± 3.9 kg/m^2 and body fat of 39.4 ± 11.0 %BF and those with paraplegia had BMI of 20.8 ± 2.6 kg/m^2 and body fat of 37.6 ± 10.8 % BF. Of note was the significant disparity between BMI and %BF by BIA.

9.5.5 Anthropometry

Anthropometry is the science of measuring size and proportions of the human body, using height, weight, skeletal breadths, circumferences, segment lengths and skinfold thicknesses. Standard techniques for assessing these measures have been validated in the AB population and are often recommended for both clinical and research trials. Anthropometric indices are relatively simple, inexpensive measures often used for large-scale epidemiological surveys in populations whose risk factors have been validated and correlated with these variables, and include such metrics as BMI, waist-to-hip ratio (WHR), waist circumference and sagittal abdominal diameter.

Height is often difficult to obtain for persons with SCI due to contractures, neurogenic scoliosis, bony fusions and spasticity, although alternative measures such as arm span and lower leg length may be used to predict height for those special instances. Unfortunately, accurate weight is often not measured in clinical or even SCI research settings due to inadequate scales or transfer equipment, and even when obtained, is seldom performed with the subject in gown and without shoes. It is recommended that persons with SCI first be weighed in their wheelchair on a digital, calibrated wheelchair scale, then transferring the individual out of their wheelchair and weighing the chair with the person's shoes/clothing to derive an accurate body weight. Mechanical lifts with calibrated built-in scales may be utilized for persons who use power chairs or have great difficulty with transfers. Anthropometry has yet to be validated for populations with SCI, and it is unclear whether it can be used to measure obesity or accurately predict cardiovascular risk factors as has been done in AB populations. For example, abdominal muscle paralysis may impact abdominal circumference and sagittal abdominal depth, whereas lower extremity muscular atrophy may render limb circumferences meaningless in the SCI population, relative to current standards.

Skinfold thickness represents an indirect measure of subcutaneous adipose tissue used to estimate Db and subsequently %BF. Standardized techniques have been published and should be adhered to ensure accuracy. Specific assumptions when performing anthropometry for determination of %BF, and include the following: (1) the skinfold is a good measure of subcutaneous fat; (2) subcutaneous and visceral fat distribution is similar for all persons within a gender class; (3) the sum of several skinfolds can be used to estimate total body fat, indicating a linear relationship between subcutaneous fat and total body fat; (4) there is a relationship between the sum of skinfolds and Db; and (5) that age is an independent predictor of Db for both men and women. With regard to the SCI population, it is unclear if paralysis alters usual fat distribution patterns and skinfold thicknesses, or if the relationship between subcutaneous fat and visceral fat remains constant as is described in AB populations.

BMI has already been discussed as an inappropriate estimate of adiposity in persons with SCI. Although the waist-to-hip ratio is a fairly good predictor of central (visceral) obesity in the AB population, it may not be a valid metric in the population with SCI due to potential abdominal muscle paralysis, uncertain fat distribution patterns, and proximal lower extremity muscle wasting. Magnetic resonance imaging (MRI) and selective computerized tomography (CT) may be necessary to establish the relationship between visceral fat and these anthropometric measures, although these imaging modalities may be prohibitively expensive in most clinical settings. Anthropometric regression equations specific to the SCI population have yet to be appropriately validated against the gold standard 4-Compartment model. One group has recently reported body composition using Durnin and Womersley's 4-site skin fold equation (Durnin and Womersle 1974) for 53 men with SCI noting the following results. Those with tetraplegia vs. high paraplegia vs. low paraplegia (below T6) were found to have BMI's of 21.5, 22.4 and 21.6 kg/m^2 and body fat of 21.3 $\pm$ 7.0, 21.9 $\pm$ 7.3 and 20.7 $\pm$ 7.7 %BF, respectively (Neto and Lopes 2011). Of note, the equation used was developed using AB men and women, and has never been validated for persons with SCI.

9.6 Three Compartment Models

Before the turn of the century, dual-energy X-ray absorptiometry (DXA) was developed to assess total body bone density (TBBD) and bone mineral density (BMD) in response to the public health issues associated with osteoporosis. DXA uses an X-ray tube with a filter to convert a polychromatic X-ray beam into low (40 kV) and high energy (70 kV) peaks; hence the term "dual-energy." It has been referred to as a 3C model because it estimates total body bone mineral (TBBM), Bone-free Lean Tissue Mass (LTM) and fat mass (FM). The same device can be used to estimate body composition by comparing the relative attenuation of the high and low energy in the bone-free pixels, i.e., soft tissue. The ratio of the attenuation

between low energy and high energy in soft tissue (R_{ST}) reflects the relative amount of fat and lean tissue in each pixel, such that:

$$RST = (R_{ST} - R_f)/(R_l - R_f)$$

where R_f is the attenuation constant for pure fat, and R_l is the attenuation constant for bone-free lean tissue. Pixels can then be summed and relative fat mass (FM) and bone-free lean tissue mass (LTM) determined for individual regions or for whole body mass. Three primary assumptions underlie the determination of body composition by DXA. Constant values are assumed for R_f and R_l. Measures are assumed to be unaffected by anterior-posterior body thickness. Finally, fat content within unmeasured pixels (i.e., those pixels containing bone) is assumed to be the same as that in the measured (R_{ST}) pixels.

The attenuation constant R_f is fairly well accepted, but it somewhat controversial that R_l can be assumed constant for those individuals who are either edematous or dehydrated, since underlying or overlying interstitial edema may additionally attenuate the passage of high and low energy beams. Further, relative hydration of the LTM may vary considerably in persons with SCI, as discussed above. The assumption that tissue thickness won't alter measurements appears to be accurate for individuals with body thickness of $<$20 cm, however, significant error is introduced for those with body thickness exceeding 20 cm. Of greatest concern, the third assumption appears problematic for persons with SCI, since muscle atrophy in the lower extremities would alter the ratios between lower extremity tissue girth and bone diameter, while the relatively unchanged tissue girth to bone diameter ratios at the upper extremities and trunk would under-represent bone-free pixels due to the relatively large areas of bone in these regions. It is estimated that $>$60 % of the 21,000 pixels in a typical whole body scan contain bone and are subsequently excluded from the calculation of values for soft tissues in persons with SCI, raising concerns about the validity of body composition assessment by DXA in this unique population. Regional and whole body composition analysis by DXA appears to provide a quick, relatively accessible, convenient and non-invasive technique. However, DXA remains relatively expensive, is hydration- and position-dependent, and provides significant variability between current instrument brands and software analysis programs. Testing is recommended early in the day and after at least 30 min of lower extremity elevation in order to minimize lower extremity edema. Acquiring data for persons with paralysis, bowel and urological appliances, instrumented or bony fusions, spasticity, and/or contractures can prove problematic with regard to positioning and motion artifact; lifts or ramp platforms are recommended for safe transfers onto and off of the equipment. Multiple studies have reported body composition by DXA for persons with SCI (Astorino et al. 2015; Beck et al. 2014; Cirnigliaro et al. 2015; Doherty et al. 2014; Gorgey and Gater 2011; Gorgey et al. 2011, 2012a; Griffin et al. 2009; Jeon et al. 2010; Jones et al. 2003, 2004; Maggioni et al. 2003; Maimoun et al. 2004; Manns et al. 2005; Maruyama et al. 2008; Mojtahedi et al. 2009; Spungen et al. 2000, 2003; Willems et al. 2015; Yarar-Fisher et al. 2013). All demonstrated that BMI

poorly characterizes obesity in persons with SCI, whose average per cent body fat across all studies approaches 32 %BF, well above the cut-off for obesity, while BMI across the same studies (~24 kg/m^2) would indicate these individuals were in normal range, i.e., not even overweight, much less obese. Of note, one study reported persons with SCI are roughly 13 % fatter than age, height and ethnicity matched non-SCI controls at the same BMI (Spungen et al. 2003).

9.7 Four Compartment Model

None of the techniques described above accurately yields a direct estimate for assessing all compartments of body composition, particularly for the SCI population. Notably, FFB mass for persons with SCI has been demonstrated to have less water in different distribution, less protein mass and reduced total body bone mineral than the standard "reference body." The American Society for Exercise Physiologists (ASEP) has endorsed the 4-Compartment (4-C) model as the "gold standard" for body composition assessment in humans using estimates of total body density (Db), total body water (TBW) and total body bone mineral (TBBM) to most appropriately determine the four compartments of fat, mineral, water and protein. Db is determined by hydrodensitometry, total body water through deuterium dilution or BIA and TBBM is determined by DXA. Unfortunately, such testing requires a great deal of time, energy, effort and financial resources that are simply unattainable in most clinic situations. It is recommended that appropriate predictive equations using field methods of BIA, skinfolds and anthropometry should be developed and carefully validated for persons with SCI so that they might be easily employed in the clinic. These predictive equations should be validated against the gold standard 4-C model, ideally including $>$ 100 randomly selected individuals with SCI, have a high correlation between the reference measure (4-C) and predicted scores ($r_{y,y} > 0.8$), have a small prediction error or standard error of estimate, and be cross-validated on additional independent samples from the population. The only reported study using 4-C modeling to assess body composition in SCI demonstrated BMI of 24.3 $\pm$ 3.5 kg/m^2 with 27.7 $\pm$ 2.8 %BF; notably two of the male subjects had $<$10 %BF which may have skewed the results in that small investigation (Clasey and Gater 2007). A validation trial comparing 4-C modeling to other body composition assessment methods has recently been completed and data analysis is underway.

9.7.1 Exercise on Body Composition After SCI

The overall objective of exercise in the SCI population is to reverse obligatory sarcopenia, increase energy expenditure and basal metabolic rate, and improve alerted body composition to ultimately enhance cardiovascular, glucose, and lipid

profiles following SCI (Gorgey et al. 2015). There currently is no established consensus on the recommended intensity and volume of exercise to ameliorate several of the body composition alterations following SCI. Neuromuscular electrical stimulation (NMES), functional electrical stimulation (FES), arm crank ergometry (ACE), adaptive forms of upper and lower body resistance training, and combinations of such modalities have all been suggested to restore lean body mass (LBM) and decrease fat mass (FM). NMES and FES-leg cycling ergometry (LCE) are two of the most widely used forms of exercise intervention in the SCI population that send low-level electrical impulses through superficial tissues to evoke contractions of the paralyzed muscles below the level of the injury. Both forms of exercise have led to increases in muscle mass with variable alterations in FM and bone mineral density (BMD) (Gorgey et al. 2012a, b). In nine individuals with SCI, hypertrophy was detected through the use of magnetic resonance imaging (MRI) in the quadriceps femoris and hamstring muscle groups following 12 weeks of NMES progressive resistance training + diet compared to a diet group alone. The authors also reported a reduction in visceral fat, the ratio of visceral to subcutaneous fat, and percent intramuscular fat in the NMES + diet group (Gorgey et al. 2012a; Gorgey and Shepherd 2010). A similar study showed a significant increase in thigh muscle mass via MRI and a significant decrease in intramuscular fat following home-based electrically induced progressive resistance training 2 times per week over the course of 16 weeks (Ryan et al. 2013). One study demonstrated that FES-LCE was more effective at reversing muscle atrophy and increasing LBM, as quantified by DXA, of both the lower extremity and trunk when compared to NMES isometric exercise and a control group over 6 months (Baldi et al. 1998). Other studies have shown no effects on trunk LBM following MRI assessment with the use of lower extremity NMES or FES-LCE (Gorgey et al. 2013; Skold et al. 2002). Following 1 year of FES-LCE, computed tomography (CT) revealed a 12 % increase in the cross-sectional area (CSA) of the thigh after training, as well as an increase in type I oxidative muscle fibers, which demonstrates improved oxidative capacities and resistance to muscle fatigue (Mohr et al. 1997a). Eight weeks of FES-LCE in individuals with tetraplegia demonstrated a decrease in whole body FM by 2 %, as well as a 2 % increase in DXA-obtained FFM. These latter changes stemmed from increases in CSA of the gluteus maximus and minimus, hamstrings, and quadriceps femoris muscles following training, as measured by CT (Hjeltnes et al. 1997). Reductions in waist circumference, a marker of visceral fat, and DXA and CT obtained percent trunk and android fat were shown in two groups undergoing 16 weeks of either hand-cycle exercise or hybrid cycle consisting of both hand-cycle exercise and FES-LCE (Bakkum et al. 2015). In another study, the authors used BIA to demonstrate a significant decrease in percent FM and a significant increase in LBM after 6 weeks of FES-rowing (Kim et al. 2014). The use of hand-bike exercise resulted in a significant decrease in BMI (Kim et al. 2015); however, one study documented no changes in BMI at the conclusion of 12 weeks of ACE at 3 sessions per week (Rosety-Rodriguez et al. 2014a). Moreover, with the same exercise prescription another study showed improvements in waist circumference in motor complete SCI (Rosety-Rodriguez

et al. 2014b). Twelve weeks of FES-rowing exercise at 3 to 4 times a week demonstrated a trend toward a significant reduction in FM in 4 out of 6 participants (Jeon et al. 2010), whereas 10 weeks of FES-LCE at 60-–90-min per week lead to a small, non-significant increase in FM with a 3.3 % increase in LBM as quantified by DXA (Griffin et al. 2009). However this study, as well as many others, did not monitor dietary intake.

The mechanical stresses placed on the working muscles in turn apply stress to the bone; however, both increases and decreases in BMD have been reported with the use of electrical stimulation (Gorgey et al. 2015; Gater et al. 2011). Following 12 weeks of FES-LCE an 18 % increase in DXA obtained BMD was reported. Another study also using DXA evaluated the effects of 2 bouts of 15-min of exercise 5 days per week with FES-LCE and demonstrated a significant difference in lower extremity BMD between the exercise and control groups (Clark et al. 2007). Site-specific changes in BMD were reported showing increases at the proximal tibia and distal femur (Mohr et al. 1997a, b; Bloomfield et al. 1996; Chen et al. 2005; Frotzler et al. 2008), as well as the lumbar region (Bloomfield et al. 1996), following FES-LCE. These studies used DXA or peripheral quantitative CT to assess BMD. Alternatively, no changes have been reported in the lower extremity following electrical stimulation exercise (Lauer et al. 2011), and with exercise cessation DXA-quantified BMD has been shown to decrease (Chen et al. 2005).

There are a limited number of studies examining the effects of electrical stimulation in conjunction with other exercise modalities and even fewer looking at alternative forms of exercise as a means to alter body composition following SCI. In a 3-phase exercise training program that included quadriceps femoris muscle strengthening (phase 1), cycle progression (phase 2), and 30-min of FES-LCE (phase 3), the authors exhibited increases in MRI- assessed CSA of rectus femoris, sartorius, adductor magus (hamstring portion), vastus lateralis, and vastus medialis-intermedius muscles with no changes in adductor longus or gracilis muscles (Scremin et al. 1999). Moreover, they noted the ratio of muscle to adipose tissue increased significantly in thighs and calves. When NMES was combined with partial body weight support (30–50 % BWS) performed over the course of 6 months for 20-min two times a week it resulted in a 15 % increase in knee extensor CSA versus a control group, as measured by MRI (de Abreu et al. 2009). In a 6-month activity based therapy rehabilitation and exercise program consisting of 17 individuals undergoing load bearing, resistance training, locomotor training, and/or FES-LCE, no changes in body weight, percent body fat, or fat free mass of the arm, leg, or trunk were reported. The authors did, however, note whole-body fat free mass, as determined through DXA, was significantly reduced by 1.2 kg following the program (Astorino et al. 2015). Three groups consisting of tetraplegia (C5-C8), high paraplegia (T1-T6), and low paraplegia (T7-L2) underwent skinfold measurements and supervised physical activity ranging from 1 to 5 days a week for 30–60-min Skinfold-measured absolute and percent FM significantly decreased in the high and low paraplegia groups only; a significant reduction in body weight was

noted only in individuals with tetraplegia and high paraplegia after physical activity (Neto and Lopes 2011).

9.8 Conclusion

Neurogenic obesity is present in epidemic proportions in persons with SCI, but has been relatively undetected because of limitations posed through current methods of body composition assessment. 4-C modeling, the gold standard for body composition assessment, should be used to validate and compare techniques currently in use, but is very time consuming, expensive and labor intensive. Simple and inexpensive tools should be developed and validated for use in the clinical setting in order to more accurately characterize obesity in persons with SCI, and to correlate their adiposity with risk for adipose-driven comorbidities. Similarly, exercise interventions should focus on changes in body composition as they influence whole body energy metabolism, subsequently mitigating the impact of neurogenic obesity and its comorbidities.

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Chapter 10
Cardiometabolic Syndrome in SCI: The Role of Physical Deconditioning and Evidence-Based Countermeasures

Jennifer L. Maher, David W. McMillan, and Mark S. Nash

Abstract Persons with spinal cord injuries and disorders (SCI/D) frequently experience component and coalesced health risks of the cardiometabolic syndrome (CMS). The CMS hazards of overweight/obesity, insulin resistance, hypertension, and dyslipidemia—the latter as depressed high-density lipoprotein cholesterol and elevated triglycerides—are strongly associated with physical deconditioning, which is common after SCI/D and worsens the prognosis for all-cause cardiovascular disease occurring early after SCI/D. Evidence supports a role for physical activity after SCI/D as an effective countermeasure to these risks, and often represents the first-line approach to CMS abatement. This evidence is supported by authoritative guidelines that recommend specific activities, frequencies, and activities of work. In many cases, the most effective exercise programming uses a combination of resistance and endurance maneuvers with limited rest taken between sets. As SCI/D is also associated with food intake that is excessive in calories and saturated fat, more comprehensive lifestyle management incorporating *both* exercise and nutrition represents a favored approach for overall health management. Irrespective of the interventional strategy, improved surveillance of the population for CMS risks and encouraged incorporation of moderate exercise and nutritional intake by health care professionals may play an important role in preservation of activity, optimal health, and preserved independence throughout the lifespan.

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10.1 Introduction

The cardiometabolic syndrome (CMS)—also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome, and metabolic syndrome—is a pandemic health hazard caused by coalescing of cardiovascular, renal, metabolic, pro-thrombotic, and inflammatory health risks. Co-occurrence of three (or more) of the following five component risks typically defines the syndrome: abdominal (central) obesity, hypertension, insulin resistance, and dyslipidemia, the latter as either hypertriglyceridemia or low high-density lipoproteinemia. When co-expressed these risks are recognized as a *disease entity* by the American Society of Endocrinology, American Heart Association (AHA), International Diabetes Federation (IDF), National Cholesterol Education Program (NCEP), NIH National Heart Lung Blood Institute (NIH-NHLBI), and the World Health Organization (WHO), among others (Castro et al. 2003). Attempts have been made to harmonize the CMS disease diagnosis, but opinions still differ by authority (Table 10.1). Notwithstanding the lack of a unified CMS diagnosis, or even consensus that CMS constitutes a distinct disease state, *any* coalescing of its five risk factors is known to worsen cardiovascular (CVD) forecast. CMS in particular, however, is reported to worsen odds for developing atherosclerotic disease, heart failure, and diabetes, and poses a health risk equivalent to that of diabetes, or existing coronary disease. Prevalence of CMS in the U.S. is estimated at 22.9 % of the adult population (Beltrán-Sánchez et al. 2013) and is increasing with population aging.

While a sole *cause* for CMS has yet to be identified, the disorder is brought about by a mismatch between excessive energy consumption and insufficient daily energy expenditure (Bremer et al. 2012). When this occurs the principal *metabolic abnormality* of the syndrome is insulin resistance, while the unified *cause* ensues unwarranted body adipose mass associated with excessive visceral and/or ectopic fat. The mismatch created by excessive energy intake and inadequate activity demand provides an overabundance of metabolites passing through mitochondrial oxidation pathways, resulting in progressive mitochondrial dysfunction and the defining hazard of insulin resistance. Not surprisingly, the component risks of CMS are not equally weighted, and overweight/obesity—a highly prevalent finding after SCI/D (Ashraf and David 2007; Buchholz and Bugaresti 2005; Gater 2007; Nash and Gater 2007; Kressler et al. 2014)—appears to be the most powerful progenitor. Notwithstanding, a disability-specific definition for CMS occurring in persons with SCI/D has not been established. Moreover, existing component risks for CMS determination omit formal recognition of health hazards imposed by both inflammatory stress and endocrinopathies, although both hazards are recognized as either cause or consequence of the CMS (Alam et al. 2007; DeMarco et al. 2010; Dandona et al. 2007).

