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Alterations in autonomic cerebrovascular control after spinal cord injury

Dong-Il Kim^{a,b,c} and Can Ozan Tan^{b,c,*}

^aDepartment of Sport and Leisure Studies, Exercise Medicine Center for Diabetes and Cancer Patients, Yonsei University, Seoul, Republic of Korea

^bCerebrovascular Research Laboratory, Spaulding Rehabilitation Hospital, Boston, MA, United States

^cDepartment of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA, United States

Abstract

Among chronic cardiovascular and metabolic sequelae of spinal cord injury (SCI) is an up-to four-fold increase in the risk of ischemic and hemorrhagic stroke, suggesting that individuals with SCI cannot maintain stable cerebral perfusion. In able-bodied individuals, the cerebral vasculature is able to regulate cerebral perfusion in response to swings in arterial pressure (cerebral autoregulation), blood gases (cerebral vasoreactivity), and neural metabolic demand (neurovascular coupling). This ability depends, at least partly, on intact autonomic function, but high thoracic and cervical spinal cord injuries result in disruption of sympathetic and parasympathetic cerebrovascular control. In addition, alterations in autonomic and/or vascular function secondary to paralysis and physical inactivity can impact cerebrovascular function independent of the disruption of autonomic control due to injury. Thus, it is conceivable that SCI results in cerebrovascular dysfunction that may underlie an elevated risk of stroke in this population, and that rehabilitation strategies targeting this dysfunction may alleviate the long-term risk of adverse cerebrovascular events. However, despite this potential direct link between SCI and the risk of stroke, studies exploring this relationship are surprisingly scarce, and the few available studies provide equivocal results. The focus of this review is to provide an integrated overview of the available data on alterations in cerebral vascular function after SCI in humans, and to provide suggestions for future research.

1. Introduction

Every year up to half a million people suffer a spinal cord injury (SCI) worldwide (WHO, 2013). While advances in acute care resulted in greatly reduced mortality in the initial few years following a SCI (Shavelle et al., 2007; Strauss et al., 2006), improved life expectancy after SCI highlights the importance of alleviating chronic conditions consequent to SCI-related cardiovascular and metabolic alterations, as well as immobility. In addition to loss of

*Corresponding author at: CVLab, Spaulding Hospital Cambridge, 1575 Cambridge Street, Cambridge, MA 02138, United States. cotan@mgh.harvard.edu (C.O. Tan).

sensory-motor ability and diminished quality of life, individuals with chronic SCI are at increased risk for developing an array of cardiovascular problems. Among these is an up to four-fold greater risk for ischemic and hemorrhagic stroke. One study of ~ 9000 veterans with SCI found that within one year of study onset, almost half of the patients had at least one macrovascular complication (including cardiovascular, such as coronary artery or peripheral vascular disease, as well as cerebrovascular complications, such as intracerebral hemorrhage or cerebral artery occlusion) (Banerjee et al., 2008). A more recent study reported ~40% higher odds for stroke in veterans with SCI compared to both able-bodied veterans and the general population (LaVela et al., 2012). Another four- year study explicitly explored the association between SCI and stroke risk, and found that the incidence of stroke in men with SCI was threefold higher than able-bodied controls, even after accounting for differences in other known risk factors, such as age, sex, other comorbidities, and medication exposure (Wu et al., 2012). Indeed, these findings were confirmed by a much larger study that included ~ 60,000 individuals (Cragg et al., 2013), even after accounting for sex, age, daily energy expenditure, body mass index, hypertension, smoking status, daily alcohol consumption, daily consumption of fruits and vegetables, and diabetes. Thus, there is a clear link between SCI and exacerbated risk of stroke.

An increased risk of stroke suggests that individuals with SCI cannot maintain stable cerebral perfusion (Derdeyn et al., 1999; Silvestrini et al., 2000; Yonas et al., 1993). Short-term stability of the cerebral perfusion depends primarily on two mechanisms: the systemic control of arterial (and thus, cerebral perfusion) pressure, and the ability of cerebral vasculature to appropriately respond to fluctuations in arterial pressure, blood gases, and metabolic demand. Most SCI patients experience low arterial pressure (attributed to reduced systemic vascular resistance due to sympathetic dysfunction below the level of injury, decreased venous return from the immobile lower extremities, or frank venous insufficiency of the paralyzed limbs) (Hopman, 1994; Hopman et al., 1996). While cardiac baroreflex control may partly compensate for the disruption in sympathetic vascular control, baroreflex function may also be impaired after both high and low-level SCI (Grimm et al., 1998; Wecht et al., 2006), rendering the body unable to control arterial pressure (see the reviews by Draghici and Taylor and by Macefield in this issue). In fact, individuals with injuries at or above T6 level are prone to episodes of autonomic dysreflexia when exposed to noxious stimuli (Erickson, 1980), including everyday events such as bladder and bowel distension (Shergill et al., 2004). These episodes are characterized by intermittent surges in arterial pressure, partly attributed to impaired baroreflex control. This has significant consequences in SCI patients; arterial pressure can rise to the point where crisis headache results, and cerebral hemorrhage and death may ensue (Kewalramani, 1980; Kursh et al., 1977; Lindan et al., 1980). Thus, chronic reduction and intermittent excessive elevation of arterial pressure may put individuals with SCI at risk for adverse cerebrovascular events.