Table 10.1 Component risks of the Cardiometabolic Syndrome (CMS)

Authority	Diagnosis	
IDF, Alberti et al. (2006), Unwin et al. (2002)	Central obesity (defined as waist circumference[#] with ethnicity-specific values) AND any two of: [#]NOTE: Central Obesity is assumed if BMI > 30 kg/m^2	TG triglycerides: >150 mg/dL (1.7 mmol/L), or treatment for elevated TG
		HDL cholesterol: <40 mg/dL (1.03 mmol/L) in males, <50 mg/dL (1.29 mmol/L) in females, or treatment for low HDL
		Raised blood pressure (BP): systolic BP >130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension
		Raised fasting plasma glucose (FPG): >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes
NCEP (2002), AHA/NHLBI, Grundy et al. (2004a, b)	At least three of: NOTE: NCEP and AHA/NHLBI are identical except for the AHA definition of fasting plasma glucose	Waist circumference: Men—greater than 40 inches (102 cm) Women—greater than 35 inches (88 cm)
		Plasma triglycerides: = >150 mg/dL (1.7 mmol/L)
		Reduced HDL ("good") cholesterol: Men—Less than 40 mg/dL (1.03 mmol/L) Women—Less than 50 mg/dL (1.29 mmol/L)
		Elevated blood pressure: Equal to or greater than 130/85 mm Hg or use of medication for hypertension
		Fasting glucose: ≥110 mg/dL (6.1 mmol/L) or use of medication for hyperglycemia AHA: Fasting glucose ≥100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia
WHO, Alberti and Zimmet (1998)	Any one of diabetes mellitus, impaired glucose tolerance (IFG), impaired fasting glucose or insulin resistance, AND two of the following: NOTE: IFG is two-hour glucose levels of 140–199 mg per dL (7.8–11.0 mmol/l) on the 75-g oral glucose tolerance test	Blood pressure ≥140/90 mmHg
		Triglycerides (TG) ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤1.0 mmol/L (female)
		Central obesity: waist:hip ratio >0.90 (male); >0.85 (female), or body mass index >30 kg/m^2
		Microalbuminuria: urinary albumin excretion ratio ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

10.2 Physical Deconditioning in the Origins of Post-SCI Cardiometabolic Disease

All-cause disorders of the integrated cardioendocrine system have been reported in persons with spinal cord injuries and diseases (SCI/D) since the early 1980s (Bauman et al. 1992a; Cowan and Nash 2010; Nash and Cowan 2010a) and are thought to hasten cardiovascular (CV)-related morbidity and mortality (Bauman and Spungen 2008; Banerjea et al. 2008; Nash and Cowan 2010b; Kressler et al. 2014). Genesis of these disorders is primarily attributed to CMS risk factors observed in the non-disabled population, although reported at elevated prevalence after SCI/D. These risks include a widely-cited atherogenic dyslipidemia with low levels of the cardioprotective high-density lipoprotein cholesterol (HDL-C) (Bauman et al. 1992b, 1998, 1999; Brenes et al. 1986; Nash and Mendez 2007; Bauman and Spungen 1994), a dyslipidemia thought to ensue to post-injury/disease immobilization-related physical deconditioning (Dallmeijer et al. 1999), and frequently associated with sarcopenia (Spungen et al. 2000) and diminished resting energy expenditure (Buchholz and Pencharz 2004; Monroe et al. 1998). Otherwise, inadequate caloric expenditure by lowered resting energy expenditure daily and the combination of limited non-exercise and exercise activities is thought to increase body fat mass, which is practically a *sine qua non* of CMS after SCI/D.

While physical deconditioning per se is not included among the five component risks of CMS, it is clearly linked with, and considered a major cause of obesity, insulin resistance, hypertension, and dyslipidemia. Several factors, however, point to physical deconditioning after SCI/D as a major contributor to a CMS diagnosis. First, the SCI/D population was long ago identified at the lowest end of the human fitness continuum, making physical deconditioning suspect as a cause for CMS-related risks (Brenes et al. 1986; Dearwater et al. 1986; LaPorte et al. 1983, 1984). Second, a common finding after SCI/D is a low HDL-C, (Bauman et al. 1992b; Nash and Mendez 2007; Zlotolow et al. 1992) which is known in persons without disability to be strongly linked with low levels of cardiorespiratory fitness (Halle et al. 1999; Franks et al. 2004; Carnethon et al. 2005). Third, barriers to exercise participation are altogether common after SCI/D, and may include either self-imposed obstacles to exercise participation or those associated with legitimate physical barriers to exercise, lack of adapted exercise equipment, limited professional assistance, societal moirés, and financial limitations (Cowan et al. 2013; Ginis et al. 2010; Scelza et al. 2005; Vissers et al. 2008). Notwithstanding these impediments to maintaining or achieving a healthy lifestyle, increased exercise as either as therapeutic programs of physical activities or recreational activities may offer substantial benefits to those with SCI/D as legitimate countermeasures to CMS component risks, or the CMS diagnosis itself. The following sections address ways in which volitional and assisted exercise after SCI/D might be used to achieve these goals.

10.3 Exercise as an Evidence-Based Countermeasure to CMS Risk Components

Exercise is a fundamental element in maintaining CV and metabolic health among individuals of all age groups and clinical populations. The American College of Sports Medicine (ACSM) defines exercise as "a type of physical activity consisting of planned, structured, and repetitive bodily movements done to improve and/or maintain one or more components of physical fitness" (Thompson et al. 2010). The unified ACSM and the World Health Organization (WHO) guidelines (Garber et al. 2011) prescribe exercise and provide physical activity guidelines for supporting health and wellness in the general population (Table 10.2). Notwithstanding their physical impairments, many individuals with SCI/D can still undergo exercise and physical conditioning programs, and are thus are encouraged to follow recommendations that are set for the non-disabled population (Thompson et al. 2010). These guidelines are in substantial agreement with both ACSM Guidelines for Exercise Resting and Prescription (9th Edition) (Garber et al. 2011) and also the Physical Activity Guidelines for Adults with SCI that were established for SCI Action Canada (www.sciactioncanada.ca/guidelines) (Ginis et al. 2011). They are also similar to the Physical Fitness for Special Populations (PFSP) recommendations of the American Physical Therapy Association (www.apta.org/PFSP/).

In adapting the general guidelines for use by those with SCI/D exercise is viewed as an effective non-pharmacological approach for reducing CMS risks, and should be considered by health care professionals as a first-line intervention. Volitional exercise using arm-crank ergometry, wheelchair propulsion, hand cycling, and circuit resistance training has been widely recommended to improve cardiovascular fitness and metabolic health in individuals with SCI/D (Nash 2005; Nash et al. 2012; Devillard et al. 2007; Jacobs and Nash 2004). Examples of endurance and circuit resistance exercises are shown in Figs. 10.1, 10.2 and 10.3.

Table 10.2 Exercise guidelines to improve health and wellness in individuals with SCI/D

Aerobic exercise		
Intensity	Moderate	Vigorous
Weekly total	≥150 min	≥75
	*Can be accrued in ≥10 min bouts	
Lay intensity guide	"somewhat hard." "you can talk but not sing." 5 or 6 on a 0–10 scale	"really hard." "you can't say more than a few words without pausing for breath." 7 or 8 on a 0–10 scale
Resistance training		
Frequency	2–3 days per week	
Number of exercises	All major muscle groups (~4–5 upper body exercises)	
Sets and repetitions	Three sets of 8–12 reps each exercise	
Weight	Enough to create a feeling of "quite challenged" at the end of each set	

Fig. 10.1 An individual with mid-thoracic paraplegia performing endurance exercise on a Vitaglide upper extremity recipricating ergometer

Fig. 10.2 An individual with neurologically incomplete (AIS C) C5 tetraplegia performing a wide-grip latissimus pulldown as part of a circuit resistance training program

Fig. 10.3 An individual with neurologically complete paraplegia performing a 'preacher curl' as part of a circuit resistance training program

A growing body of evidence specifically supports the beneficial effect of such exercise on CMS component risks of dyslipidemia, glycemia and visceral adiposity in individuals with SCI/D. This evidence has been comprehensively reviewed in some scholarly monographs (Kressler et al. 2014; Nash 2005; Nash et al. 2012; Myers et al. 2007, 2012; Cragg et al. 2012).

10.4 Volitional Exercise

10.4.1 Volitional Exercise and Dyslipidemia After SCI/D

Dyslipidemia is a widely reported health risk after SCI/D (Nash and Mendez 2007; Libin et al. 2013; Bauman and Spungen 2000), whose most consistent feature is a depressed blood plasma concentration of HDL-C (Bauman et al. 1992b; Nash and Mendez 2007). Lowered HDL-C is normally associated with, and likely a direct result of a sedentary lifestyle (Jacobs et al. 2001), as cross-sectional studies in individuals with SCI/D observe an association between low peak aerobic capacities and low HDL-C (Manns et al. 2005), and also consistently find more favorable lipid profiles in those who are habitually highly active or fit (Janssen et al. 1997). In subjects with SCI/D, a prospective interventional study investigating effects of a moderate intensity (70–80 % of maximum heart rate reserve) eight-week wheelchair ergometry training program performed 20 min daily and three times weekly reported improved fitness as assessed by increased peak oxygen uptake (VO_2peak). This fitness improvement was accompanied by increased HDL-C and decreases in TG, LDL-C and TC/HDL-C ratio (Hooker and Wells 1989), the latter a proxy for global CVD risk. Noteworthy was the finding that the observed conditioning benefit was limited to those participants undergoing moderate-intensity training, and not low-intensity conditioning. A more recent study examining moderate-intensity arm crank ergometry demonstrated similar intensity-dependent beneficial effects on the lipid profile of individuals with SCI/D (El-Sayed and Younesian 2005). An intensity-dependent benefit of exercise was further shown in a 2003 study by de Groot et al. (2003) when comparing high and low intensity interval training programs, in which participants with SCI/D undergoing higher intensity work demonstrated more pronounced lowering of both fasting TG and the TC:HDL ratio.

As adoption of wheelchair ergometry and arm cycle ergometry as exercise conditioning modes may not be best suited for long-term use by persons with SCI/D, and may also not engender essential long-term compliance, the need for higher work intensities to achieve improved lipid profiles can be readily satisfied by use of interval training. Circuit resistance training (CRT) employing a series of alternating resistance exercises and low-resistance arm ergometry has been described for persons with both paraplegia and tetraplegia (Jacobs et al. 2002). A 12-week CRT program for persons with SCI/D improved VO_2peak by nearly 30 %, accompanied by lowered LDL-C, increased HDL-C and reduction in both LDL:

HDL and TC:HDL ratios in men (Nash et al. 2001). These fitness improvements reflected a CV risk reduction by almost 25 % (Nash et al. 2001), a benefit also reported in a cohort of middle-aged men with paraplegia who underwent an identical CRT program for 16 weeks (Nash et al. 2007). Other studies of twice-weekly CRT shown similar benefits of circuit training on both fitness and dyslipidemia (Pelletier et al. 2015). These studies provide convincing evidence that physical reconditioning can be accomplished through multiple modes of exercise and that moderate intensity effort lessens the dyslipidemia risk component for CMS. Circuit resistance training, however, better satisfies guidelines for incorporation of resistance training into the overall exercise conditioning plan, and unlike wheelchair and arm ergometry improve upper extremity strength, and anaerobic power needed to support essential activities of daily living (Jacobs et al. 2001; Nash et al. 2007).

10.4.2 Volitional Exercise to Improve Insulin Sensitivity/ Glycemic Response

When compared with non-disabled individuals, persons with SCI/D have a substantially greater risk for developing type 2 diabetes (Bauman and Spungen 1994), with 20–33 % of individuals having SCI/D living in a state of frank diabetes, insulin resistance, or dysglycemia (Jacobs and Nash 2004). Early studies in SCI/D report subjects with diabetes having significantly higher average glucose-stimulated plasma insulin levels than those individuals with normal glucose tolerance, suggesting a common state of insulin resistance (Bauman and Spungen 1994; Duckworth et al. 1980). This risk has been attributed to post-injury changes in body composition as well as reduced levels of exercise and non-exercise physical activity. A cross-sectional study of persons with SCI/D reported an association between low activity levels and higher fasting glucose (Manns et al. 2005), while a similar study found that 23 % more physically inactive individuals than active people with SCI/D were classified as insulin resistant (Buchholz et al. 2009).

It is well documented that exercise can reduce insulin resistance and improve insulin sensitivity (Borghouts and Keizer 2000; Mosher et al. 1998). A recent cross-sectional study examining glucose homeostasis in physically active and non-active individuals with chronic SCI/D reported significantly lower fasting plasma insulin and homeostasis model assessment of insulin resistance (HOMA-IR) values in persons undertaking regular physical activity (D'Oliveira et al. 2014). Upper extremity interval training programs also appear to be an effective method for improving insulin sensitivity (de Groot et al. 2003; Bakkum et al. 2015) with a recent study (Kim et al. 2015), reporting 37 % and 40 % reductions in fasting insulin and HOMA-IR levels, respectively, after a 6-week indoor hand-cycle exercise program.

10.4.3 Volitional Exercise to Attenuate Central Obesity

While beneficial effects of exercise on dyslipidemia and dysglycemia are well supported after SCI/D, less persuasive evidence documents the impact of exercise monotherapy on overall body composition (Tanhoffer et al. 2014; Martin Ginis et al. 2012), and especially clinically significant loss of body fat mass (FM). Gain in FM after SCI/D is clearly associated with physical immobilization, but is also attributable to alterations in sympathoadrenal medullary function accompanying SCI/D, and to a great extent food intake that is both hypercaloric for daily needs (Groah et al. 2009; Feasel 2009; Levine et al. 1992). It is thus not surprising that body mass gains are greatest during a period that is 2–7 months post injury. Higher abdominal sagittal diameters have been associated with low activity levels in SCI/D (Manns et al. 2005), while individuals who engage in regular exercise had 39 % lower total FM, up to 48 % lower FM in the trunk (D'Oliveira et al. 2014; Jones et al. 2004) and greater percent fat free mass (Buchholz et al. 2009) than those who did not regularly engage in exercise.

Notwithstanding these factors evidence still suggests a salutary effect of exercise monotherapy on body metabolism and composition (Gorgey et al. 2012). For example, a 16-week interval hand-cycling program induced a significant reduction in waist circumference (3.1 cm, 3.5 %) and trunk (3.6 %) and android (4.7 %) fat percentage (Bakkum et al. 2015). A recent study yielding promising results compared those who achieve the 150 min of moderate intensity exercise per week recommended by the ACSM and WHO for sedentary individuals. The study revealed that those who reach the target exercise recommendations have approximately 12 % greater FFM and approximately 10 % lower FM than those who do not, further confirming that the ACSM and WHO guidelines for healthy adults are useful as a guide for individuals with SCI/D (Tanhoffer et al. 2014).

10.5 Exercise as Part of a Therapeutic Lifestyle Intervention (TLI) Plan for CMS Risk Reduction

Effectiveness of exercise as a countermeasure to CMS risks is enhanced when integrated as part of comprehensive TLI that also incorporates nutrition and behavioral components (Table 10.3). Longstanding compliance with moderate physical activity, diet-induced body mass reduction, rigorous blood pressure control, correction of dyslipidemia, and strict glycemic control has been shown beneficial in reversing component risks of the cardiometabolic syndrome. Unfortunately, these changes are seldom long-lasting, and rarely address so-called 'hard end-points' that define *disease* rather than *disease risks* or *surrogates*. To address these limitations a Diabetes Prevention Program (DPP) intensive lifestyle intervention program, called "Lifestyle Balance," was developed to address limitations in CMD risk abatement provided by exercise alone (Diabetes Prevention Program Outcomes Study

Table 10.3 Dietary and behavioral modification key points (Kressler et al. 2014)

Component of TLI	Key points
Dietary	• Specific evidence for individuals with SCI is lacking; diet recommendations should follow general guidelines except for BMI targets and energy requirement estimates • General dietary guidelines include increased whole grain, fruit, and vegetable intake while reducing salt, simple sugar, saturated fat and cholesterol intake. • Balanced energy intake and output is critical to avoiding or reducing obesity and prevention and improvement of cardiovascular disease and CMS risk components
Behavioral Modification	Structured behavior modification therapy should include: • Education/instruction on diet and exercise components and role in lowering CMS component risks • Self-monitoring of body weight, calorie intake, and exercise levels • Understanding of psychosocial barriers to diet and exercise goals and developing cognitive strategies to overcome these barriers

Research et al. 2013). Unlike most weight loss programs the DPP lifestyle intervention (DPP-LI) was based on empirical literature in nutrition, exercise, and behavioral weight control to lessen the near pandemic of type-2 diabetes mellitus (T2DM) (The Diabetes Prevention Program (DPP) Research Group 2002). The intervention enrolled persons from all genders, races, and geographic regions, and adopted focused case management, frequent contact, a structured 16-session initial core curriculum with individualized maintenance programming, and a "toolbox" of strategies to manage non-adherent participants. Documents that provide detailed description and structure for implementing the DPP-LI are available in the public domain.[1]

The overarching goals of the DPP-LI were to achieve a sustained *weight reduction goal* greater than 7 % of initial body mass and maintain a *physical activity goal* of at least 700 kcal per week from physical activities.

Several studies examining persons with SCI have supported the benefits of a combinatorial approach to CMS risk reduction. In work by Gorgey et al. (2012) nine individuals with motor complete spinal cord injury were randomly assigned to treatment with either diet monotherapy or the combination of twice-weekly resistance training and diet. Results showed greater whole thigh skeletal muscle hypertrophy in the exercise conditioning plus diet group, and that visceral adipose tissue (VAT), VAT cross-sectional area, the ratio of VAT to subcutaneous adipose tissue ratio at L5-S3, and percent intramuscular fat decreased significantly with combination treatment. Further, challenge and post-load glucose levels were reduced following combination therapy, as were plasma triglycerides and the ratio of total cholesterol to HDL. Chen et al. (2006) studied 16 individuals with chronic SCI, who were overweight or obese and underwent a weight management program

[1] http://www.cdc.gov/diabetes/prevention/pdf/curriculum.pdf
http://www.cdc.gov/diabetes/prevention/recognition/curriculum.htm

consisting of 12 weekly classes covering nutrition, exercise, and behavior modification. Weight loss averaged 3.5 ± 3.1 kg (3.8 % of the initial weight) at week 12 and 2.9 ± 3.7 kg (3.0 % of the initial weight) at week 24. There was a significant reduction at weeks 12 and 24 in body mass index and fat mass, and improvement in diet behavior and psychosocial and physical functioning, while lean mass was maintained. Correlation analysis showed that a greater weight loss was associated with a greater reduction in total cholesterol at weeks 12 and 24 and in systolic and diastolic blood pressure at week 24. Several factors were important ($r > 0.4$ or $r < -0.4$) in determining the success in weight loss, including age, race, marital and employment status, family history of overweight/obesity, level and duration of injury, and cholesterol level at baseline.

As the circuit resistance training program of Nash and colleagues (Jacobs et al. 2001; Nash et al. 2001, 2007) satisfies the DPP guidelines for both recommended weekly activity and caloric expenditure we studied seven males aged 48.1 ± 7.4 (mean ± S.D.) years who were 14.5 ± 9.2 years post-injury with motor-complete (AIS A/B) at the C5-T7 levels. Subjects were obese and pre-diabetic by authoritative standards. Participants underwent a 6-month LI program incorporating 3-times weekly circuit resistance exercise, Mediterranean-style diet (1200–2000 kcal/day), and 16 educational sessions with a lifestyle coach. After 6 months of intervention, we observed that body mass was significantly reduced after LI compared to baseline ($P = 0.015$). Fasting plasma glucose and HBA_1C (%) were significantly lowered (P's = 0.039 and 0.029, respectively). Cardiopulmonary endurance (as VO_{2Peak}) was significantly improved after LI ($P = 0.007$) with increased peak and average anaerobic power (Watts) (P's = 0.031) and upper extremity strength ($P = 0.0078$). Thus, improvement in the DPP body mass criterion for diabetes prevention was observed with enhanced fasting glucose levels and HBA_1C. Values reflected a change from "pre-diabetic" to "low risk/normal" according to guidelines. As the exercise model use in this program has been adapted for use by persons with moderate to severe traumatic brain injury (Jankowski and Sullivan 1990; Bhambhani et al. 2005), these preliminary data provide evidence that the LI program can be effectively adapted for persons with neurological disabilities.

10.6 Exercise After SCI: Knowledge Limitations

Benefits of volitional exercise on various component risks of the CMS are well established, although the literature lacks evidence examining exercise intervention on so-called 'hard endpoints' such as disease state, disease progression, or CV *events* including myocardial infarction, stroke, and sudden death. Also less studied are gender-specific effects of disease and exercise intervention on CMS, as well as the impact of chronological age and age at SCI/D onset on disease susceptibility. Relatively little is known about the component risk of *hypertension* as a longitudinal health risk, or the extent to which hypotension resulting from injury above the

level of spinal sympathetic outflow at T1 might forestall CV disease progression imposed by other risk factors. While we are now beginning to appreciate effects of intermittent bouts of hyperreflexia-related crisis hypertension on CVD (Krassioukov and Weaver 1995; Krassioukov et al. 2003), the contribution to these bouts of mass reflex to overall disease progression is unknown, and benefits of exercise for controlling these episodes is limited to studies of experimental animals undergoing passive lower extremity movement (West et al. 2015).

One of the challenges posed by CMS determination is that the five risk components shown in Table 10.1 are both categorical and dichotomous. Therefore, small differences in component risk assessment—even occurring with acceptable degrees of measurement imprecision or possible short-term variation—can either confer or nullify the diagnosis. Further, the CMS diagnosis is based upon an assumption that risk determinants are equally weighted. However, the absence of obesity occurring among any other three eligible component risks is thought to lessen substantially the probability for eventual atherosclerotic development (Wildman et al. 2008), and it is established that risks of obesity and insulin resistance are weightier in CMS determination than all other risk factors (Wilson et al. 2005). Insulin sensitivity is improved by voluntary (Gorgey et al. 2012) and electrically-stimulated exercise (Mohr et al. 2001; Jeon et al. 2002), however, significant reduction of BF may require more aggressive treatment than provided by exercise alone, The pursuit of more extensive lifestyle modification incorporating nutrition and behavioral programs may be needed to lessen the risk from the more prevailing disease-determining risk of overweight/obesity. Such a belief would be consistent with the longstanding dictum that ‘one cannot exercise enough to offset an imprudent diet.”

10.7 Conclusion

An alarming number of individuals with SCI/D develop component risks for CMS including dyslipidemia, insulin resistance, and obesity. Exercise offers an effective strategy for attenuation of these risks, although evidence better supports treatment with voluntary than either involuntary or assisted exercise. Notwithstanding, benefits of exercise on overall health and function after SCI/D should not be overlooked. In our view, an exercise program should be the cornerstone of a comprehensive lifestyle treatment plan, especially if optimal health and function are to be maintained throughout the lifespan. When reduction of body fat mass is indicated, adoption of nutritional and behavioral modification will most effectively lessen CMS component risks and their effects on people living with SCI/D.

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Chapter 11
The Effect of Acute and Chronic Exercise on Inflammatory Markers in SCI

Christof A. Leicht and Nicolette C. Bishop

Abstract A spinal cord injury (SCI) is associated with an increased prevalence of physical inactivity and obesity, conditions linked to illnesses with inflammatory etiology, such as diabetes or cardiovascular disease. This may at least partly explain the elevated inflammatory risk marker profile and the higher occurrence of the associated diseases found in individuals with SCI. In able-bodied populations, exercise helps to improve this risk marker profile prompting the question whether exercise can mitigate some of the SCI related risk through acute disturbances of the inflammatory environment. Despite a smaller active muscle mass during upper body activities, a similar acute inflammatory response has been observed with this modality when compared with lower body exercise. This supports the use of upper body exercise interventions to combat disease linked to inflammation in individuals not able to participate in other exercise activities. However, more dramatic reductions in active muscle mass and/or sympathetic dysfunction found in those with cervical SCI can result in an absent or blunted acute inflammatory response. Nonetheless, intervention strategies like exercise, functional electrical stimulation or passive elevation of core temperature induce some modest positive acute responses even in individuals with high level SCI. The evidence base for chronic interventions is small but suggests that long term exercise can indeed improve the inflammatory risk marker profile in individuals with thoracic and, to a lesser extent, with cervical SCI. Future challenges include defining disability-specific minimal exercise or temperature stimuli required to induce meaningful chronic changes in inflammatory markers.

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11.1 Inflammation and Exercise

Chronic low grade inflammation is a risk factor for disease driven by metabolic imbalance and inflamed adipose tissue. It has been linked to cardiovascular disease, insulin resistance and tumor growth (Gleeson et al. 2011). Inflammatory markers that have been studied extensively include the cytokines interleukin-6 (IL-6) and IL-8, C-reactive protein (CRP) and tumor necrosis factor (TNF), with increased resting levels indicative of chronic low grade inflammation. Anti-inflammatory markers (such as IL-10) can further help to describe the resting inflammatory state, with low resting concentrations of anti-inflammatory markers and a high ratio of pro- vs anti-inflammatory markers (i.e., IL-6/IL-10 ratio) also describing an inflamed state.

Obesity and physical inactivity are associated with chronic low grade inflammation. The abundance of evidence in the able-bodied population is supported by data in individuals with spinal cord injury (SCI). For example, waist circumference is related to low grade inflammation in SCI (Davies et al. 2007; Gibson et al. 2008). Increased leisure time physical activity after SCI is not only associated with a lower body mass index, lower fat mass, and higher fat free mass, but also a reduction in the concentration of resting inflammatory markers (Buchholz et al. 2009). Even within a group of athletes with SCI, the lowest resting concentrations of IL-6 and CRP can be found in the fittest athletes (Sasaki et al. 2014), underpinning the negative relationship between resting pro-inflammatory marker concentration and physical activity. The sedentary lifestyle and reduced physical function in individuals with SCI therefore likely contribute to their heightened risk for cardiovascular disease and may also partly explain the higher prevalence of insulin resistance, diabetes and metabolic syndrome in this population (Myers et al. 2007).

A few mechanisms by which physical activity may positively influence and reduce chronic low grade inflammation have been proposed. To begin, exercise interventions can acutely increase pro-inflammatory markers such as IL-6 or IL-8. At first, this may seem counterintuitive—why should exercise reduce chronic low grade inflammation if it induces acute elevations of *pro*-inflammatory markers? It is therefore important to note that cytokines have messenger functions. Altered cytokine levels may hence impact on the production of other cytokines/messenger molecules or alter immune cell number and function directly, which can influence the inflammatory environment (Pedersen and Febbraio 2008). This can help explain why the acute, rather short increase (~0–2 h) in pro-inflammatory markers is followed by longer lasting rises (>2 h) in anti-inflammatory markers. Repeated exercise sessions therefore result in the repeated creation of an anti-inflammatory environment. This may have an effect on immune cell cytokine secretion, reducing the production of pro-inflammatory cytokines, and ultimately reducing resting levels of pro-inflammatory cytokines.

Another likely mechanism by which physical activity affects inflammation is through the inhibition of monocyte release of TNF, partly through the actions of the anti-inflammatory hormone cortisol produced during exercise. Exercise can also

chronically down-regulate the pro-inflammatory monocyte subtype and mobilize regulatory T-cells that are a major source of the anti-inflammatory cytokine IL-10. Exercise can further down-regulate the expression of Toll-like receptors on immune cells, which are crucial in the initiation of an inflammatory response. Finally, regular exercise can reduce the volume of adipose tissue, accompanied by a reduction of the macrophage number and a change of the macrophage phenotype residing there. This may hence result in a reduced secretion of IL-6 and TNF, but an increased secretion of IL-10 from adipose tissue as a result of the body composition changes induced by regular exercise (Gleeson et al. 2011).

So why should we be interested in inflammation and SCI? As already discussed, chronic low grade inflammation is more prevalent in individuals with SCI than in the general population—but this is true for many individuals, such as for those with reduced physical activity, obesity, or advanced age. A crucial difference to these populations is the loss of muscle innervation after SCI, and as a result, a marked reduction in active muscle mass. In addition to immune cells that secrete cytokines, contracting muscle is a major producer of cytokines that can affect the inflammatory state. Any decrease in muscle activity and muscle mass could therefore decrease the potential to mount an inflammatory response and muscle-contraction mediated cytokine secretion, placing individuals with SCI at a disadvantage. Secondly, the autonomic nervous system governs a range of immune functions; as a result, the sympathetic dysfunction in high level SCI could further affect the inflammatory responses to exercise.

11.1.1 Inflammation and the Autonomic Nervous System

To fully appreciate the effect of exercise on inflammatory markers in SCI, we first need to look further at the autonomic nervous system and its involvement in inflammatory responses. Two major systems are involved in the inflammatory response through constant interaction: the brain and the immune system (Elenkov et al. 2000). These systems can communicate via the autonomic nervous system, either through direct innervation of lymphoid organs or through the action of catecholamines (norepinephrine and epinephrine) on adrenergic receptors that are expressed on the vast majority of lymphoid cells (Elenkov et al. 2000). Evidence for the modulating effect of the inflammatory response by catecholamines is given by the close correlation of catecholamine concentration and the altered distribution of pro- and anti-inflammatory leukocyte subtypes following exercise (Landmann et al. 1984), or by experiments observing an inflammatory response induced by epinephrine infusion (Steensberg et al. 2001).

In addition to the sympathetic arm of the autonomic nervous system, the parasympathetic nervous system can modulate immune responses. For example, efferent fibers of the *vagus* nerve inhibit the release of pro-inflammatory cytokines and regulate inflammation, which has been referred to as cholinergic anti-inflammatory pathway (Pavlov and Tracey 2004). This explains why peripheral *vagus* nerve

stimulation can prevent the development of acute inflammation in animal models (Borovikova et al. 2000). The importance of innervation on immune control is also evident in humans: leukocyte infiltration in denervated skin is greatly reduced following local damage. This is associated with a reduction in the rate of wound healing compared with innervated skin (Downing and Miyan 2000).

In addition to mounting an immune response through efferent fibers, the autonomic nervous system also has a sensory component. Afferent *vagus* nerve fibers relay information to the brain, which can then trigger immunomodulatory responses (Pavlov and Tracey 2004). Peripheral sensory nerves are hence involved in reflex pathways that can influence inflammatory events, for example by triggering vasodilation or mast cell activation (Downing and Miyan 2000). Apart from afferent neurons, sensory receptors, integration centers in the central nervous system, efferent neurons, and effector organs also form part of reflex pathways (Garstang and Miller-Smith 2007). Reflex pathways may also be activated by causes other than injury or inflammation; for example, they are involved during muscle contraction, which increases adrenal sympathetic nerve activity in rats (Vissing et al. 1991). In the context of SCI, it is worth noting that whereas the brain can take part in some reflexes, it does not take part in spinal reflexes. The reader may be familiar with the patella tendon reflex from check-ups with their primary care physician, where the patella tendon is stretched by tapping it with a mallet. This induces a sensory signal which is processed on the spinal level and causes a motor response, i.e. the knee to extend. Analogously, reflex arcs can also cause sympathetic activity in response to afferent feedback as long as peripheral innervation and the integration centers within the spinal cord are intact (Fig. 11.1). In many cases, a SCI leaves reflex arcs below the level of lesion intact, which would explain some

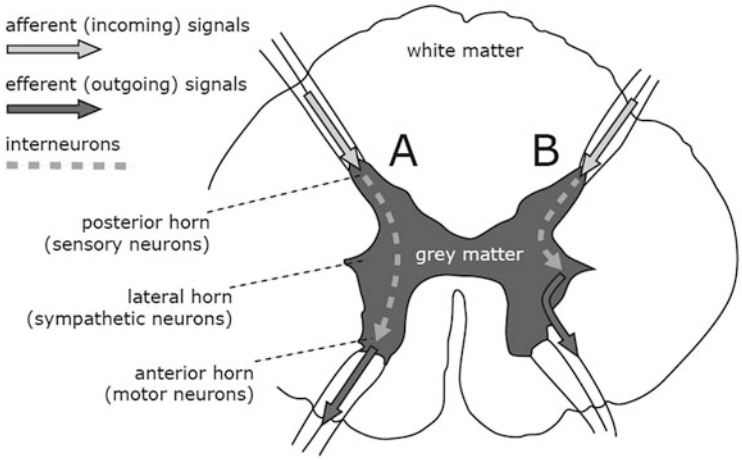

Fig. 11.1 The anatomical basis for reflex activity: Cross-section of the spinal cord with afferent and efferent spinal nerve fibers. Sensory signals triggering motor (**A**) or sympathetic (**B**) activity

remaining sympathetic activity despite a missing neural link between effector organs and the brain.

11.1.2 Inflammation and Humoral Factors

In addition to the autonomic nervous system that conveys information through neural pathways, humoral factors are involved in the communication between the brain and the immune system. The hypothalamus-pituitary-adrenal (HPA) axis is a prominent example: adrenocorticotropic hormone (ACTH) released from the pituitary stimulates cortisol secretion in the adrenal gland (Gleeson et al. 2011; Pavlov and Tracey 2004) (Fig. 11.2). This impacts on the inflammatory status as cortisol is generally immunosuppressive and has anti-inflammatory effects (Elenkov et al. 2000). Similar to neural feedback, humoral feedback mechanisms can modify

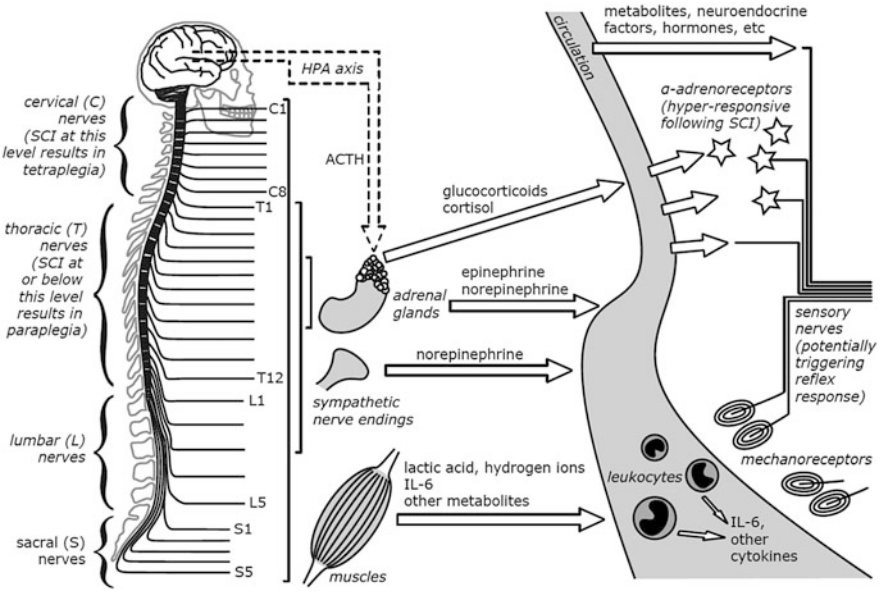

Fig. 11.2 The inflammatory response in spinal cord injury (SCI): Anatomical and physiological basis. The origin of nerves is indicated for glands, sympathetic nerve endings and muscles; the SCI lesion level hence influences the extent of intact sympathetic, motor and sensory innervation. Leukocyte cytokine secretion is partly governed by catecholamines acting on adrenoreceptors and stimulation by circulating cytokines, but temperature elevations can also independently induce systemic cytokine increases. Reflex activity on the spinal level can potentially be triggered by a range of factors, such as mechanoreceptor activity or circulating metabolites acting on adrenoreceptors. Spinal reflex activity could hence be responsible for modest cytokine and catecholamine responses in the presence of sympathetic dysfunction. See text for more details. *ACTH* adrenocorticotropic hormone; *HPA* hypothalamus pituitary adrenal, *IL-6* interleukin-6

immunological actions through central integration centers: cytokines and other soluble factors secreted by immune cells in response to infection or inflammation not only attract and modulate other immune cells locally, but may also act on sensory neurons or on the brain directly. Humoral feedback may hence represent another mechanism by which immunological actions can be modified in a SCI leading to sympathetic dysfunction.

11.2 Autonomic Function and Inflammation Following SCI

11.2.1 Catecholamines

The relationship between catecholamine secretion and the inflammatory response is well supported by the literature (Landmann et al. 1984; Steensberg et al. 2001; Klokker et al. 1997); understanding the changes in the catecholamine profile may therefore help understanding alterations in the inflammatory profile following SCI. The anatomical basis for SCI lesion-level dependent alterations in the resting or exercising catecholamine concentration is given by the location of the sympathetic neurons that exit the spinal cord between vertebrae T1 and L3 (Garstang and Miller-Smith 2007; Krassioukov 2009). The majority of sympathetic neurons innervating the adrenal medulla originate from T5-T9 (Garstang and Miller-Smith 2007) (Fig. 11.2). The abolition of neural pathways to the adrenal gland and dysfunction of sympathetic pathways therefore explain the blunted catecholamine release in higher level SCI (Paulson et al. 2013; Kouda et al. 2012).

A cervical and high thoracic SCI is associated with lower resting plasma catecholamine concentrations when compared with able-bodied individuals or individuals with a lower level paraplegia; the exercise-induced catecholamine increase is smaller in high level SCI (Schmid et al. 1998a, b; Klokker et al. 1998) or not present at all (Paulson et al. 2013; Kouda et al. 2012) (Fig. 11.3). The majority of studies show that even strenuous exercise in individuals with a cervical SCI does not alter plasma epinephrine and norepinephrine in both laboratory conditions (performing a graded exercise test to exhaustion) (Paulson et al. 2013; Wheeler et al. 1994; Frey et al. 1997) or following simulated racing conditions. Even an actual wheelchair half marathon race, where both physical and psychological stresses may act in conjunction, does not increase plasma epinephrine concentration in cervical and high thoracic SCI, whereas it does increase in individuals with T4-L1 lesions (Banno et al. 2012). Similarly, individuals with T1-T6 SCI lesions exhibit a reduced catecholamine response to a graded exercise test to exhaustion when compared to those with T7-T12 lesions (Steinberg et al. 2000). While both epinephrine and norepinephrine (to a lesser extent) are released from the adrenal medulla, it is only norepinephrine that is released from the non-synaptic sympathetic nerve terminals. This explains why serum norepinephrine is significantly elevated after exercise in both the T1-T6 and T7-T12 group, whilst epinephrine is

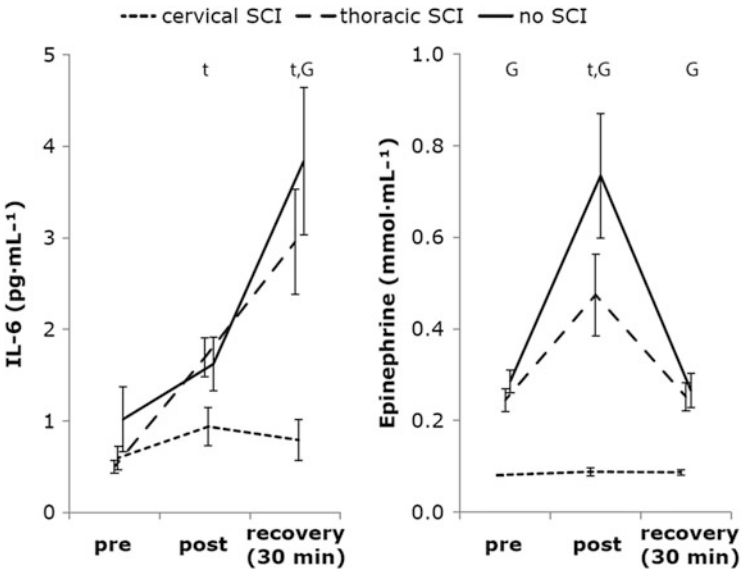

Fig. 11.3 Plasma IL-6 and epinephrine response to acute incremental exercise to exhaustion in athletes with cervical and thoracic spinal cord injury (SCI) and a control wheelchair athlete group with no SCI. Note the blunted response in both markers for cervical SCI. Significant effects: t (time effect): thoracic and no SCI different to pre; G (group effect): thoracic and no SCI different to cervical SCI ($P < 0.05$) (data from Paulson et al. 2013)

only elevated in the T7-T12 group (Steinberg et al. 2000), underpinning the physiological relevance of intact adrenal gland innervation in the context of epinephrine secretion.

11.2.2 Acute Exercise and the Inflammatory Response

As cortisol release is governed through humoral mechanisms, it may be expected that the cortisol response to exercise is unaffected in SCI. Indeed, the exercise-induced increases in plasma cortisol concentrations normally found in able-bodied individuals can be observed in cervical SCI, for example after simulated race conditions (Wheeler et al. 1994). The similar rise in plasma cortisol concentration following exercise for both individuals with cervical SCI and able-bodied controls (Kouda et al. 2012; Castellani et al. 2001) further supports the concept that cortisol is governed independently of sympathetic nervous system function. However, perturbations in cortisol metabolism after SCI have been documented; cortisol release after SCI is impaired following administration of corticotropin-releasing hormone (Huang et al. 1998), and higher resting concentrations of cortisol have been found in individuals with SCI when compared with able-bodied control populations (Campagnolo et al. 1999). Cortisol has also been shown to remain

elevated for longer following exercise in individuals with cervical SCI when compared with able-bodied controls (Kouda et al. 2012; Yamanaka et al. 2010) thus creating an anti-inflammatory environment for a longer duration. The neuroendocrine-immune loop involving the HPA axis (Pedersen and Febbraio 2008) may therefore be altered in individuals with cervical SCI, with no clear evidence whether this could negatively impact on the anti-inflammatory effects of exercise through the actions of cortisol after cervical SCI.

As mentioned when introducing this chapter, a prominent marker of inflammation is the cytokine IL-6, particularly relevant as it mediates a range of inflammatory responses: administering an IL-6 dose corresponding to levels of strenuous exercise to a resting individual induces acute increases in neutrophil numbers, cortisol, IL-10 and IL-1 receptor antagonist (Steensberg et al. 2003). Leukocytes secrete cytokines, and specifically, IL6, but muscle tissue is another major producer of IL-6 through contraction dependent mechanisms. As a result, the IL-6 response is dependent on exercise intensity, strongly related to the muscle mass involved. Early studies have therefore questioned whether upper body exercise *per se* is sufficient to increase IL-6 above resting levels (Pedersen and Febbraio 2008)—however, it must be said clearly that these studies employed exercise protocols of very light intensity, or they investigated small isolated muscle groups.

Despite their limitations, these early results provided little rationale to investigate the IL-6 response in SCI: if upper body exercise fails to induce a response in general, why should a response be expected in a population whose active muscle mass is even further reduced for the same exercise modality? However, recent evidence suggests that an acute IL-6 response to upper body exercise occurs in both able-bodied individuals but also in individuals with thoracic SCI for moderate to strenuous exercise intensities involving the whole upper body (Sasaki et al. 2014; Paulson et al. 2013; Kinoshita et al. 2013; Umemoto et al. 2011). Furthermore, directly comparing intensity matched bouts of upper and lower body exercise results in a similar IL-6 response (Leicht et al. 2016). These more recent findings provide a strong foundation to further investigate the use of exercise interventions to mount a cytokine and inflammatory response in SCI.

Similar to the catecholamine response, the acute cytokine response to strenuous exercise appears to be lesion level dependent. In general, a cervical SCI is associated with blunted IL-6 responses following acute exercise. Sympathectomized animals show complete attenuation of the plasma IL-6 response to exercise (Yu et al. 2001). This is confirmed in human experiments, where plasma IL-6 concentrations increase in response to 20 minutes of upper body exercise (Kouda et al. 2012) or a test to exhaustion (Paulson et al. 2013) in individuals with thoracic SCI and able-bodied individuals whereas they remain unaffected in individuals with cervical SCI (Kouda et al. 2012) (Fig. 11.3). The level of fitness does not appear to influence this increase as a similar pattern is found for recreationally trained (Kouda et al. 2012; Yamanaka et al. 2010) and elite athletes (Paulson et al. 2013).

The lack of an acute IL-6 response in individuals with cervical SCI may be partly explained by reductions in active muscle mass, but autonomic dysfunction also impacts on IL-6 production, as catecholamines directly influence cytokine secretion

(Pavlov and Tracey 2004). This is shown by infusing catecholamines into resting individuals: this causes a rise in plasma concentrations of IL-6, albeit lower than the rise found following exercise (Steensberg et al. 2001; Frost et al. 2004). Additionally, adrenergic antagonists can block epinephrine-stimulated IL-6 expression (Frost et al. 2004). The consistent low levels in both catecholamines and IL-6 found in individuals with cervical SCI (Paulson et al. 2013; Kouda et al. 2012; Yamanaka et al. 2010) therefore likely demonstrate a cause and effect relationship. Taken together, the combination of less active, cytokine producing muscle mass and autonomic dysfunction are the most likely reasons for the blunted elevation of IL-6 plasma concentration in individuals with cervical SCI in response to acute exercise.