In able-bodied individuals, the cerebral vasculature is able to regulate cerebral perfusion to buffer against swings in arterial pressure, and to regulate blood flow to appropriately respond to changes in blood gases and neural metabolic demand (Jeong et al., 2014; Tan and Taylor, 2014). Available data suggests that this ability depends, at least partly, on intact autonomic function. The involvement of autonomic (sympathetic and parasympathetic)

nervous system in cerebrovascular function, and its disruption after SCI, has significant implications for the cerebrovascular and neural health in individuals with chronic SCI.

Alterations in the autonomic nervous system due to SCI are summarized in Section 2. Subsequently, in Sections 3 and 4, we provide a brief overview of cerebrovascular function and the role the autonomic system plays in this function in healthy able-bodied individuals. This overview is not intended to be exhaustive, however, and we refer the reader to other reviews for an in-depth treatment of this topic in able-bodied individuals (Goadsby, 2013; Tan and Taylor, 2014; Willie et al., 2014). In Section 5, we discuss data on alterations in cerebral vascular function after SCI. Lastly, in Section 6, we provide a brief review of the data that link cerebrovascular dysfunction to the risk of stroke and other cerebrovascular diseases.

2. Disruption of the autonomic control due to SCI

While sympathetic nerve fibers surround virtually all arteries with a density that is roughly proportional to the diameter of the vessel, cerebral arteries are among the most densely innervated for arteries of a given diameter (Edvinsson and MacKenzie, 1976a; Goadsby, 2013). For example, small pial arteries, 100 μm or less, have 2–3 fibers running irregularly along the adventitia, and single fibers can be found on arterioles as small as 15 μm in diameter (Edvinsson and MacKenzie, 1976a) (for comparison, this is as dense as seen in well-innervated vascular beds, such as mesenteric arteries). The primary source of sympathetic fibers to the cerebral vessels originates in the superior cervical ganglion (at the C2–3 level) (Edvinsson and MacKenzie, 1976a; Edvinsson et al., 1976b; Purves, 1972) as revealed by denervation experiments demonstrating the total disappearance of nerve fibers (Edvinsson et al., 1975; Iwayama, 1970; Sercombe et al., 1975) and of chemically measured noradrenaline (Edvinsson et al., 1972) soon after excision of the superior cervical ganglion. Sympathetic innervation is most dense anteriorly, with a relatively sparser supply in the vertebrobasilar territory. Nerves innervating the vertebrobasilar territory mostly arise from the vertebral ganglion between the middle and inferior cervical ganglia (C5–T1 level), with a large branch often arising from the stellate ganglia (C8–T1 level) and smaller filaments from superior and middle ganglia (Nelson and Rennels, 1970).

Conventional wisdom holds that along the sympathetic chain, the primary source of input to these ganglia is the preganglionic sympathetic nerves extending from the T1–T5 region and entering the superior cervical ganglion through the cervical sympathetic nerve. It is important to note, however, that cervical spinal cord stimulation has a dose-dependent effect on cerebral blood flow (Zhong et al., 2004), mediated by sympathetic fibers (reviewed in (Visocchi et al., 2011)) and without any significant change in systemic blood pressure (Sagher and Huang, 2000). It is possible that spinal cord stimulation is relayed to cerebral vasculature through a polysynaptic pathway, via preganglionic nerve fibers from T1–T5 region synapsing onto cervical ganglia. However, cervical vs thoracic spinal cord stimulation appears to produce different patterns of change in cerebral blood flow (increase/redistribution vs decrease) (Meglio et al., 1991; Visocchi, 2006), providing inferential evidence for potentially distinct (though perhaps interacting) pathways. This is further reinforced by reports of sympathetic preganglionic neurons with nerve endings on the upper

cervical ganglia (Asamoto, 2005). Therefore, thoracic preganglionic nerves may not be the sole source of sympathetic cerebrovascular control. Thus, while SCI at or above T4 level results in disruption of sympathetic cerebrovascular control, the level of injury that eradicates it is not clear.