However, it must be noted that the duration of exercise is strongly associated with IL-6 production, with longer lasting activities resulting in more pronounced IL-6 level increases (Pedersen and Febbraio 2008). It could hence be questioned whether exercise interventions that were rather short in duration (<~30 min) (Paulson et al. 2013; Kouda et al. 2012; Yamanaka et al. 2010) failed to induce an inflammatory response in individuals with cervical SCI also partly because the critical exercise duration was not achieved. Indeed, more recent results indicate the potential to induce an IL-6 response in individuals with cervical SCI following a half-marathon lasting around 1.5 h (Ogawa et al. 2014). Remarkably, no change in epinephrine was observed in this investigation, raising the question whether any compensatory mechanisms in the presence of sympathetic dysfunction could explain the results.

11.2.3 Inducing an Inflammatory Response Despite Sympathetic Dysfunction

Interestingly, exercise-induced increases in catecholamines have been observed in individuals with cervical SCI following maximal exercise (Schmid et al. 1998a, b; Klokker et al. 1998), when electrically stimulating paralyzed muscles below the level of lesion in both individuals with cervical and thoracic SCI (Bloomfield et al. 1994) and when peripherally stimulating the bladder in individuals with high level SCI (Karlsson et al. 1997). Even though the response is blunted for lesion levels affecting sympathetic pathways (Schmid et al. 1998a, b; Bloomfield et al. 1994), they may be pronounced enough to change the behavior of effector cells and organs, and potentially mount an inflammatory response. Lower circulating levels of catecholamines and more modest catecholamine elevations in individuals with cervical SCI lead to a chronically lower stimulation of adrenoreceptors. However, this may be counteracted by the fact that as effector organs become more sensitive, they become hyper-responsive (Fig. 11.2). This is illustrated by catecholamine infusion experiments: epinephrine and norepinephrine injected into sympathectomized rats induce a more pronounced response than the

same amount injected into control animals (Paynter et al. 1977), findings later confirmed in humans with cervical SCI (Arnold et al. 1995). It has also been observed that following SCI spinal circuits are capable of generating some sympathetic activity, and a peripheral α-adrenoreceptor hyper-responsiveness may help to maintain some function governed by catecholamines despite depressed circulating levels (Garstang and Miller-Smith 2007).

But why can catecholamine concentrations increase after cervical SCI in the first place, as no direct neural links between adrenal glands/sympathetic nerve endings and the brain exist? Spinal reflexes are a likely underlying mechanism (Schmid et al. 1998b; Bloomfield et al. 1994; Karlsson et al. 1997) (Figs. 11.1 and 11.2). As mentioned previously, spinal reflex function remains normal below the level of injury; as long as peripheral nerves and the spinal integration center are intact, a SCI would not affect it. Hence, despite the central abolition of neural pathways that normally relay information governed centrally by the sympathetic nervous system, ways remain to exert a catecholamine response. Reflex pathways may also represent a mechanism by which an inflammatory response can be increased even in the presence of a high level SCI impairing sympathetic function. This may explain some surprising findings in light of sympathetic dysfunction, such as the acute increase in IL-6 following long lasting exercise in individuals with cervical SCI (Ogawa et al. 2014). Studies during anesthesia document increases in catecholamines, ACTH, and cortisol following functional electrical stimulation (FES) of anaesthetized limbs (Kjaer et al. 1996), further suggesting that spinal reflexes and humoral feedback can potentially regulate immune responses during exercise. Spinal reflexes may also help explain the increases in IL-6 during FES in individuals with SCI (Paulson et al. 2014). Potentially, reflex activity may counteract some of the lost central function and exploring methods to exert reflex induced responses in those with a decentralized sympathetic nervous system could help to modulate and improve the inflammatory response in this population.

Increases in temperature represent another mechanism by which inflammatory markers increase following exercise. Muscle work generates heat, and if an exercise bout is long and strenuous enough, substantial elevations in core, blood and muscle temperature occur. Heat can independently induce rises in leukocytes in the circulation (Kappel et al. 1991) and increase secretion of inflammatory markers, as shown during hyperthermia in non-exercising conditions (Welc et al. 2012). This effect appears to be independent of sympathetic function, as it can also be found in humans with cervical SCI that are passively immersed in hot water (Leicht et al. 2015). Studies showing blunted inflammatory responses to exercise in cervical SCI may hence also be explained with the limited heat generating capacity of their reduced active muscle mass.

A word of caution on the interpretation of research where individuals with cervical SCI are used as a model of sympathetic dysfunction: the critical reader should be alerted to the fact that the majority of investigators do not directly establish whether a SCI lesion in human experiments is autonomically complete and rely on the fact that a decentralized sympathetic nervous system is likely in the presence of a motor and sensory complete SCI. However, recent evidence in

athletes with cervical SCI shows that some remaining centrally governed sympathetic function in the presence of motor complete lesions is possible (West et al. 2013), which could also explain exercise-induced catecholamine elevations. Just as an incomplete SCI can result in some remaining motor function below the level of injury, it can of course result in the sparing of some autonomic function. It is therefore critical to investigate studies for direct (e.g., neural responses across the SCI level) or indirect (e.g., blood pressure, heart rate response) measures of autonomic completeness when interpreting their findings on autonomic or inflammatory responses.

11.2.4 Chronic Exercise and the Inflammatory Risk Marker Profile

The higher prevalence of chronic low grade inflammation in individuals with SCI has been mentioned in the opening paragraphs of this chapter. Specifically, elevated concentrations of plasma IL-6 (Nash 2000), CRP and markers of endothelial inflammation are found after SCI (Wang et al. 2007). It has been postulated that exercise may be an appropriate intervention to improve the inflammatory profile in individuals with SCI (da Silva et al. 2013). This rationale may be influenced by observational studies that show higher risk marker concentrations in those with the lowest ability to exercise, for example due to their high injury level (Morse et al. 2008), but also due to the completeness of injury, with incomplete lesions being associated with lower CRP concentrations (Liang et al. 2008). Physical activity status in individuals with SCI is also associated with reductions in CRP (Buchholz et al. 2009), a relationship that can also be shown for cervical SCI (Koury et al. 2013).

Due to their more complex and time-consuming nature, it is not surprising that only a handful of chronic exercise intervention studies have been performed in the field of inflammation and SCI, recently reviewed by Neefkes-Zonneveld et al. (2015). However, the results of prospective training studies investigating this issue are encouraging. They indicate that chronic exercise has the potential to lower the resting concentration of a range of inflammatory markers (Fig. 11.4). This is the case for a range of exercise modalities, such as arm exercise (Rosety-Rodriguez et al. 2014; Bakkum et al. 2015), arm exercise supported by FES (Bakkum et al. 2015), isolated FES (Griffin et al. 2009) or robotic treadmill training (Turiel et al. 2011). Whereas these studies were not designed to allow for a comparison between individuals with cervical and thoracic SCI, analysis of individual data suggests that while the improvements in inflammatory markers are more pronounced in individuals with thoracic SCI, they can also be found in individuals with cervical SCI (Bakkum et al. 2015). The beneficial anti-inflammatory effects of exercise can hence also be demonstrated in SCI; however, we have to keep in mind that exercise adherence or access to exercise may be more problematic in this

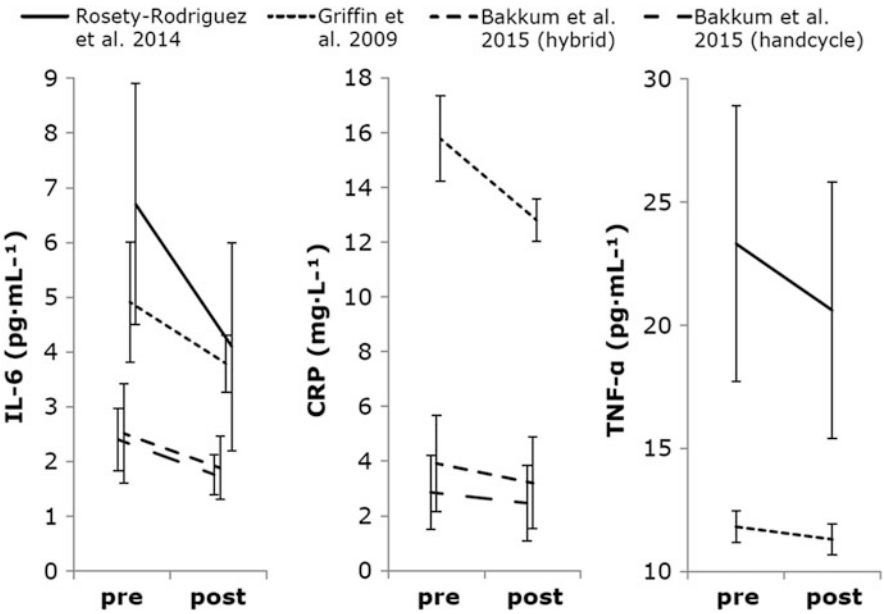

Fig. 11.4 Chronic exercise interventions (10–16 weeks duration) decrease resting plasma concentrations of inflammatory markers in SCI. Data shown are responses from both cervical and thoracic SCI (Griffin et al. 2009; Bakkum et al. 2015) or thoracic SCI only (Rosety-Rodriguez et al. 2014). Exercise interventions are arm cranking exercise (Rosety-Rodriguez et al. 2014), functional electrical stimulation (FES) (Griffin et al. 2009) and either isolated or FES-supported (hybrid) handcycle exercise (Bakkum et al. 2015). *IL-6* interleukin-6, *CRP* C-reactive protein, *TNF* tumor necrosis factor. Significant effects: All data are significantly lower post intervention ($P < 0.05$) [data from Rosety-Rodriguez et al. (2014) Griffin et al. (2009) and Bakkum et al. (2015)]

population due to disability related issues. Repeated passive elevation of body temperature could hence represent a non-pharmacological alternative, or better, supplement to exercise training. Whether or not hot water immersion can chronically lower the pro-inflammatory marker profile has yet to be established, but the positive acute responses to passively increasing core temperature in individuals with cervical SCI encourage investigation of this question (Leicht et al. 2015).

11.3 Conclusion and Outlook

Exercise has been suggested already two decades ago to be one intervention to reverse the negative immune alterations in SCI, and particularly, in individuals with cervical SCI with sympathetic dysfunction (Campagnolo et al. 1994). Importantly, the reductions in active muscle mass during upper body exercise in general or in SCI specifically do not prohibit an inflammatory response, and a range of anti-

inflammatory effects of upper body exercise can be found in both able-bodied and SCI populations. Despite the central role of sympathetic innervation in inflammation, some inflammatory responses can be evoked in the absence of a direct neural link of effector organs and the brain. Mechanisms that trigger an inflammatory response after cervical SCI are likely related to spinal reflex activity, humoral feedback, adrenoreceptor hypersensitivity, or temperature elevations. Interventions that activate such mechanisms include exercise, FES, or hot water immersion. Future challenges include defining disability-specific minimal exercise or temperature stimuli required to induce meaningful chronic changes in inflammatory markers.

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Chapter 12
Role of Exercise in Alleviating Chronic Pain in SCI

Thomas N. Bryce

Abstract Four out of five people with spinal cord injury (SCI) report chronic pain. In general this chronic pain is refractory to conventional treatments. Exercise programs designed to alleviate shoulder pain, a particular subtype of nociceptive pain after SCI, have the strongest evidence for effectiveness. There is weak evidence that long term aerobic exercise can reduce chronic pain intensity in persons with SCI. The two purported mechanisms related to the amelioration of pain by exercise are enhanced descending inhibitory activity and reduced excitatory synaptic transmission, however experimental support for these mechanisms is meager. Finally there seems to be an association between exercise, pain, and mood states which may be related to common mechanisms and requires further study.

12.1 Introduction

Approximately 80 % of persons with spinal cord injury (SCI) report chronic pain at any time; one third of these people report pain that interferes with activities of daily living and work (Cardenas et al. 2004; Dijkers et al. 2009). Regarding the different types of pain, one third of individuals with chronic pain experience at-level SCI neuropathic pain, one third experience below-level SCI neuropathic pain, and over one half experience nociceptive musculoskeletal pain (Finnerup et al. 2014; Siddall et al. 2003). As these numbers suggest, the majority of persons with SCI experience ongoing pain which is refractory to conventional treatments (Cardenas and Jensen 2006).

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12.2 Definitions of Pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such injury (IASP Taxonomy Working Group 1998). Chronic pain is defined as pain that occurs beyond the time of expected healing, most typically thought to be 3 months. Most pain can be categorized into one of two subtypes, nociceptive pain or neuropathic pain. Nociceptive pain is defined as pain arising from the activation of peripheral nerve sensory receptors capable of transducing and encoding noxious stimuli, whereas neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system (IASP Taxonomy Working Group 1998). The International SCI Pain (ISCIP) Classification was developed to help organize the different pain types seen after SCI into an understandable format (Bryce et al. 2012). In the ISCIP classification, in addition to the nociceptive and neuropathic pain types, there is also a third type of pain, 'other' pain, which must be distinguished from these two types. It is pain that occurs for which no identifiable noxious stimulus nor any detectable inflammation or damage to the nervous system responsible for the pain can be identified. It is usually unclear what causes this latter category of pain to begin or persist. Established pain syndromes of unknown etiology which fall in this category include fibromyalgia and complex regional pain syndrome type I.

12.3 Definitions of Exercise

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities (Caspersen et al. 1985). Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness. Sedentary behavior is defined as any waking behavior characterized by an energy expenditure of $\leq$1.5 Metabolic Equivalent of Task while in a sitting or reclining posture (Verschuren et al. 2016).

12.4 Survey Evidence of Exercise as a Pain Intervention

There have been several cross sectional surveys of persons with SCI and pain which asked about the treatment of pain. In one survey of 120 people living with pain after SCI in the US, nearly one half of respondents reported a considerable pain reduction with physical therapy (Widerstrom-Noga and Turk 2003). In another survey of 279 individuals from the Netherlands, 4 out of 5 respondents found physical therapy

and exercise helpful to a large extent and nearly one out of 5 found it somewhat helpful. The percentage of respondents who found exercise to be helpful far exceeded all the other treatments tried with the exception of cannabis and alcohol (Heutink et al. 2011). In another survey of 101 individuals from Sweden, of those treatments that were reported by the patients to have a rather good to very good effect, physical activities were found to have the highest satisfaction rate, however, only a small percentage of the sample had used this option (Norrbrink Budh and Lundeberg 2004).

12.5 Exercise as a Pain Intervention in General for Pain After SCI

Sedentary people have a 10–30 % greater risk for developing chronic pain than physically active people (Landmark et al. 2011). The relationship between frequency, duration, and intensity of exercise and chronic pain has been shown to be consistent and linear in large populations without SCI (Landmark et al. 2011, 2013). Regular exercise has been associated with decreased chronic pain in a variety of chronic conditions including osteoarthritis, peripheral vascular disease, low back pain, and fibromyalgia (Buckelew et al. 1998; Ettinger et al. 1997; Fransen et al. 2002; Hayden et al. 2012; Lane et al. 2014; Patterson et al. 1997; Rejeski et al. 1998; van Tulder et al. 2000). This seems also to be the case for persons with chronic pain and SCI although the quality of the evidence is weak (Boldt et al. 2014; Crane et al. 2015; Cratsenberg et al. 2015; Hicks et al. 2003; Martin Ginis et al. 2003; Norrbrink et al. 2012).

One study of persons with traumatic SCI investigating a 9 month biweekly 90–120 min duration moderately intense aerobic and resistive exercise intervention with a wait list control reported a 10 % change in underlying pain in the exercise group that was not seen in the control group (Hicks et al. 2003). Decreased levels of pain were seen after 3 months of exercise training but not of the magnitude of the decreases found at 9 months (Martin Ginis et al. 2003). As might be expected, stopping the long-term exercise program resulted in an increase in pain (Ditor et al. 2003). In a different uncontrolled study of group exercise incorporating adapted strength training and adapted endurance training performed twice weekly for 3 months, ratings of pain in persons with varying levels of SCI before and after the program showed only a non-significant trend for reduced pain (Crane et al. 2015).

In a series of 3 individuals with complete thoracic SCI who underwent over ground ambulation training for three days a week for 6 weeks with robotic exoskeletons, all of whom had at level neuropathic pain of either moderate or severe intensity (5–7 on the numeric rating scale), 2 out of 3 had significant decreases in average pain intensity (>30 % change) from baseline to the last session (Kressler et al. 2014). Of importance, during the study there were not noted to be any

significant improvements in exercise conditioning which calls into question whether the "exercise" per se provided by the ambulation training contributed to the observed decreases in pain or whether there were other more important factors. In two other studies in which pain reduction was measured before and after similar robotic exoskeleton ambulation training, pain reduction was variable with decreases in pain intensity seen before and after the sessions in a minority of subjects and an increase in pain seen in a few (Esquenazi et al. 2012; Zeilig et al. 2012).

In a series of 8 individuals who were full time wheelchair users with chronic paraplegia 7 of whom had neuropathic pain and 5 of whom had nociceptive pain who trained on a customized seated double-poling ergometer three times per week for 10 weeks with a moderate to vigorous intensity (70–100 % peak heart rate during intervals), the following outcomes were reported (Norrbrink et al. 2012). For those with neuropathic pain, pain intensity improved from 5 on a 0–10 numerical rating scale at baseline to 3 at the end of study. For those with musculoskeletal pain, pain intensity ratings improved from 4 at baseline to 0 at the end of study. All but one individual rated no musculoskeletal pain at all at the end of study and number of days with pain per week decreased from over 5 to less than one from the beginning to end.

Two main mechanisms are purported to underlie the effects of long term exercise on nociceptive and neuropathic pain: enhanced inhibitory activity and reduced excitatory synaptic transmission (Almeida et al. 2015). There is evidence for enhanced inhibitory activity mediated by opioids (Bement and Sluka 2005; Mazzardo-Martins et al. 2010), adenosine (Martins et al. 2013), and serotonin in animals. The midbrain periaqueductal gray matter (PAG) and the rostral ventromedial medulla (RVM) to which it projects are both activated by aerobic exercise (Sluka et al. 2013; Stagg et al. 2011). There is also more limited evidence for reduced excitatory synaptic transmission mediated through *N*-methyl-D-aspartate receptors (Sluka et al. 2013), interleukin-1β (IL-1β) (Chen et al. 2012) and tumor necrosis factor-α (TNF-α) both of which are proinflammatory cytokines, and voltage gated calcium channels (Shankarappa et al. 2011).

Although in humans, studies have not yet demonstrated that endogenous opioids or dopaminergic, noradrenergic and serotonergic neurotransmitters influence the central modulation of pain during exercise (Ray and Carter 2007), it has been demonstrated that in healthy individuals without SCI, higher exercise volumes are associated with higher levels of circulating cytokines specifically interleukin-6 (IL-6) and interleukin-10 (IL-10) (Jankord and Jemiolo 2004; Petersen and Pedersen 2005, 2006). IL-6 is a cytokine that is produced and released by contracting skeletal muscle fibers. It inhibits the production of the proinflammatory cytokines TNF-α, whereas IL-10 is an anti-inflammatory cytokine.

12.6 Associated Psychological Factors Related to Exercise and Pain

Pain after SCI has been associated with elevated levels of stress, anxiety, and depression (Rintala et al. 1998). Moreover, there seems to be a dose related effect between the amount of exercise and the outcomes of anxiety and depression in persons without SCI, with aerobic exercise at a dose consistent with public health recommendations found to be an effective treatment for depression of mild to moderate severity while a lower dose is found to be comparable to placebo effect (Dunn et al. 2005).

In the Canadian study referred to earlier (Hicks et al. 2003) it was noted that, exercisers reported less pain, depression, and stress, as well as greater perceived quality of life and better physical self-concept than the non-exercise controls. Regression analyses in that study revealed that changes in pain seemed to mediate exercise induced changes in stress while changes in stress mediated exercise induced changes in depression (Latimer et al. 2004). In other words, pain reduction may be a mechanism by which exercise can improve life satisfaction and reduce depressive symptoms, even if it affects pain intensity only marginally.

In a series of 14 persons with chronic incomplete SCI undergoing three sessions of body weight supported treadmill training exercise, those who had the greatest decreases in pain intensity before and after the exercise had the greatest changes in feeling states (as measured by the Profile of Mood States (POMS)) (Martin Ginis and Latimer 2007; McNair et al. 1971). Pain during the exercise was unrelated to the feeling states.

Changes in feeling states are less often seen after sporadic single sessions of exercise as compared to changes seen after participation in long-term exercise programs. Older individuals with arthritic conditions for example do not seem to respond to acute exercise in the same way with improved feeling states as do younger more physically fit populations (Focht et al. 2004). The lack of a measurable effect in this particular example may be due to the particular exercise activity itself if it causes an exacerbation to an overuse or degenerative condition and leads to worsening in feeling state.

Moreover, this differential response is not unique to older adults with arthritis, but describes the effect that acute bouts of exercise have on people who are sedentary as well (Gauvin et al. 1997). The variable response of feeling state to acute exercise might then translate to persons with more or less severe physical limitations (e.g., a more or less severe SCI) although this needs to be further evaluated. Also it is quite possible that positive feeling state responses to acute bouts of physical activity may only occur after several months of training. Further evidence of this is provided by the relationship between diurnal variations in acute bouts of vigorous exercise and improved feeling states at least in active individuals without SCI (Gauvin et al. 2000).

12.7 Exercise as a Pain Intervention for Shoulder Pain After SCI

Exercise programs designed to alleviate shoulder pain, a particular subtype of nociceptive pain after SCI, have the strongest evidence for effectiveness (Boldt et al. 2014; Cratsenberg et al. 2015). Three randomized controlled exercise trials all of which included a stretching and a strengthening component performed daily at home for a duration ranging from 2 to 6 months showed significant decreases in composite measures of pain intensity assessed during 15 different activities (Curtis et al. 1999; Middaugh et al. 2013; Mulroy et al. 2011). Other non-randomized cohort trials using similar interventions as well as aerobic exercise showed similar decreases in composite measures of shoulder pain intensity (Nash et al. 2007; Nawoczenski et al. 2006; Norrbrink et al. 2012; Van Straaten et al. 2014).

12.8 Exercise May be Under-utilized by Many Persons with SCI

Individuals with SCI may be the most physically inactive members of society especially those with more severe injuries (Dearwater et al. 1985). Despite the known health benefits of regular exercise, most persons with SCI are insufficiently active with an estimated 50 % having no leisure time physical activity at least in Canada (Ginis et al. 2010). Overall the people within this Canadian cohort spent less than 2 % of their waking time engaged in any leisure time physical activity whatsoever (Latimer et al. 2006).

There are many reasons why a majority persons with SCI are inactive and do not receive regular exercise. When comparing "exercisers" versus "non-exercisers", Kehn and Kroll found that "exercisers" were facilitated by personal motivation, independence, availability of accessible facilities and personal assistants, fear of health complications, and weight management while "non-exercisers" perceived a low return on physical investment, lack of accessible facilities, unaffordable equipment, no personal assistance, and fear of injury (Kehn and Kroll 2009). In a study of an exercise intervention discussed earlier (Hicks et al. 2003), pain seems to be an additional barrier to exercise adherence in persons with SCI (Ditor et al. 2003).

12.9 Conclusion

Pain after SCI is very prevalent with more than 80 % of persons reporting chronic pain. Exercising regularly after SCI on the other hand is much less prevalent. Exercise seems to decrease overall pain intensity marginally when performed on a long term basis. It does not seem to be helpful if performed sporadically especially

by sedentary individuals. Finally there seems to be an association between exercise, pain, and mood states which is probably related to common mechanisms. However, as always, much more study is needed.

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Chapter 13
Autonomic Alterations After SCI: Implications for Exercise Performance

Aaron A. Phillips and Andrei V. Krassioukov

Abstract The disruption of autonomic pathways after spinal cord injury (SCI) leads to a highly unstable cardiovascular system, with impaired blood pressure and heart rate regulation. In addition to low resting blood pressure, on a daily basis the majority of those with SCI suffer from transient episodes of aberrantly low and high blood pressure (termed orthostatic hypotension and autonomic dysreflexia, respectively). Due to a combination of these autonomic disturbances and a myriad of lifestyle factors, the pernicious process of cardiovascular disease is accelerated after SCI, resulting in increased risk of stroke and heart disease. Unfortunately, these secondary consequences of SCI are only beginning to receive appropriate clinical attention. Immediately after high-level SCI, major cardiovascular abnormalities present in the form of neurogenic shock. After subsiding, new issues related to blood pressure instability arise, including orthostatic hypotension and autonomic dysreflexia. Disruption of autonomic function leads to inappropriate exercise responses often resulting in blunted cardiovascular capacity. After high thoracic or cervical SCI, blood pressure responses to exercise are reduced or absent, while often heart rate cannot rise above that set by the sinoatrial node, which together reduce aerobic performance. Some athletes choose to induce potentially life-threatening episodes of autonomic dysreflexia in order increase blood pressure (termed "boosting"), as low blood pressure is a limiting factor for exercise performance in many people with SCI. Due to our understanding of the capacity of autonomic/cardiovascular disability to impact sport performance, classification of athletes with disability should consider autonomic injury to allow for equality

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between teams and help obviate the need to induce autonomic dysreflexia to improve performance.

13.1 Introduction

Spinal cord injury (SCI) is a devastating condition with the capacity to change the trajectory of life, resulting in increased morbidity and earlier mortality. Due to a combination of major autonomic disturbances and related cardiovascular dysfunction, as well as a myriad of lifestyle issues, the pernicious process of cardiovascular disease is extremely accelerated after SCI (Phillips et al. 2012a; Miyatani et al. 2009). Even after controlling for major risk factors, the risk of heart disease is almost 3-fold higher in those with SCI, while the risk for stroke is almost 4-fold higher (Cragg et al. 2013).

Disruption of the neuronal pathways of the spinal cord is well-known to lead to paralysis, but also leads to major alterations of the autonomic nervous system. Although the site of injury to the spinal cord is generally localized to a small region (including neurons, supporting cells, as well as ascending and descending neuronal pathways), the effect of this disruption is frequently associated with a wide array of dysfunctions due to malfunction of the autonomic nervous system.

Alterations in autonomic function are often dominated clinically by changes in spinal sympathetic control (Krassioukov 2009; Teasell et al. 2000). Specifically, those with SCI often suffer from unstable blood pressure, including low resting blood pressure, severe drops in blood pressure when moving to the upright position (termed orthostatic hypotension (OH)), and/or aberrant life-threatening bouts of acute hypertension termed autonomic dysreflexia (AD) (Krassioukov and Claydon 2006). The effect of SCI on autonomic/cardiovascular dysfunction is well reported in a variety of human and lower-order animal models (i.e., rodents) (Krassioukov and Claydon 2006; Claydon and Krassioukov 2006).

Autonomic issues, such as cardiovascular dysfunction, are most frequently ranked by those with SCI to be of greater priority to them than regaining their motor function (Anderson 2004). Clinically, the importance of cardiovascular dysfunction is often overlooked, poorly understood, and presents as part of complex and challenging clinical scenarios. In light of this, and the consideration that cardiovascular disorders in both the acute and chronic stage of SCI represent the most common causes of death in individuals with SCI (DeVivo et al. 1999; Garshick et al. 2005), it is imperative to understand the cardiovascular consequences of this condition. It is only during the last decade, that in addition to the assessment of motor and sensory deficits (Kirshblum and Waring 2014), newly developed international Autonomic Standards were developed for clinical evaluation and management of autonomic dysfunctions following SCI (Krassioukov et al. 2012).

The present review is focused on delineating cardiovascular dysfunction after SCI. Specific areas to be reviewed include: autonomic regulation of cardiovascular function, major cardiovascular clinical conditions after SCI such as orthostatic

hypotension and autonomic dysreflexia, the underlying mechanisms of cardiovascular dysfunction after SCI, changes in cardiovascular disease risk factors and end-organ maladaptation after SCI, as well as management recommendations for those with SCI in order to mitigate cardiovascular dysfunction.

13.2 Autonomic Control of the Cardiovascular System

Arterial blood pressure and heart rate regulation are under constant control of the autonomic nervous system, which is comprised of two primary divisions: sympathetic and parasympathetic (Fig. 13.1) (Krassioukov and Weaver 1996a, b). Activation of the sympathetic nervous system plays an excitatory role and results in an increase in sympathetic peripheral nerve activity leading to increased heart rate, increase in cardiac contractility, and generalized systemic vascular constriction; together leading to increased arterial blood pressure. On the other hand, activation of the parasympathetic nervous system typically is limited to reducing heart rate and cardiac contractility (via the vagal nerve), and is widely accepted to not extend to the vasculature itself, except in specific regions including blood vessels of the salivary glands, gastrointestinal glands, genital erectile tissue, and potentially the cerebrovasculature (Suzuki et al. 1990; Kano et al. 1991; Hamner et al. 2012).

Although some cortical areas and hypothalamic regions (Krassioukov 2009) with tonic and inhibitory influences on cardiovascular functions have been identified, it is medullary neurons within the rostral ventral lateral medulla that are considered to be the major sympathetic cardiovascular region responsible for maintenance and regulation of blood pressure (Dampney et al. 2003). These sympathetically active central neurons project to the spinal cord and travel primarily through the dorsolateral funiculus synapsing on the spinal sympathetic preganglionic neurons (SPNs), which are located predominately within the lateral horns of spinal grey matter in spinal segments T1–L2. The axons of SPNs (preganglionic fibers) exit the spinal cord via ventral roots and synapse on the sympathetic ganglionic neurons within paravertebral chain ganglia or prevertebral ganglia (Krassioukov and Weaver 1995b). Finally, the postganglionic neurons innervate target organs such as blood vessels (adrenergic sympathetic innervation), sweat glands, and piloerectors (cholinergic sympathetic innervation) (Krassioukov and Weaver 1995b). Both the central and peripheral autonomic nervous system provide crucial coordinated regulation of the cardiovascular system in order to provide appropriate blood pressure throughout daily living including such activities as exercise and various orthostatic challenges.

In terms of the parasympathetic division, the vagal nerve exits the central nervous system supraspinally as cranial nerve X, and reaches target organs such as the heart and cerebral blood vessels without traversing the spinal cord. Some sacral parasympathetic cell bodies of the parasympathetic division are located in the spinal segments S2–S4, however, they do not play a role in cardiovascular control. Both sympathetic and sacral parasympathetic preganglionic neurons receive supraspinal tonic and inhibitory nervous system control via spinal autonomic

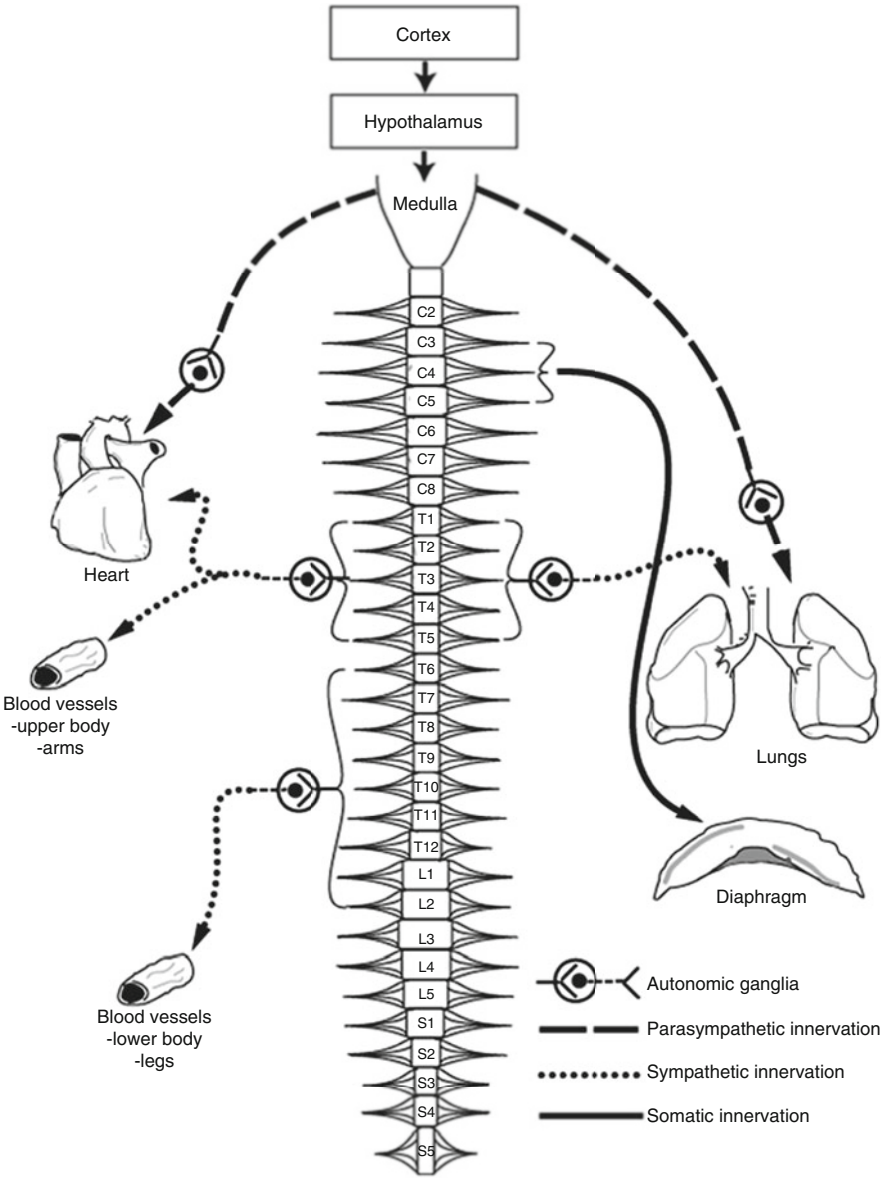

Fig. 13.1 Autonomic control of cardiorespiratory end-organs. Medullary supraspinal centres control both sympathetic and parasympathetic regulation of the heart, lungs, diaphram, as well as systemic blood vessels. Together, these systems regulate blood pressure and ventilation

pathways that (Calaresu and Yardley 1988; Lebedev et al. 1986), unfortunately, are frequently disrupted after SCI (Furlan et al. 2003).

The baroreflex is the primary mechanism responsible for short-term regulation of blood pressure (Phillips et al. 2012b; La Rovere et al. 2008), and also plays a critical role in long term blood pressure regulation (Heusser et al. 2005). The baroreflex is comprised of two interdependent systems (Taylor et al. 1995; Fu et al. 2009), that work in concert as one reflex system. The first, a low-pressure system, is made up of cardiopulmonary stretch receptors located in the heart and lungs, which augments sympathetic nervous system activity in response to reductions in central venous pressure and volume (Abboud and Thames 1983). The second, a high-pressure baroreflex system, consists of stretch receptors located in the tunica adventitia of the aortic arch and carotid bulbs (Fadel et al. 2003). These spray-like nerve endings generate a more rapid rate of depolarization, and hence increase the frequency of action potentials in afferent nerves during periods of increased wall distension (Abboud and Thames 1983). The signal is transmitted from the carotid bulb via the glossopharyngeal nerve (vagal nerve), and the aortic arch via the vagal nerve , to the nucleus of the solitary tract in the medulla oblongata (Krassioukov and Weaver 1996a). This transmission, which provides surrogate information on systemic blood pressure, is integrated with other afferent information (such as chemoreceptor afferent signals) in order to modulate efferent nervous activity transmitted through the vagal nerve and sympathetic system to target organs, with the aim of rapidly maintaining blood pressure around a set point (Fig. 13.1) (Abboud and Thames 1983). For example, when a human moves from the supine to upright position, approximately 500 ml of blood is translocated away from the heart and brain, and towards the blood vessels of the gut and legs (Sjostrand 1953). Central baroreceptors detect reductions in stretch, and respond by decreasing vagal tone to the heart, and increasing peripheral sympathetic activity. The increase in sympathetic tone results in increased heart rate and peripheral vasoconstriction that is responsible for maintaining stable arterial blood pressure (Phillips et al. 2012b). After SCI, although the baroreceptors certainly detect reductions in central blood volume during orthostasis, disrupted descending sympathetic pathways precludes the capacity to adjust vascular tone, often resulting in abnormal fluctuations in blood pressure with changing body position (Phillips et al. 2012b). Our most recent understanding, as well as mechanistic insight, surrounding these episodes and other cardiovascular conditions after SCI will be discussed in the following sections.

13.3 Pathophysiological Mechanisms of Cardiovascular Dysfunction Following SCI

We are just beginning to unravel the mechanisms underlying abnormal cardiovascular function after SCI. Using rat models, the morphological changes within the spinal autonomic circuits after SCI have been established relatively recently (Krassioukov et al. 1999). Furthermore, the role these changes are playing in the development of autonomic dysfunction has only just been solidified (Krassioukov et al. 2002; Ramer et al. 2012; West et al. 2013a). A variety of autonomic circuits have been highlighted that likely contribute to abnormal cardiovascular control after SCI (Krassioukov and Claydon 2006). Specifically, the disruption of descending spinal cardiovascular pathways leads to a minimum of six neuroanatomical changes that influence autonomic cardiovascular control: (1) initial sympathetic hypoactivity due to loss of supraspinal tonic sympathetic excitation (Mayorov et al. 2001; Maiorov et al. 1997a), (2) alterations in the morphology of sympathetic preganglionic neurons (SPN's) (Krassioukov and Weaver 1995b; Krassioukov et al. 1999), (3) plastic changes of the spinal circuits (i.e., dorsal root afferent sprouting, potential formation of aberrant synaptic connections (Krenz et al. 1999), or aberrant inputs to the spinal interneurons) (Krassioukov et al. 2002), (4) altered symapatho-sensory plasticity (Ramer et al. 2012), (5) altered peripheral neurovascular responsiveness, and (Arnold et al. 1995) (6) cumulative effects of tertiary factors. Several of these factors will be discussed below.

Autonomic Pathways and SPN Plasticity It is now appreciated that in the acute stage after SCI, SPN's atrophy. However, over time, they re-gain somewhat normal morphology (similar soma size as pre-injury, but a more extensive dendritic arbor and aberrant connections) (Krassioukov and Weaver 1996b). It is most likely that the loss of descending projections of medullary neurons result in the initial atrophy of SPNs, as many of these are thought to synapse directly. In the very early phase after SCI, loss of descending inhibitory pathways predisposes individuals to early AD episodes, while later, atrophy of SPN's leads to an intermediate period where AD is less severe (Krassioukov and Weaver 1996b). Disrupted descending pathways as well as atrophied SPN's likely contribute to the lack of sympathetic tone and very low resting blood pressure in the early phase of injury as well as the extremely high prevalence of OH. As the phase of injury transitions into the more chronic stage, AD manifests again (Krassioukov and Claydon 2006; Mathias and Bannister 2002). For example, AD is most commonly documented during the sub-acute and chronic stages of SCI. AD often becomes clear within 2–3 months after SCI in those with SCI above the T6 spinal segment (Krassioukov 2004).

Dorsal Root Afferents and Intraspinal Plasticity Exaggerated sensory input to the spinal cord occurs caudal to the site of injury after SCI. For example, evidence from non-human animal studies suggests that dorsal root afferents sprout along with an enlargement of soma size in the dorsal root ganglia after SCI (Krenz et al. 1999; Murray 1993; Ackery et al. 2007). Specifically, it is likely that primary afferents

such as calcitonin gene-related peptide immunoreactive (CGRP+) axons of the dorsal root ganglion neurons sprout and extend from their proper site of termination in the dorsal horn (Lamnae I–II) (Krassioukov and Weaver 1996b), with an intrusion of CGRP+ afferent fibres further into the spinal cord (quantified as increased CGRP+ fibres in Lamina II–V post SCI) (Krenz and Weaver 1998). Increased sprouting of primary afferents has the potential to generate new intraspinal circuits (Krassioukov et al. 2002), and is a suspected mechanism for AD due to both similar time-courses (Krassioukov et al. 2002; Krenz and Weaver 1998; Krassioukov and Weaver 1995a; Maiorov et al. 1997b) and its relation to AD severity (Cameron et al. 2006). Furthermore, this is accompanied by somal hypertrophy of the transient receptor potential cation channel sub family V member 1 (TRPV1) in the dorsal root ganglia, which further implicates neuroplastic afferent changes in the development of AD (Ramer et al. 2012).

Vasculature Peripheral Component An additional autonomic alteration associated with AD after SCI includes hyper-responsiveness of blood vessels to alpha-adrenergic stimulation. It has been shown that the mesenteric artery is hyper-responsive to pressor agent phenylephrine in rodents after SCI due to increased sensitivity secondary to impaired neuronal reuptake (Alan et al. 2010; Brock et al. 2006). Furthermore, a number of studies have shown exaggerated pressor responses to alpha sympathomimetic administration (Groothuis and Thijssen 2010; Wecht et al. 2005; Mathias et al. 1976). It has also been shown that sympathetically correlated spinal interneurons are hypersensitive to afferent stimuli after SCI (Krassioukov and Weaver 1996a, b; Krassioukov et al. 2002). Together, the combination of hyper-responsive interneurons and vascular smooth muscle, as well as the increased influence from primary afferents, creates a 'perfect-storm' of reorganization predisposing to episodes of transient hypertension in response to nociceptive or non-nociceptive afferent stimulation (i.e., AD). It is interesting to highlight however the multifaceted contributions to the presence of AD. For example, reductions in AD severity have been shown after interventions showing no reduction in blood vessel hyperresponsiveness (Alan et al. 2010), suggesting other factors such as altered sympatho-sensory plasticity may be playing a more central role.

Clearly, there are a number of factors after SCI that predispose to the frequent and widespread occurrence of AD and OH, which are major clinical conditions after SCI affecting both the quality and quantity of life in this population.

13.4 Clinical Consequences of Cardiovascular Control Following SCI

Over the past 10 years, our knowledge regarding the underling pathophysiology of autonomic dysfunction after SCI has been enhanced greatly (Teasell et al. 2000; Krassioukov et al. 2002; Mathias and Bannister 2002; de Groat and Yoshimura

2006). The most prominent outcomes of the mechanistic maladaptations described above are low resting blood pressure (Krassioukov and Claydon 2006) as well as extremely labile blood pressure characterized by frequent and pronounced episodes of low blood pressure when assuming an upright position (OH), and episodes of high blood pressure in response to afferent stimuli below the level of injury (AD). These cardiovascular conditions will be discussed in detail throughout the next sections.

13.4.1 Low Resting Blood Pressure

In addition to hypotension during the acute period following SCI (neurogenic shock, see below), individuals with high thoracic and cervical SCI frequently experience a reduced blood pressure at rest that is notably lower than in able-bodied individuals (West et al. 2012a). Clinical evidence indicate that the extent and severity of hypotension correlates well with the level and severity of SCI (Fig. 13.2) (Mathias and Bannister 2002; Hadley 2002; Nacimiento and Noth 1999; Vale et al. 1997). In the non-SCI population an "inverted-U relationship" exists between resting blood pressure and overall health; in addition to well-established risks associated with high-blood pressure, there are significant clinical conditions associated with a blood pressure that is too low (Hebert et al. 2004; Duschek et al. 2007; Duschek and Schandry 2004). This has recently been corroborated in the SCI population, where impaired cerebrovascular and cognitive function has been shown to be associated with low resting blood pressure (Phillips et al. 2014a). Low resting blood pressure after SCI is also associated with a number of conditions, including exacerbated dizziness and the development of syncope, as well as poor mood, lethargy and fatigue (Claydon et al. 2006; Wecht and Bauman 2013; Phillips et al. 2014b; Cariga et al. 2002; Illman et al. 2000). Considering this, low blood pressure should be appreciated and clinically addressed in those with SCI.