The source of parasympathetic fibers innervating the cerebral vasculature is the sphenopalatine ganglion (innervated by the greater petrosal nerve), internal carotid plexus, and cranial nerves IX and X (Edvinsson and MacKenzie, 1976a; Goadsby, 2013). Activation of postganglionic neurons (e.g., stimulation along the trigeminal nerve) has long been known to dilate dural and cortical arteries in animals (Suzuki et al., 1990) and humans (Goadsby et al., 1988). Since these nerves originate above the spinal cord level, parasympathetic (cholinergic) autonomic control of cerebral vasculature is expected to be intact after SCI (Krassioukov and Weaver, 1996). However, although parasympathetic control is usually preserved (Teasell et al., 2000), the synergistic relationship between parasympathetic and sympathetic control may be lost particularly in those with cervical and high thoracic injuries.

It should be noted that completeness of the spinal cord injury is a critical factor that determines the degree of autonomic dysfunction. However, sensory/motor and autonomic completeness of SCI do not always correspond (Claydon and Krassioukov, 2006; West et al., 2013). Unfortunately, current classification of completeness in SCI exclusively relies on sensory and motor function, and there is no routine and reliable assessment of remaining autonomic function (Round et al., 2016). It is also worth noting that prolonged immobility, sedentary lifestyle, and physical deconditioning may further exacerbate already impaired autonomic and vascular function. In able-bodied individuals, the decline in autonomic function (Hamner et al., 2010; Hasser and Moffitt, 2001; Hughson and Shoemaker, 2015), as well as vascular function (Thijssen et al., 2010), consequent to physical inactivity and deconditioning, is well documented. For example, physical (in)activity alone is reported to influence sympathetic nervous outflow by altering central neural transmission (Mueller, 2007; Mueller, 2010). While the degree to which this inactivity-mediated decline in autonomic function impacts cerebrovascular function is not fully elucidated, several reports show detrimental impact of physical inactivity on cerebrovascular function. For example, in able-bodied individuals, even a single day of bed rest reduces cerebral blood flow for 4 to 5 h during the seated recovery phase (Kawai et al., 1993). Additionally, frequent physical activity and aerobic conditioning are associated with more effective cerebral blood flow regulation and improved cognitive function (Guiney et al., 2015). Thus, it is possible that alterations in autonomic and/or vascular function, secondary to physical inactivity, may also impact cerebrovascular function after SCI independent of, or at least in addition to, disruption of autonomic cerebrovascular control due to injury.

3. Cerebrovascular function in able-bodied individuals

Neural cell bodies have high demand for oxygen such that ischemic neurodegeneration can occur within minutes (Fukuda et al., 2006; Stamford et al., 1999). Although the human brain is only ~ 2% of the body mass, it represents ~ 20% of total body oxygen consumption (Shulman et al., 2003) and 25% of energy consumption (Bloom and Kupfer, 1995), thus

oxygen and glucose must be supplied to the brain on a relatively steady basis. However, the evolution of the skull to house the brain coupled with upright posture and two legged motion has put fairly complex demand on the control mechanisms for maintaining adequate cerebral blood flow. Although inadequate blood flow (thus, oxygen and nutrient delivery) leads to neural degeneration and brain damage, increased perfusion leads to increased intracranial pressure, which can also lead to damage to the microvasculature, neural degeneration and cell death due to blood vessel and tissue compression (Roy and Sherrington, 1890). Thus, it is apparent that adequate control of cerebral blood flow in the face of changing systemic arterial pressure, arterial gas concentrations, or metabolic demand is vital to neural health. While the brain seems to lack the survival advantage of other organs that are more tolerant to ischemic and/or hypoxic damage, this disadvantage is compensated for by three primary mechanisms which ensure that brain perfusion is maintained - cerebral autoregulation, cerebral vasoreactivity to arterial gases, and neurovascular coupling.