13.4.2 Autonomic Dysreflexia

Episodes of AD are characterized by an acute elevation of systolic blood pressure of at least 20 mmHg, which may or may not be accompanied by a decrease in heart rate (Krassioukov et al. 2009), and occurs in response to afferent stimuli that would be considered painful or non-painful visceral or somatic stimulation below injury, including a full bladder or bowel (see Fig. 13.3 for example of AD during bladder filling). It is now well-appreciated that AD episodes can occur in both the acute and chronic phases of SCI (Krassioukov 2004; Ekland et al. 2008). In fact, systolic blood pressure can rise above 300 mm Hg during AD (Wan and Krassioukov 2014). It is understood that AD episodes can occur in both the acute and chronic phases of

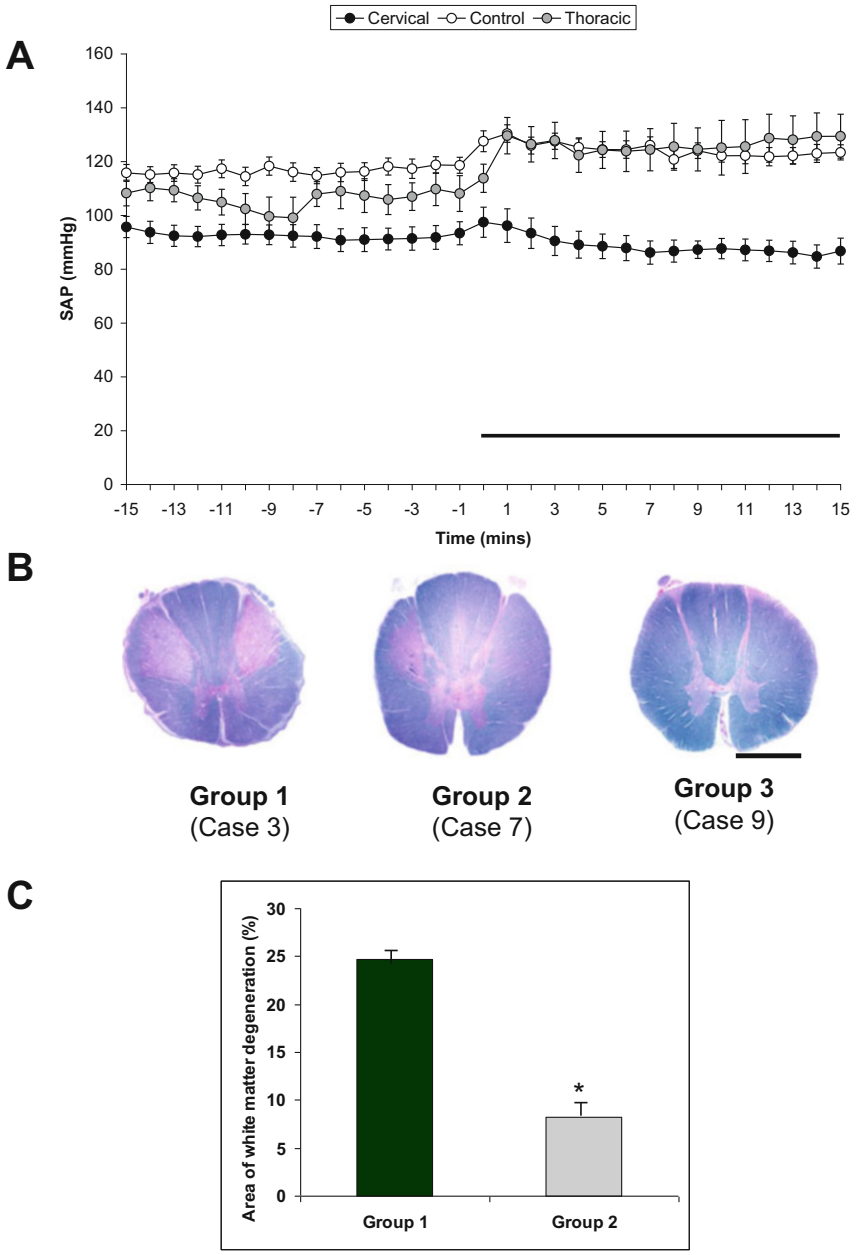

Fig. 13.2 Illustrating the effect of completeness of injury on blood pressure stability. Groups 1, 2 and 3 represent the same groups of participants in Parts **a**, **b** and **c**. Part (**a**): Daily mean ± standard error of systolic blood pressure from days 1–35 after spinal cord injury (SCI). Patients with severe cardiovascular complications (empty circles; Group 1) were compared to those not developing major cardiovascular complications (filled circles: Group 2) were significantly different. Part (**b**): Sections of portmortem human spinal cord tissue stained for myelin with Luxol Fast Blue from representative cases of Group 1, Group 2, and Group 3 (non-SCI controls). Part (**c**): Areas of significantly more extensive axonal degeneration (pink areas within grey white matter) are present

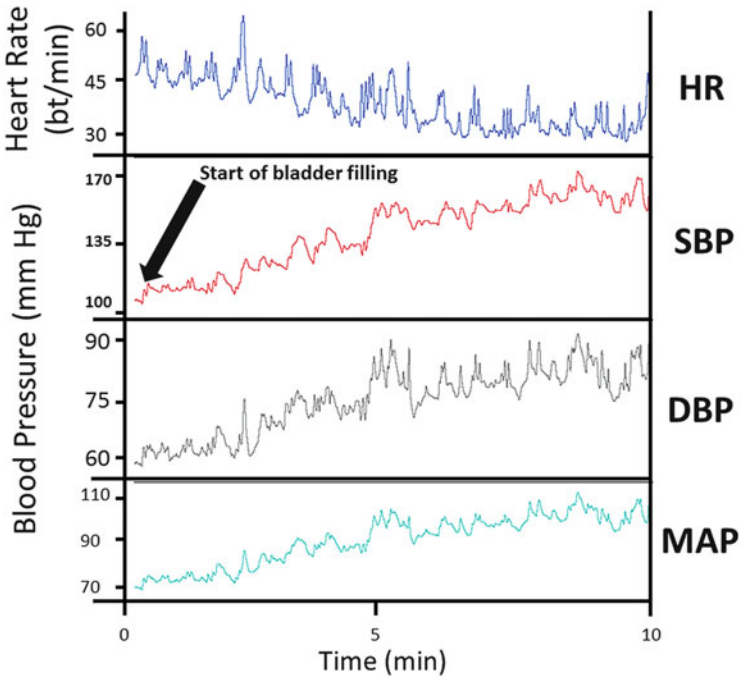

Fig. 13.3 Continuous beat-by-beat changes in heart rate as well as systolic, diastolic and mean blood pressure (SBP, DBP, MAP) during autonomic dysreflexia induced by urodynamic bladder filling in one individual with a male with a T2 motor complete (AIS:A) spinal cord injury. Clinical observation from our laboratory. Note that SBP increases by 70 %, up to 170 mmHg

SCI (Krassioukov 2004; Ekland et al. 2008), and in the chronic phase of SCI episodes of AD are now known to occur up to 41 times/day (average of 11 times/day) in the majority of those with high-level SCI above the T5 level (Hubli et al. 2014). Episodes of AD are often accompanied by a pounding headache and flushing above the injury (Krassioukov and Claydon 2006; Krassioukov et al. 2009; Claydon et al. 2006). Left untreated, episodes of AD could result in life–threatening complications including cerebral hemorrhage, retinal detachment, seizures, cardiac arrhythmias, and death (Wan and Krassioukov 2014; Pine et al. 1991; Zhang et al. 2013).

The most common stimuli to trigger AD include bladder and bowel distention, but can also be brought on other noxious stimuli to include spasms, pressure sores, or even something as simple as tight shoe laces (Teasell et al. 2000). Catheterization

Fig. 13.2 (continued) in individuals from Group 1 as compared to Groups 2 or 3. *represents $P < 0.05$). From Furlan JC, Fehlings MG, Shannon P, et al. Descending vasomotor pathways in humans: correlation between axonal preservation and cardiovascular dysfunction after spinal cord injury. Modified from J Neurotrauma 2003;20:1351–1363

or manipulation of an indwelling catheter, urinary tract infection, detrusor sphincter dyssynergia, and bladder percussion can also lead to AD. There are also a number of iatrogenic triggers including: cystoscopy, penile vibrostimulation or electrostimulation for ejaculation, as well as the electrical stimulation of muscles (as is often preformed in formal physical or occupational therapy) (Chang et al. 1991; Giannantoni et al. 1998; Sheel et al. 2005). The intensity of AD episodes is variable and not all episodes are severe, especially if the triggering stimulus is resolved promptly. In fact, many AD episodes are asymptomatic (i.e., the patient does not recognize AD even though blood pressure is increasing) or characterized by sweating and/or piloerection alone (Kirshblum et al. 2002). The level and completeness of the injury are the critical determinants for the presence of AD, which is three times more common in complete versus incomplete quadriplegics (Curt et al. 1997), and typically occurs primarily when the SCI is at or above the T6 spinal segments (Teasell et al. 2000; Mathias and Bannister 2002). As will be discussed in detail below, changes in the autonomic circuits in the spinal cord are major contributing factors to the development of AD (Krassioukov et al. 2002).

Although AD is certainly a life-threatening emergency (Eltorai et al. 1992) and known to be unpleasant (Elliott 2006), some individuals with SCI voluntarily induce AD in order to increase their blood pressure, as it may in some cases improve athletic performance (Harris 1994). The inducement of AD is referred to as "boosting" and is considered unethical and illegal by the International Paralympic Committee. The occurrence of boosting in competition is a testament to the devastating functional and performance limitations imposed by the autonomic cardiovascular dysfunctions present after SCI. Boosting is discussed in detail below.

13.4.3 Orthostatic Hypotension

Episodes of OH are characterized by substantial declines in blood pressure when assuming the upright posture (Fig. 13.4). After SCI, the interruption of sympathoexcitatory pathways from the brainstem to the SPNs impairs the capacity of the arterial baroreflex to efficaciously cause vasoconstriction and maintain blood pressure (Blackmer 2003; Claydon et al. 2006c). Although the cardiovagal baroreflex is impaired after SCI, it is the sympathetic system that is primarily responsible for blood pressure maintenance during an orthostatic challenge. It is only the first 2–3 s after an orthostatic challenge that the cardiovagal effect on heart rate impacts blood pressure stability (Phillips et al. 2012b; Ogoh et al. 2003a, b, 2006). The result is both low venous return secondary to blood pooling in the vasculature caudal to the site of injury, as well as low arterial blood pressure/vessel tone (Phillips et al. 2012b). Additionally, there is low resting catecholamine levels after cervical SCI and no discernable increase with supraspinal sympathetic activation induced by upright tilt (Claydon and Krassioukov 2006). The presence of stiffer central arteries (which are responsible for detecting changes in blood pressure) after SCI further

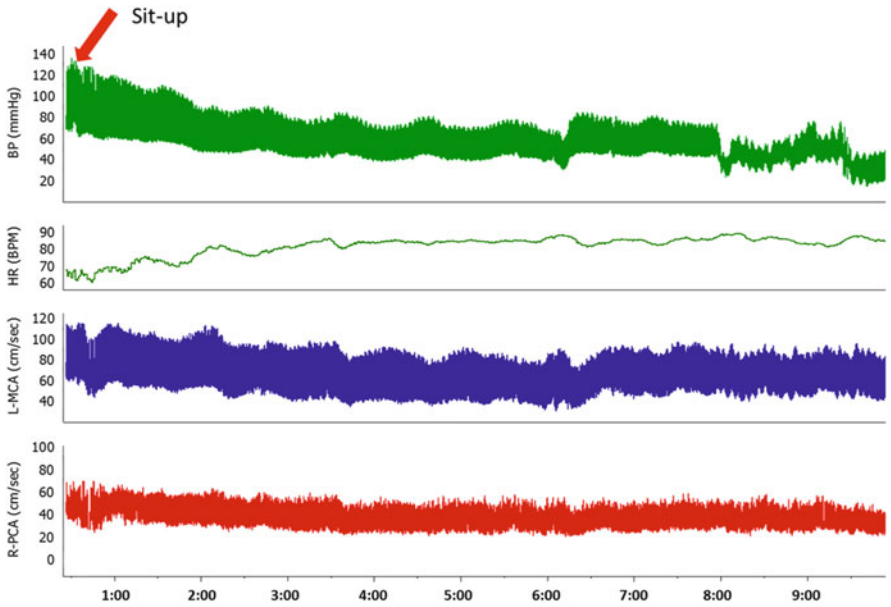

Fig. 13.4 Orthostatic response to a sit-up test in a 26 year old make with a C7 (AIS A) traumatic spinal cord injury. Blood pressure (BP), middle cerebral artry (MCA) and posterior cerebral artery (PCA) blood flow steadily decreased over the 10 min protocol which had to be ceased due to extremely low BP, and symptoms of presycope (i.e., excessive yawning). Blood pressure cannot be maintained due to the loss of supraspinal sympathoexcitory signals to sympathetic preganglionic neurons regulation vascular resistance. Heart rate (HR) increased in an attempt to compensate for rapidly reducing BP, however pleateus at sinoatrial spontanouse depolarization pace of 90–100 beats per minute due to lack of supraspinal sympathoexcitory signals to sympathetic preganglionic neurons regulating the heart

impairs baroreflex function (Phillips et al. 2012a). Orthostatic hypotension is most common and severe in the acute phase of SCI, but also can be observed in the chronic phase among individuals with high cervical injuries (Cariga et al. 2002; Mathias 1995). Similar to resting blood pressure, the severity and level of injury to descending cardiovascular autonomic pathways is directly associated with OH (Figs. 13.2 and 13.4) (Claydon and Krassioukov 2006), indicating that the extent of cardiovascular instability after SCI is related to the completeness of injury to autonomic pathways within the spinal cord. Clinically, OH is defined as a decrease in systolic blood pressure of at least 20 mm Hg, or a decrease in diastolic blood pressure of at least 10 mm Hg when assuming an upright posture from the supine position, regardless of presence of symptoms (Kaufmann 1996). This definition was agreed upon by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology (Kaufmann 1996). Presyncopal symptoms after SCI are no different from the able-bodied population (Cleophas et al. 1986), and include light-headedness, dizziness, blurred vision, fatigue, nausea, dyspnea, and restlessness (Frisbie and Steele 1997; Sclater and Alagiakrishnan 2004).

Orthostatic hypotension is extremely common in those with SCI. For example, one study showed that OH occurs in up to 74 % of individuals during the acute period of SCI when performing orthostatic maneuvers during physical therapy and mobilization (Illman et al. 2000). Similar to AD, OH does not always lead to presyncopal symptoms and more than 40 % of those with SCI are asymptomatic during episodes of OH (Claydon and Krassioukov 2006). Recently, we have shown that often OH persists into the chronic stage of SCI, however presyncopal symptoms may partially subside (Claydon and Krassioukov 2006). In terms of prevalence, in the chronic SCI phase OH occurs in up to 50 % of individuals with cervical SCI, and 18 % of those with thoracic SCI; however, from this "OH-positive" group, presyncopal symptoms were only present in 1/3 and 1/5 of individuals (Claydon and Krassioukov 2006). Reduced symptoms of presyncope but similar OH in the chronic phase of SCI suggests that tolerance to low blood pressure and cerebral perfusion pressure may improve with time after SCI (Phillips et al. 2013, 2014b; Horowitz and Kaufmann 2001). Considering there is a clear association between OH and elevated risk of stroke in the able bodied population (Eigenbrodt et al. 2000), as well as the fact that stroke risk is 3–4 times greater after SCI, it is logical to posit that the presence of OH after SCI plays a contributing role (Cragg et al. 2013; Wu et al. 2012). The mechanisms underlying this association are unclear but have been speculated to be the result of: (1) repetitive cerebral hypoperfusion leading to inward cerebral vascular remodeling predisposing to ischemic episodes and an overall lowering of cerebral blood flow, as well as (2) a leftward shift of cerebral autoregulation predisposing to hemorrhagic stroke (Eigenbrodt et al. 2000).

Other factors contributing to the presence of OH after SCI include reduced plasma volumes caused by hyponatremia (Frisbie and Steele 1997), insufficient increases in the capacity of the renin-angiotensin system to maintain blood pressure (Groothuis and Thijssen 2010) and cardiac deconditioning (Vaziri 2003; West and Krassioukov 2012; Shibata et al. 2010). A similar contribution from these mechanisms leads to low resting blood pressure after SCI as well (Krassioukov and Claydon 2006).

To summarize, episodes of OH can lead to syncope, nausea, fatigue and dizziness while significantly impeding rehabilitation. Over the long-term, OH likely contributes to an elevated risk of stroke after SCI. Resting hypotension may also play a role in cognitive dysfunction by exacerbating the severity of orthostatic hypotension and cerebral hypoperfusion. Approaches to combat the abnormal cardiovascular responses after SCI are only in the early stages of development, and will be discussed below.

13.5 Implications of Autonomic Dysfunctions After SCI on Exercise

The severity of dysfunction of the autonomic nervous system is dependent on the level, and the neurological and autonomic completeness of the SCI itself (Krassioukov and West 2014). The sympathetic nervous system controls cardiac and vascular smooth muscle to increase HR and contractility as well as BP during exercise (Phillips et al. 1998). SPNs that are involved in the control of the myocardium and upper limb vasculature arise from the T1 to T5 spinal cord levels, while those located T6–L2 are involved in the control of mesenteric and lower limb vasculature (Krassioukov 2009). Following this, an individual with an autonomic complete SCI (and the resulting loss of supraspinal control of spinal autonomic circuits at or above these levels) will suffer greater autonomic/cardiovascular dysfunction than an individual with an autonomic incomplete SCI , with more intact spinal autonomic pathways (Krassioukov 2012).

An autonomic complete high level SCI will result in the loss of descending supraspinal control over sympathetic spinal circuits and result in decreased sympathetic activity below the level of the injury. The outcome of this dysfunction is bradycardia, hypotension, and a significantly diminished hemodynamic response to exercise (Phillips et al. 1998; Krassioukov 2012; Hopman et al. 1998) compared with individuals with autonomic incomplete SCI (West et al. 2013b). The reduced hemodynamic response to exercise in individuals with SCI is further compounded by cardiac atrophy and reduced stroke volume (Kessler et al. 1986; West et al. 2012b), as well systemic vascular remodelling (Thijssen et al. 2010; Rowley et al. 2011; Phillips et al. 2015). Those with high-level SCI also suffer from blood pooling in the vasculature without supraspinal sympatho-excitatory signals, and also due to the reduced capacity of the venous muscle pump (Hopman et al. 1998, 2002), and as such these individuals will not have redistribution of blood during exercise (Thijssen et al. 2009). As a result of the loss of the muscle pump, combined with lower systemic metabolic activity (and requirements of skeletal muscle), there is a limited rise in preload, and a predictably blunted rise in cardiac output and stroke volume (as cardiac output is primarily determined by systemic metabolic requirements). With elevations in blood pressure, it is likely that perfusion of skeletal muscle is improved which may increase metabolic activity and therefore venous return and cardiac output. Blood pooling may also lead to resting and exercise induced hypotension which would result in reduced athletic performance due to fatigue, dizziness, and even potentially syncope (Claydon et al. 2006c; Krassioukov 2012; Low et al. 2012). Functional electrical stimulation (Hopman et al. 1998; Davis et al. 1990), abdominal binding (Hopman et al. 1998; West et al. 2014a), and/or anti-gravity suits (Hopman et al. 1993, 1998), (as well as preliminary human data on lumbosacral epidural stimulation; *unpublished data*) can prevent peripheral blood pooling, likely increased venous return, and therefore allow redistribution of blood to the working muscle tissue.

Outside of direct stimulation of cardiac and vascular smooth muscle, sympathetic stimulation of the adrenal medulla will increase circulating epinephrine and is another means of enhancing hemodynamic response to exercise due to systemic vasoconstriction. The adrenal medulla is controlled by SPNs originating primarily between the T5–T9 spinal cord levels (Schmid et al. 1998a; 2001) however, and the ability of individuals with autonomic complete injuries above such level to elevate HR and BP via the adrenal medulla is impaired. Athletes may also have sudomotor and piloerector dysfunction that play a role in thermoregulation and increase the risk of hyperthermia with exercise (Theisen 2012; Price and Campbell 2003). The thermoregulatory response to exercise in individuals with SCI is discussed elsewhere in Chap. 7.

In addition to AD, individuals with SCI can experience episodes of OH on a daily basis, which will require management. The majority of activities of daily living require individuals with SCI to be seated in an upright posture in their wheelchair, which predisposes them to orthostatic instability, as a significant amount of blood accumulates in their abdomen and lower extremities (see above). The initial, most simple, preventative strategies of OH include the following: ensuring appropriate fluid intake, avoiding diuretics, avoiding large meals (postprandial hypotension) and heat stress, as well as wearing compression bandages/stockings and potentially engaging in a semi-upright sleeping position (i.e., 10–20° head-up) (Claydon et al. 2006a; Houtman et al. 2000; Freeman 2003; Ten et al. 1992; Chaudhuri 2003). The assumption of a recumbent or semi-recumbent position during daily living can often resolve OH but can significantly influence the patient's quality of life. Pharmacological intervention may be required if these approaches are not effective at reducing OH. Typically these include volume expansion with fludrocortisone (Ten et al. 1992; Groomes and Huang 1991) and/or increasing vascular tone with alpha$_1$ adrenoreceptor agonist midodrine hydrochloride (Phillips et al. 2014b; Mukand et al. 2001; Barber et al. 2000). There are reports that maintaining cerebral blood flow using 10 mg midodrine prevents OH and helps prevent presyncopal symptoms by preserving perfusion of the brainstem where discrete regions responsible for consciousness are located (Shin et al. 1999). These approaches are most commonly used in combination, depending on the patient's responsiveness to each intervention, and the severity of autonomic cardiovascular disturbances. For example, often the combination of normalized hydration, increased sodium intake, compression stockings, abdominal binding and midodrine are employed together to treat OH. Appropriate management of OH will likely improve exercise performance in athletes with high-level SCI; both through hemodynamic mechanisms directly improving muscle perfusion, and by improving cerebral perfusion leading to increased capacity decision making/cognitive function in complex activities such as wheelchair rugby (Phillips et al. 2014a).

13.5.1 Boosting

It is known that in those with high-level SCI, low blood pressure that does not appropriately rise with exercise is a limiting factor for aerobic capacity, and would therefore impact performance in a variety of sports where higher aerobic capacity would be of benefit (Table 13.1). Boosting is the intentional induction of AD for the purpose of enhancing performance (Webborn 1999) through the elevation of blood pressure. Boosting will also likely prevent the symptoms of low arterial BP such as reduced physical capacity, fatigue, dizziness, cognitive dysfunction and syncope (Low et al. 2012) which also have the potential to impac performance. Although bradycardia is often observed during AD at rest, boosting is often accompanied by tachycardia (see Table 13.1). This is most likely due to exercise induced vagal withdrawal and the resulting unopposed sympathetic stimulation of cardiac β receptors which alter the depolarization rate of cardiac myocytes and increase HR (Robinson et al. 1966). Considering the abnormal autonomic/cardiovascular response to exercise in many athletes with cervical and high thoracic SCI, and the resulting effect on sport performance, those participating in sport which stresses the cardiovascular system (e.g., wheelchair rugby and middle- and long-distance races (Bhambhani et al. 2010) may gain a performance advantage by boosting.

Research on the effects of boosting is limited, and likely due to a combination of the risk associated with episodic bouts of transient hypertension (Wan and Krassioukov 2014), ethical considerations, and the potential for response bias for athletes' attitudes (Bhambhani et al. 2010). For these reasons, the prevalence of boosting in high-performance athletes is controversial and is not clearly established. We have recently reviewed this topic (Gee et al. 2015). The two major studies on the potential for boosting to improve aerobic capacity are consistent in that they both show a substantial improvement in maximal oxygen consumption and performance (Table 13.1) (Schmid et al. 1998b; Burnham et al. 1994).

To date, no study comparing performance in the boosted versus unboosted state has included an assessment of the spinal autonomic circuits. Autonomic assessments of athletes will likely provide governing bodies with an understanding as to which athletes can effectively boost blood pressure, and reduce the likely of false positives when assessing whether an athlete is boosting or not. For example, an athlete with intact autonomic function may present with elevated blood pressure and heart rate due to pre-race anxiety rather than boosting. Furthermore, a normal pre-race BP value is variable between individuals (Webborn 1999), and this is a potential weakness in collecting a single SBP measure. To remedy this, routine autonomic testing or assessments of blood pressure would generate a blood pressure history or "blood pressure passport" and help testers understand what an expected resting blood pressure should be for a given individual.

The World Anti-Doping Code, to which the IPC is a signatory (Van de Vliet 2012), has identified that for a practice to be deemed illegal it must meet two of the following criteria: (1) having the potential to enhance or enhances sport

Table 13.1 The role pressor blood presure elevations play in aerobic performance (mean ± SD)

	n	Level	Blood Pressure Elevation Strategy	Performance Measure	Baseline SBP (mmHg)	Pressor SBP (mmHg)	Baseline VO_2 Peak (L/min)	Pressor VO_2 (L/min)	% Performance Improvement
Burnham et al.	8	C6-8	Bladder distension (7), prolonged sitting (1) S	Simulated 7.5-km race time	106 ± 16	155 ± 20	1.44 ± 0.26	1.68 ± 0.37	9.7
Schmid et al.	6	C7-T5	Bladder distension (7), prolonged sitting (1) S	Peak power	113 ± 22	138 ± 25	1.85 ± 0.73	1.96 ± 0.70	6.9
Niehoff et al.	4	C	Administration of 10 mg midodrine	Maximal aerobic test wheelchair ergometer	98 ± 5.2	118 ± 19	12.4 ± 1.2* (placebo)	13.5 ± 3.5*	8.8
Mean					106	137			8.5

SBP, systolic blood pressure; VO_2 , oxygen consumption. * L/min/kg

performance; (2) represents an actual or potential risk to the athlete; and/or (3) is against the spirit of the sport. Boosting was initially prohibited by the IPC in 1994 due to concerns surrounding both the ethics and performance-enhancing functions. The IPC also forbids athletes from competing in a dysreflexic state whether intentional or not (Bhambhani et al. 2010; Van de Vliet 2012), as they have a duty of care to ensure athletes are competing in a safe manner at sanctioned events and have recognized AD to also be a safety risk.

Until recently the IPC's Position Statement on Autonomic Dysreflexia and Boosting stated following "a hazardous dysreflexic state is considered to be present when the SBP is 180 mmHg or above". These criteria for AD were used in one of the most recent publications by IPC team members when describing their recommendations for evaluating athletes at the Beijing Paralympics games (Blauwet et al. 2013). With this in mind, the current approach of the IPC is to test an athlete's BP before competition, if their SBP is found to be at or above the threshold of 180 mmHg they will be re-examined approximately 10 min later. If the athletes SBP is again measured to be $\geq$180 mmHg at the re-examination, the athlete will be withdrawn from competition. Considering that the average SBP of an athlete with a high level autonomically complete SCI is 90–120 mmHg (West et al. 2012a), and the definition of autonomic dysreflexia is a rise of SBP of 20 mmHg, this is a lenient definition. To put this value in perspective, SBP does not rise above 180 during the majority of urodynamic filling procedures (one of the most common triggers of AD) in high-thoracic and cervical SCI patients, where the bladder is filled to very high volumes up to 500 ml (Liu et al. 2013). It should be noted that not a single athlete has ever tested positive for boosting at an IPC-sanctioned event (Blauwet et al. 2013). It was very recently announced that the IPC will be reducing the threshold for defining Boosting to 160 mmHg (International Paralympic Committee 2016).

13.5.2 Ensuing Equality and Safety Using Standardized Autonomic Testing

Presently, the classification of SCI athletes is almost entirely dependent on motor function (Tweedy and Vanlandewijck 2011). Recent evidence suggests that the autonomic completeness of injury, assessed via orthostatic blood pressure responses, can predict aerobic performance in elite athletes with SCI (West et al. 2013b, 2014b). Under the current classification system of the IPC, individuals with autonomic complete SCI may compete against individuals with an intact ANS because they have similar motor function. The reality is that these athletes are not equal. The athlete with the autonomically incomplete injury will be able to mount a more appropriate cardiovascular response, and the increased blood pressure will allow for more skeletal muscle and brain perfusion during competition, thereby improving aerobic performance, muscle force, and cognitive function/decision

making (Phillips et al. 2014a, b; Hogan et al. 1994; Murthy et al. 2001). The best option for balancing this inequality is the incorporation of autonomic injury into the classification of athletes. New data from our group clearly shows that the strongest predictor of cardiovascular capacity during aerobic performance in SCI athletes is a simple sit-up test (Squair et al. 2016). This easy to implement test involves the athletes resting supine for 5 min and then assuming a seated posture for 10 min while blood pressure is measured each minute. The magnitude of decline in systolic blood pressure during the 10 min of being seated is related to the amount of disruption of descending sympathetic-excitatory signals in the spinal cord, and significantly predicts the cardiovascular capacity of the athlete. The implementation of such a simple test, would not only benefit in detecting which athletes can boost blood pressure (discussed previously), but also ensure equality between athletes, and teams, as well as obviate the benefit of dangerously inducing autonomic dysreflexia to improve performance to 'level the playing field'.

13.6 Summary

Disrupted autonomic pathways result in an unstable cardiovascular system characterized by impairments in blood pressure and blood flow regulation. The majority of those with SCI suffer from daily episodes of blood pressure fluctuation including episodes of AD and OH. In addition, resting blood pressure is often very low in this population. In the period immediately after high-level SCI, the first major cardiovascular abnormality presents itself in the form of neurogenic shock. After this, other autonomic cardiovascular conditions develop into chronic blood pressure instability. Other contributing factors to cardiovascular disease after SCI include widespread physical inactivity, impaired glycemic control, inflammation, and lipid abnormalities. Together, autonomic dysfunction, and these other factors accelerate the age-related decline of end-organs such as the central arteries, heart, and brain blood vessels. Cardiovascular dysfunction in those with SCI is a leading cause of morbidity and mortality in this population and therefore requires careful clinical consideration. The clinical consequences of these conditions extend beyond the obvious mortality risk through heart attack and stroke to also include orthostatic intolerance, cognitive dysfunctions, and impediments to rehabilitation. Although our understanding of blood pressure abnormalities following SCI has certainly been greatly enhanced, we still do not understand the long-term consequences of these conditions and the full extent of their underlying clinical implications.

Exercise performance is significantly impaired by autonomic dysfunctions after SCI, and blunted cardiovascular capacity demonstrated by reduced blood pressure and heart rate responses to exercise, have been shown to impair aerobic performance. Inducing autonomic dysreflexia to increased blood pressure and improve aerobic performance (termed boosting) is a banned practice by the IPC, and is considered doping. To date, no autonomic assessments are included in the classification of athletes at IPC events. The utilization of a sit-up test with concurrent

blood pressure recordings would help to 'level the playing field' and reduce the temptation to boost since teams would be balanced in terms of autonomic/cardiovascular capacity and those without autonomic injury would not be unfairly categorized as equal to those with autonomic injury.

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Chapter 14
Hybrid Functional Electrical Stimulation Exercise for Improved Cardiorespiratory Fitness in SCI

Shuang Qiu and J.Andrew Taylor

Abstract Aerobic exercise in persons with spinal cord injury (SCI) is greatly beneficial to health and improves quality of life. However, exercise must meet certain intensity and volume criteria to induce significant benefits across multiple systems. Additionally, more vigorous exercise results in greater benefits, but individuals with SCI can have difficulty achieving high exercise intensities because the paralyzed muscles cannot contribute to overall oxygen consumption. One solution is functional electrical stimulation (FES) exercise, especially hybrid FES exercise involving both innervated upper body and electrically stimulated lower body muscles. This chapter will focus on the acute and chronic responses to FES-cycling and hybrid FES exercise and summarize the advances in application of FES for exercise in SCI. It should be noted that there can be striking differences between the two forms of exercise and the majority of the data indicate if hybrid FES exercise is achievable, this form of exercise is ideal for gains in aerobic capacity in those with SCI.

14.1 Introduction

Over the past 50 years, functional electrical stimulation (FES) has been refined as a way to induce contractions in paralyzed muscles to increase independence and potentially improve physical fitness (Peckham and Knutson 2005; Deley et al. 2015). Although early application of FES in individuals with SCI focused on finger and wrist extension (Long and Masciarelli 1963), by the 1980s,

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application of FES had moved to larger muscle groups and, at one point, there were more than 17 laboratories investigating FES for standing and walking in those with paraplegia (Kralj and Bajd 1989; Marsolais and Kobetic 1987). There are now advanced FES systems with closed loop feedback (Chen et al. 1997; Kostov et al. 1995), however the realization of FES systems for ambulation remains a challenge. Nonetheless, FES can be employed to help those with SCI realize the benefits of regular aerobic exercise by increasing the amount of muscle mass that can be engaged (Pollack et al. 1989; Goss et al. 1992). FES-induced leg exercise combined with voluntary arm effort has been proposed as a hybrid form of exercise to increase the aerobic demand of exercise (Krauss et al. 1993; Gurney et al. 1998). Moreover, FES exercise alone is currently employed as a form of exercise for individuals with SCI and commercial devices are available for home use (Davoodi et al. 2002). However, the differences in cardiorespiratory responses to FES-induced leg exercise as compared with upper body exercise or with the two in combination are under-appreciated. The aim of this review is to compare and contrast various forms of exercise for those with SCI and to provide an overview of the implementation of FES and the possible benefits of combining innervated muscle exercise with FES of functionally denervated muscle—hybrid FES exercise—for those with SCI.

14.2 FES of Skeletal Muscles

FES applies a series of intermittent stimulations to skeletal muscles, with the aim to induce visible and functional muscle contractions. Depending upon which muscles are stimulated, FES can be used to restore a range of functions in patients with SCI.

14.2.1 Applications of FES

The use and utility of FES is dependent upon the level of SCI. For example, those with tetraplegia require augmentation of arm and hand function as well as trunk stability whereas those with paraplegia require restoration of trunk and lower body function (Anderson 2004). For upper body function, FES has been applied for a range of arm movements using both surface and implanted electrodes (Hart et al. 1998; Grill and Peckham 1998). However, the utility of upper body FES for aerobic exercise in high level injuries is limited. Therefore, the widest use of FES for exercise is for lower body movement. In addition, it should be noted that after an SCI, the ability to perform functional movement induced by FES is largely limited by, and also negatively correlated with the time since injury (Ibitoye et al. 2016).

14.2.2 Parameters of FES

Responses to FES depend on three parameters of stimulation: amplitude, pulse width, and frequency (Fig. 14.1). These parameters will directly determine torque production. The strength of muscle contraction is controlled by adjusting the pulse amplitude (usually reported in milliamperes, mA) or pulse width (μs). Higher intensity pulse amplitudes induce stronger contractions (Doucet et al. 2012) and greater pulse widths from 0.1 to 1 ms increase isometric torque, with little effect on stimulated muscle fatigue (Marsolais and Kobetic 1987). Typically, shorter pulse widths between 300 and 500 μs are used to produce dynamic quadriceps extensions for FES exercise. Frequency is defined as the pulses applied per second in Hertz (Hz). The lowest frequency that produces repetitive functional movements is approximately 20 Hz (Kebaetse et al. 2005) whereas 50–60 Hz produces near-maximal force (Kesar et al. 2008) with no appreciable force difference from 50 Hz up to 100 Hz (Scott et al. 2007). Most FES devices employ constant medium frequencies (20–50 Hz) to induce contractions (Kroon et al. 2005). Additionally, the stimulation waveform is generally biphasic in shape, consisting of a negative followed by a positive phase (Mortimer 1981). This use of charge-balanced waveforms is especially important to avoid tissue damage during high intensity stimulation training.

14.2.3 Muscle Fatigue

Although FES can improve functional mobility for individuals with SCI, the rate of muscle fatigue induced by electrical stimulation is much greater than that during

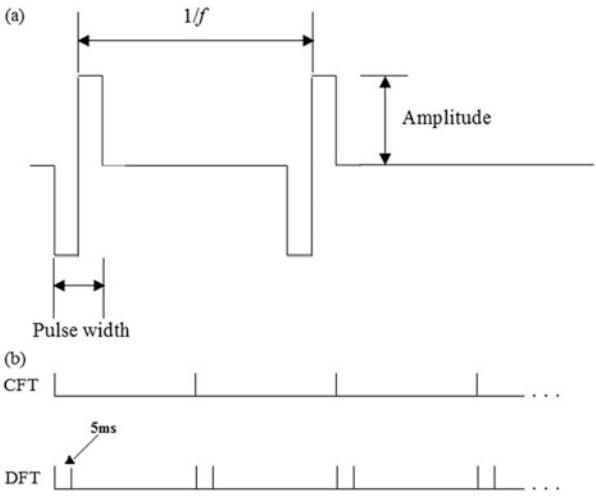

Fig. 14.1 Stimulation waveform and examples of the two stimulation patterns

voluntary movements, possibly limiting the utility of FES (Binder-Macleod and Snyder-Mackler 1993). In addition to force produced, both pattern and frequency of stimulation can also influence the rate of muscle fatigue (Kebaetse et al. 2001, 2002). Traditionally, FES uses constant-frequency trains (CFTs), i.e. stimulation pulses are separated by regular interpulse intervals (Thomas et al. 2003). However, it has been suggested that doublet-frequency trains (DFTs) composed of close-spaced (~5 ms interpulse intervals) pairs of pulses separated by longer intervals, may result in lesser fatigue compared with CFTs (Binder-Macleod and Scott 2001). An example of these two stimulation patterns is shown in Fig. 14.1b. In addition, there is evidence that stimulation frequency may determine muscle fatigue with higher-frequency trains performing better than lower-frequency trains (Kebaetse et al. 2002). However, the vast majority of studies comparing stimulation parameters on muscle fatigue have been performed in able-bodied persons. There are only three studies in those with SCI and these suggest that, in contrast to the able-bodied, low-frequency trains result in lesser fatigue than high-frequency trains (Kebaetse et al. 2005; Deley et al. 2014). Thus, data from able-bodied subjects may not be applicable to paralyzed muscles. Furthermore, several studies have suggested that switching stimulation patterns may be an approach to offset the rapid fatigue that occurs with FES in those with SCI (Kebaetse et al. 2005; Deley et al. 2014). Hence, current implementation of FES may not be employing the optimal stimulation parameters to produce greater force and lesser fatigue.

14.3 Three Types of FES Exercise

To date, three types of FES-exercise systems have been developed and evaluated: FES-cycling, hybrid FES-cycling (leg cycling combined with simultaneous arm-crank exercise) and FES-rowing (leg extension/flexion in concert with upper body rowing). To perform FES-exercise, a certain level of leg muscle strength and endurance is needed; however, most persons with SCI have pronounced atrophy. For example, Jung et al. (2012) reported that the quadriceps muscles in six of ten individuals with complete SCI may not show responses to FES. Hence, before FES training, preliminary FES strength training for the quadriceps and hamstring muscle groups may be necessary to produce functional movements.

14.3.1 FES-Cycling Exercise

FES-cycling exercise was first introduced in the 1980s and is probably the most widely used form of FES exercise in those with SCI. Most FES-cycling systems use surface electrical stimulation of the quadriceps, hamstring, and gluteus muscles to enable the legs to perform a cycling movement. The benefits observed in clinical studies include improved muscle strength (Duffell et al. 2008) and bone density

(Frotzler et al. 2008). However, a critical drawback of FES-cycling exercise is the low efficiency and power output (Hunt et al. 2012). These may limit the magnitude of adaptations across numerous physiologic systems, and most importantly provide very little stimulus for beneficial cardiorespiratory effects. Sufficiently high levels of aerobic work cannot be achieved in those with SCI by employing stimulation alone. Indeed, FES-cycling exercise cannot produce training effects comparable to similar work in able-bodied individuals (Whipp and Wasserman 1969; Glaser et al. 1989).

14.3.2 Hybrid FES-Cycling Exercise

To induce greater exercise benefits in individuals with SCI, the combination of FES-cycling of the legs with voluntary arm-crank exercise, hybrid FES-cycling has been explored. This allows for training of both the upper and lower body simultaneously. Previous studies demonstrated that graded hybrid FES-cycling exercise resulted in a significant higher peak VO_2 than either upper or lower body exercise alone (Mutton et al. 1997). And it is capable of achieving greater cardiovascular responses and workloads than either component alone (Brurok et al. 2011).

14.3.3 FES-Rowing Exercise

The other whole-body exercise for those with SCI can be performed with an adapted ergometer for FES-rowing, allowing for exercise that specifically mirrors that performed by the able-bodied (Hettinga and Andrews 2007). Self-controlled stimulation of quadricep and hamstring muscles induces leg extension and flexion, which combined with voluntary upper body exercise results in a whole-body rowing action. Compared with hybrid FES-cycling exercise, FES-rowing enables those with SCI to achieve higher exercise intensities (Hettinga and Andrews 2008). The full rowing stroke is produced by both the stimulated legs and the voluntary arms, increasing the active muscle mass and resulting in hemodynamic profile that produces the beneficial cardiac loading conditions of large muscle mass exercise (Taylor et al. 2011).

14.4 Aerobic Benefits

Regular aerobic exercise with sufficient intensity can improve health. Dose-response relationships between exercise training and physiologic changes determine the magnitude of improvements in exercise capacity, body composition, and cardiac structure and function. For example, to achieve superior health benefits,

regular exercise must be sustained at or above 6 metabolic equivalents (METs 6 = 21 ml/kg/min). However, skeletal muscle denervation, as a consequence of SCI, lessens exercise capacity. And, the exercise responses in individuals with SCI are considerably different from those in the able-bodied population.

14.4.1 Acute Response

Maximal oxygen consumption (VO_2max) reflects the functional limitations of the cardiovascular system as well as indicates aerobic fitness (Astorino et al. 2000; Noakes 1998). Achievement of VO_2max is based on objective criteria, including a plateau in oxygen uptake despite an increase in work rate, high levels of lactic acid in the blood in the minutes following the exercise test, elevated respiratory exchange ratio, and achievement of some percentage of an age-adjusted estimate for maximal heart rate (Howley et al. 1995).

We reviewed literature in the PubMed and Google Scholar databases to identify studies that reported VO_2 values during FES-exercise in those with SCI between 1980 and December 2015. There are 35 published studies attempting to define the magnitude of aerobic capacity that can be achieved with these three types of FES-exercise, but the vast majority do not use a standardized protocol or follow the widely accepted criteria to ensure achievement of true maximum oxygen consumption. In fact, since Pallack and colleagues presented data from FES-cycling exercise more than 25 years ago (Pollack et al. 1989), most studies have followed their testing paradigm—increasing resistance in 6 W increments every 3 min until the subject fails to maintain a pedaling frequency of 35 rpm to determine aerobic capacity (Goss et al. 1992; Hooker et al. 1992, 1995). Indeed, this is a graded test, but does not provide sufficient objective criteria for VO_2max. As a result, exercise capacity from these studies seems to have mis-estimated the magnitude of effect. Constant workload tests have also been used to determine aerobic capacity (Nash et al. 1995; Faghri et al. 1992), but this cannot define VO_2max. Other studies have termed their values VO_2max, but without details on either the protocol or criteria. Hence, only a few studies have reported objective VO_2max values from FES-cycling, hybrid FES-cycling and FES-rowing. These are listed in Table 14.1.

14.4.2 Arms-Only Exercise

Given the motor loss of the lower limbs, most aerobic exercise options for those with SCI are typically limited to some form of arms-only exercise. It is well known that arms-only exercise can achieve health benefits of physical activity (Jacobs et al. 2001), but is insufficient to achieve high levels of aerobic work. Van Loan et al. reported metabolic parameters and cardiovascular responses of able-bodied,

Table 14.1. VO2 max values during FES-cycling, hybrid FES-cycling exercise, FES-rowing (*SE)

Study (year)	Subjects (n)	Criteria	The type of test, absolute VO2max (L/min) (mean ± SD)	Relative VO2max (mL/kg/min)
Mohr et al. (1997), Kjaer et al. (2001) FES-cycling (0–6–12 months)	4 para, 6 tetra, 8M, 2F	N = 1	FES-cycling: 1.2 ± 0.08* (0 month); FES-cycling: 1.41 ± 0.10(1.38 ± 0.10)* (6 month); FES-cycling: 1.43 ± 0.09*(12 months)	NA
Bhambhani et al. (2000)	4 para, 3 tetra, 5M, 2F	N = 2	FES-cycling: 0.32 ± 0.1 (rest); 0.65 ± 0.18 (peak)	NA
Verellen et al. (2007)	4 para (A), 1 C7-T4(C), 5M	N = 1	Arms-only: 1.81 ± 0.4 FES-cycling: 1.1 ± 0.25 Hybrid FES-cycling: 2.13 ± 0.44 FES rowing: 2.15 ± 0.2	21.56 ± 4.58 13.26 ± 3.9 25.38 ± 6.03 25.62 ± 2.98
Brurok et al. (2011) Hybrid FES-cycling (0–8 weeks)	5 para, 1 tetra, 6M	N = 3	Arms-only: 1.6 ± 0.47 (0 week) 2.00 ± 0.52 (8 weeks) FES-cycling: 0.63 ± 0.12 (0 week) 0.78 ± 0.14 (8 weeks) Hybrid FES-cycling: 1.92 ± 0.35 (0 week) 2.43 ± 0.52 (8 weeks)	20.1 ± 4.8; 25.3 ± 6.4 8.1 ± 2; 10.0 ± 1.9 24.6 ± 3.9; 30.6 ± 5.2
Taylor et al. (2011)	6 para, 6M	N = 3	NA	Arms-only: 15.7 ± 1.5; FES-rowing: 20.0 ± 1.9
Jung et al. (2012)	10 para, 7M, 3F	N = 1	NA	Arms-only: 17.86 ± 5.17 Motor row: 21.78 ± 6.23
Brurok et al. (2012, 2013)	SCI-high (C4-T5; N = 8; 8M) SCI-low (T8-T12; N = 7, 5M, 2F)	N = 3 / N = 2	Arms-only: 1.24 ± 0.40 Hybrid FES-cycling: 1.8 ± 0.4 Arms-only: 1.74 ± 0.24 Hybrid FES-cycling: 1.91 ± 0.38	1.77 ± 5.0 24.4 ± 4.1 23.7 ± 3.6 25.6 ± 4.1

(continued)

Table 14.1. (continued)

Study (year)	Subjects (n)	Criteria	The type of test, absolute VO2max (L/min) (mean ± SD)	Relative VO2max (mL/kg/min)
Gibbons et al. (2016) FES-rowing (0–8 weeks)	2 para, 3 tetra, 1M, 4F	ACSM Guidelines for Exercise Testing and Prescription.	Arm-only: 0.82 ± 0.27 (0 week); 0.87 ± 0.30 (8 weeks) FES-rowing: 0.97 ± 0.22 (0 week); 1.08 ± 0.26 (8 weeks)	Arm-only: 15.0 ± 4.4 (0 week); 16.0 ± 5.1 (8 weeks) FES-rowing: 17.8 ± 3.5 (0 week); 19.7 ± 4.1 (8 weeks)
Taylor et al. (2014) FES-rowing (0–6 months)	14 para, 13M, 1F	N = 3	NA	FES-rowing: 19.6 ± 6 (0 month); 21.4 ± 6.6 (6 months)
Deley et al. (2016) FES-rowing (0–9 months)	1 para, 1F	N = 3	NA	FES-rowing: 18.1 (0 m); 28.6 (9 m)
Wilbanks et al. (2016) FES-rowing (0–6 weeks)	10 para, 8M, 2F	N = 1	NA	Arm-only: 18 ± 5 (0 week); 19.5 ± 6 (6 weeks) FES-rowing: 18.2 ± 7 (0 week); 20 ± 7 (6 weeks)
Qiu et al. (2016) FES-rowing (0–6 months)	10 tetra, 2 para, 13M, 1F	N = 3	NA	FES-rowing: 15.3 ± 17.1 (0 month); 17.1 ± 1.6 (6 months)

paraplegic and tetraplegic subjects to maximal arms-only exercise (Van Loan et al. 1987). VO_2max was lower in those with SCI than in able-bodied and decreased with increasing level of SCI. Maximal heart rate (HRmax) is unaffected in those with SCI up to T3–4 level, while those with higher level injuries have decreasing values with increasing injury level. Both maximal stroke volume (SVmax) and maximal cardiac output (Qmax) are lower in those with SCI and is further reduced in those with higher level injuries. Also, compared with able-bodied subjects, arteriovenous oxygen difference tends be higher in individuals with SCI despite lower VO_2max. In addition, studies of arm-only exercise-induced changes in blood flow to nonactive regions show that vasoconstriction of inactive beds (i.e., the splanchnic and inactive muscle) respond differently to the same exercise stimulus in those with SCI depending on injury level.

In individuals with SCI, arms-only exercise can elicit only modest increases in cardiorespiratory responses (Tordi et al. 2001a), partly due to a smaller active muscle mass. Furthermore, the lack of effective vasoregulation in areas below the lesion produces venous blood pooling in the legs and splanchnic beds. Sympathetic denervation precludes vasoconstriction to redistribute flow to the active arms and lower cardiac preload reduces stroke volume, hence limiting cardiac output and thus VO_2max. FES exercise of the denervated muscles, which has been widely advocated as an effective exercise for individuals with SCI could be a solution to overcome these limitations.

14.4.3 FES-Cycling Exercise

It should be noted that studies examining changes in aerobic capacity with FES-cycling have rarely employed sufficient objective criteria to ascertain true VO_2max. For example, the study by Bhambhani et al. (2000) showed much lower VO_2max values than that published by Mohr and Kjaer (Mohr et al. 1997; Kjaer et al. 2001) but was consistent with the study of Brurok and co-workers (2011). This could simply result from the fact that both Brurok and Bhambhani used more objective criteria to determine VO_2max than Mohr and Kjaer, and hence the values may be more reliable. Nonetheless, pooling all observations on VO_2max during FES exercise shows that FES-cycling produces low aerobic demand compared to arms-only, hybrid FES-cycling or hybrid FES-rowing exercises. Judging from the small muscle mass activated and the low VO_2max, FES-cycling exercise alone is probably not an effective cardiovascular training tool for individuals with SCI. According to the Fick principle, maximal aerobic power is the product of cardiac output and arterio-venous oxygen (a-vO_2) difference. In two hemodynamic studies (Nash et al. 1995; Faghri et al. 1992), the increase in VO_2 during FES-cycling was attained through increases in both cardiac output and a-vO_2 difference. Hence, the increased oxygen demand is met by increases in not only O_2 extraction at the muscle, but also systemic O_2 delivery. However, Faghri et al. reported that mean arterial pressure (MAP) did not significantly change from rest to exercise (Faghri

et al. 1992). Considering that total peripheral resistance decreases in response to FES exercise, the increased cardiac output may simply derive from lesser resistance to flow and or reflex adjustments to maintain pressure. Nonetheless, it is clear that FES-cycling exercise does not engender the high flow/low resistance hemodynamic state characterized by voluntary dynamic exercise. Moreover, it should be considered that induced muscle contractions in paralyzed muscles via FES does not result in feedforward input to the cardiorespiratory system from the central nervous system (i.e., central command) and minimal or no feedback from the periphery (i.e., group III and IV afferents). Hence, it represents the response to increased local metabolism as a result of paralyzed muscle contractions, and so training may only result in peripheral adaptations.

14.4.4 Hybrid FES-Cycling and Hybrid FES-Rowing Exercise

Although arms-only exercises are more widely available than hybrid FES exercise because of specialized equipment, clinical oversight, and potentially high costs, hybrid FES exercise can be worth the effort considering its potential benefits. Moreover, the overuse of the chest and shoulder muscles, a serious issue in wheelchair athletes, might be avoided with hybrid FES exercise while reaching high intensities of physical exercise (Wilbanks et al. 2016). Brurok et al. and Verellen et al. observed ~20 % increase in aerobic capacity during hybrid FES-cycling exercise as compared to arms-only exercise in persons with SCI (Brurok et al. 2011; Verellen et al. 2007). Their results also showed that aerobic capacity during hybrid FES-cycling was double the aerobic capacity during FES-cycling tests. Thus, it is worthwhile for those with SCI to consider adding FES-cycling to arms-only exercise even given the added expense of FES. Interestingly, these data were reported twice (Brurok et al. 2012, 2013)—once using three criteria to determine VO_2max and once using two out of the three criteria. The data suggest that hybrid FES-cycling exercise can produce a 45 % greater aerobic capacity than arms-only exercise for those with injuries above T6, but only a 10 % greater aerobic capacity in individual with injuries below T6. One explanation for this may be the diverse methodological approaches and individual differences in FES training status. Nonetheless, those with tetraplegia have a low aerobic capacity before training (Brurok et al. 2012, 2013) and large FES-induced muscle mass compared to voluntary upper body muscle mass. This is consistent with the previous finding that the increase in VO_2max was greatest in those with higher level injuries.

Hybrid FES-rowing exercise, as another whole-body exercise, results in higher VO_2max than arms-only exercise.VO_2max was ~20 % greater when arm-row exercise was combined with FES-leg exercise in three studies (Jung et al. 2012; Taylor et al. 2011; Gibbons et al. 2016), which is comparable to the increase with hybrid FES-cycling exercise. However, one study reported no significant difference

between VO_2max during arm-only exercise and FES-rowing exercise (Wilbanks et al. 2016), perhaps due to only meeting one criterion for VO_2max. In addition, level of injury and time since injury varied greatly (T4–T12 and 2–39 years), and the ASIA range was also great (A–C). Our previous work, in those with injury level T4–T9 and ASIA (A), aged 32–37 years, using a standardized protocol and criteria demonstrated an almost 30 % increase in peak aerobic capacity during FES-rowing exercise as compared to arms-only rowing (Taylor et al. 2011). Moreover, HRmax was somewhat lower ($P = 0.19$), although peak oxygen pulse was significantly greater with FES-rowing exercise (Taylor et al. 2011; Yoshiga and Higuchi 2002). These findings suggest that, compared to arms-only exercise, the involvement of more muscles during rowing facilitates venous return and elevates central blood volume, but this should be confirmed with measurements of cardiac output and stroke volume.

In summary, aerobic capacity is significantly higher during hybrid FES exercise in comparison with exercises only involving the upper or lower limbs. The likely explanation for this increased VO_2max is involvement of a larger muscle mass, creation of a muscle pump in synchrony with upper body work, and elimination of the need for vasoconstriction in the legs (Taylor et al. 2011).

14.4.5 Responses to Exercise Training

14.4.5.1 Arm-Only Exercise

Much work has shown that regular arms-only training in individuals with SCI effectively improves aerobic capacity and work output (Jacobs et al. 2001; Maggioni et al. 2012; Hopman et al. 1996; Taylor et al. 1996). For those with tetraplegia, however, there is no evidence that either maximal stroke volume or cardiac output increases (Hopman et al. 1996), perhaps due to the small upper-body muscle mass recruited and lack of sympathetic innervation, limiting cardiac output. Thus, a marked central cardiovascular adaptation by arm-only training may not be expected in this population. On the other hand, individuals with paraplegic and more available muscle mass demonstrate improved aerobic capacity associated with an increased maximal ventilation and oxygen pulse (Eriksson et al. 1988; Tordi et al. 2001b). The increase in oxygen pulse could reflect an increase in stroke volume (Taylor et al. 2011; Hooker et al. 1992). Moreover, arm training is associated with an increase in peripheral artery diameter, suggestive of peripheral adaptations in the upper limbs as well.

14.4.5.2 FES-Cycling Exercise

Two studies of individuals who participated in FES-cycle training for up to 12 months reported that VO_2max plateaus at 6 months of training (Mohr

et al. 1997) and that it progressively increases if training volume is maintained (Kjaer et al. 2001). Although heart rate may be greater after FES-cycle training (Kjaer et al. 1999; Raymond et al. 1999), inconsistent responses to training have been reported. One study observed a greater heart rate after training (Faghri et al. 1992), whereas another found decreased heart rate (Hooker et al. 1992). It appears that total peripheral resistance during exercise may be lower due to peripheral adaptations after FES-cycle training (Faghri et al. 1992; Hooker et al. 1992; Figoni et al. 1990). However, it is unclear if there are increases in stroke volume after FES-cycle training. Both increased (Faghri et al. 1992) and virtually unchanged (Hooker et al. 1992) peak stroke volume have been reported after 3–4 months of training. There is a report of increased peak cardiac output after FES-cycle training without any increase in stroke volume (Nash et al. 1995). If this latter finding is correct, it would support the supposition that a greater metabolic stimulus during FES cycling after training results in a larger drop in total peripheral resistance and hence a larger heart rate response to maintain blood pressure. Nonetheless, it does appear that FES-cycling exercise increases peak power output and peak VO_2 and may promote certain health and fitness benefits for those with SCI (Pollack et al. 1989; Krauss et al. 1993; Mohr et al. 1997; Barstow et al. 1996). However, it seems that peripheral adaptations are solely responsible for the observed improvement in peak aerobic fitness. It is noteworthy that the load resistance and power output level commonly used in FES-cycling exercise are quite low compared to those for able-bodied individuals during voluntary leg-cycling exercise (Raymond et al. 2002). Hence, the magnitude of increases in aerobic fitness may be similar to able-bodied individuals with walking or slow jogging (Faghri et al. 1992). This would imply that FES-cycling exercise is insufficiently intense to provide significant aerobic exercise benefits in those with SCI.

14.4.5.3 Hybrid FES-Cycling and FES-Rowing Exercise

Long-term training with hybrid FES exercise results in a significant increase in VO_2max (Brurok et al. 2011; Taylor et al. 2014). Two studies of FES-row training over 6 weeks and 8 weeks showed an increase in aerobic capacity of ~10 % (Wilbanks et al. 2016; Gibbons et al. 2016), which is comparable with the magnitude of increase after 6 month of FES-row training (Taylor et al. 2011). A third study of six months of training with average training intensity ranging from 62–89 % (lower than the former two studies) and compliance averaging 1.7 rowing sessions per week (fewer than the former two studies) suggests that high-intensity training can be effective for improving VO_2max (Taylor et al. 2011). Moreover, Brurok et al. found a 25 % increase in VO_2max in 6 individuals with SCI after 8 weeks (24 sessions) of high-intensity hybrid FES-cycling training (Brurok et al. 2011). We have recently found that one key aspect of the responses to hybrid FES exercise training is the ability to generate sufficiently high levels of exercise ventilation. Six months of FES-row training in those with injuries at T3 and below

improved not only aerobic capacity but also ventilatory capacity. In these individuals, increased ventilatory capacity matched the greater aerobic exercise capacity engendered by training and aerobic capacity was no longer related to injury level (Taylor et al. 2014). However, those with higher level injuries and hence greater

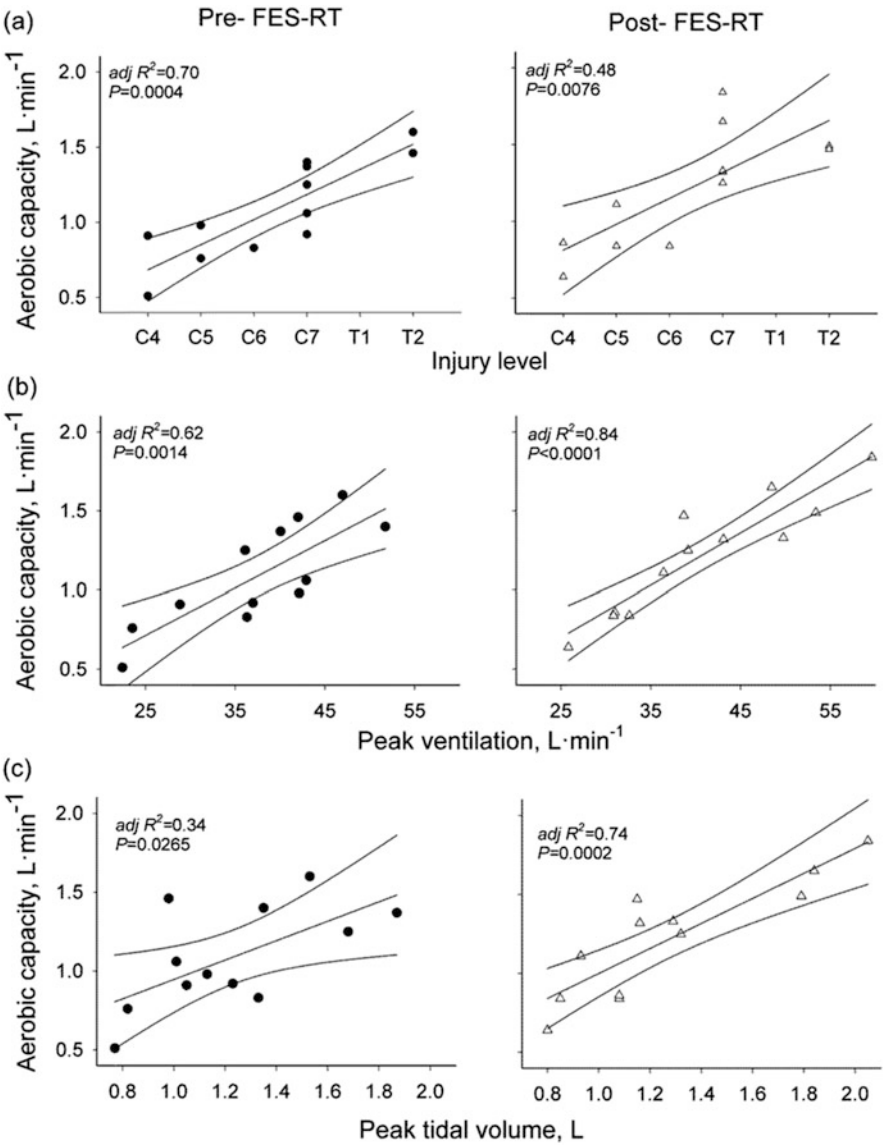

Fig. 14.2 Relations of peak aerobic capacity to injury level, peak exercise ventilation and peak tidal volume pre- and post FES-rowing training (FES-RT). Linear regression with 95 % confidence intervals are presented

pulmonary denervation demonstrate a strikingly different response to training. After six months of training, the relationship of aerobic capacity to injury level remained and the relative role of peak ventilation in determining aerobic capacity increased (Qiu et al. 2016). In fact, the relationship of aerobic capacity to peak tidal volume was markedly stronger and predictive of aerobic capacity. Thus, the inability to increase tidal volume limited peak ventilation and restricted the increase in aerobic capacity. This suggests that in those with a high injury level, hybrid FES-exercise training results in a greater capacity of both the innervated upper body and denervated leg skeletal muscles to consume oxygen that effectively outstrips the restricted ventilatory capacity (See Fig. 14.2).

There has been very little work examining the impact of hybrid FES- exercise training on hemodynamics. One investigation reported that 8 weeks of high-intensity training resulted in a central cardiovascular training effect reflected by an ~30 % increase in stroke volume and cardiac output at 80 % peak workload during hybrid FES-cycling (Brurok et al. 2011). Surprisingly, though not reported, the greater cardiac output appears to fully account for the increase in aerobic capacity, suggesting that a-v O_2 difference is unchanged after hybrid FES-cycle training. However, aerobic capacity for hybrid FES, arms only, and FES only exercise were all increased to a comparable extent. If whole body a-v O_2 difference is unaffected by training, this would suggest that greater systemic flow is wholly responsible for the increases and that, surprisingly, FES training does not impact leg skeletal muscle oxidative capacity. However, hybrid FES-cycling training can induce vascular adaptations in the thigh (Thijssen et al. 2005), suggesting that hybrid FES-cycling can elicit peripheral adaptations. Nonetheless, hybrid FES training provides a form of regular aerobic exercise for a unique exercise stimulus that circumvents a primary limitation to vigorous exercise for those with SCI-compromised innervation of skeletal muscle mass. Moreover, hybrid FES training in those with SCI improves aerobic capacity and likely leads to both central cardiac and peripheral vascular adaptations.

14.5 Discussion

Generally, comparing among arms-only, FES-cycling, and hybrid FES exercise, aerobic capacity is lowest with FES-cycling and highest with hybrid FES exercise. Arms-only exercise is widely available in individuals with SCI and though it can increase aerobic capacity and power output, it can be insufficient to produce high levels of aerobic work and may not induce central adaptations. FES cycling exercise has become a popular form of exercise for persons with SCI, but efficiency and power output for this exercise are very low and it appears to induce only peripheral adaptation with training. Hybrid FES exercise can achieve greater aerobic capacity and has the advantages of increasing the active muscle mass, creating a muscle pump in synchrony with the upper body work, and eliminating the need for vasoconstriction in the legs. Hence, hybrid exercise at a sufficient

intensity can induce adaptations across multiple physiologic systems in those with SCI, and importantly result in central adaptations. Therefore, hybrid FES training may be an important intervention to reduce cardiovascular risk, may be efficient for enhancing bone mass, and might promote plasticity both rostral and caudal to the injury. Therefore, hybrid FES training represents a unique approach to exercise that can enhance health and even promote recovery in persons with SCI.

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