The first mechanism counteracts the fluctuations in arterial pressure that occur in everyday activities. For example, changes in posture can result in as much as a 50% drop in systolic pressure and produce pre- syncopal symptoms, as well as frank and vasovagal syncope (brief loss of consciousness), if blood flow to reticular brain cells rapidly falls (Roy and Sherrington, 1890). Effective regulation maintains cerebral blood flow via changes in cerebrovascular resistance in response to changes in arterial pressure (Paulson et al., 1990; Strandgaard and Paulson, 1984). This mechanism is termed **cerebral autoregulation**, and it is critical to neurophysiologic health because cerebral circulation is a high-flow vascular bed encased in a non-distensible skull; too little flow causes ischemia whereas too much raises intracranial pressure. Second, cerebral blood flow is highly sensitive to changes in arterial oxygen and carbon dioxide (CO₂) partial pressures (though it is not very sensitive to changes in arterial oxygen when PO₂ is above 60 mm Hg (Rowell, 1993)). High CO₂ (hypercapnia) leads to vasodilation and increases in flow, whereas low CO₂ (hypocapnia) leads to vasoconstriction and decreases in flow (Brian et al., 1996; Willie et al., 2012). In essence, elevations in flow with hypercapnia attenuate the rise in hydrogen ion concentration and subsequent fall in pH, whereas declines in flow with hypocapnia attenuate the fall in hydrogen ion concentration and increase in pH. This highly sensitive flow response to changes in CO₂ is termed **cerebral vasoreactivity** and is a vital homeostatic function; arterial CO₂ can fluctuate widely from one breath to the next and can change significantly with everyday stressors, such as moving from supine to upright postures or physical activity (Serrador et al., 2006). Third, the distribution of cerebral flow is regulated according to the neural activity of different regions of the brain. Because neuronal activity requires delivery of adequate oxygen and glucose to specific brain regions to meet metabolic demand and removal of metabolic waste products (CO₂, hydrogen ions, lactate), cerebral blood flow and cerebral metabolic rate are normally coupled. This link between increased metabolic demand and increased blood flow is termed **neurovascular coupling**; its alterations can impair the ability of the brain to provide sufficient flow to active regions, leading to neural dysfunction (Girouard and Iadecola, 1985).

4. Autonomic control of cerebrovascular function

The autonomic mechanisms that underlie cerebral autoregulation are relatively well established. In contrast, it remains unclear whether the autonomic nervous system plays a critical role in cerebral vasoreactivity and neurovascular coupling. Data delineating these mechanisms have been thoroughly discussed elsewhere (Goadsby, 2013; Tan and Taylor, 2014; Willie et al., 2014). Here, we provide a brief overview as a vantage point to understand the impact of SCI and subsequent autonomic dysfunction on cerebrovascular function (next section), and refer the reader to prior reviews for an in-depth discussion.

4.1. Cerebral autoregulation

Over half a century ago Guyton and associates (Hu et al., 1999; Sagawa and Guyton, 1961) isolated the cerebral circulation of one dog from his peripheral circulation by supplying it from another donor dog. The carotid sinus nerves of the recipient dog were cut, eliminating baroreceptor and chemoreceptor responses to arterial pressure changes, and the recipient dog showed no signs of cerebral autoregulation. Since then, it has been shown that the magnitude of fluctuations in cerebral blood flow in relation to those in arterial pressure is related to the severity of carotid stenosis (Hu et al., 1999), which can markedly impair autonomic control (Nasr et al., 2005). Additionally cerebrovascular resistance increases in response to acute sympathoexcitatory stimuli, such as isometric exercise (Ainslie et al., 2005), simulated orthostatic stress (Guo et al., 2006), and the cold pressor test (Wilson et al., 2005). These data provide inferential evidence that sympathetic control may play a role in cerebral autoregulation. There is also some evidence, from animal studies, of parasympathetic involvement in cerebral autoregulation. In anaesthetized dogs, stimulation of the superficial petrosal nerve (which supplies cholinergic fibers to cerebral vessels, see Section 2) and intra-arterial acetylcholine infusions, produce cerebral vasodilatation proportional to stimulation frequency and infusion dose (D'Alecy and Rose, 1977). However, in cats, stimulation of the same nerve did not alter cerebral blood flow (Busija and Heistad, 1981). Thus, until recently, the presence of cholinergic vasodilator control in the cerebral circulation remained unclear.

Zhang et al. (Zhang et al., 2002) provided the first direct evidence for autonomic (both sympathetic and parasympathetic) control of cerebral autoregulation, showing that ganglionic blockade following trimethaphan administration in conscious humans reduces the degree of cerebral counter-regulation of arterial pressure fluctuations. It should be noted, however, that ganglionic blockade abolishes both sympathetic and parasympathetic nervous control, and so the observed effect could have been due to impairment of either or both. In two more recent studies, we explored the relation between fluctuation in systemic pressure and cerebral blood flow before and after α -adrenergic blockade via phentolamine (Hamner et al., 2010) and muscarinic blockade via glycopyrrolate (Hamner et al., 2012) in young healthy volunteers. We found that when the vascular effect of sympathetic or cholinergic nervous outflow was blocked, the linear relationship between arterial pressure and cerebral blood flow fluctuations increased significantly within the time scales wherein cerebrovascular regulation is most active. Subsequently, we demonstrated the relative contributions of sympathetic and cholinergic (as well as local myogenic) mechanisms to

cerebral autoregulation (Hamner and Tan, 2014). We note the general assumption that circulating vasoactive amines do not influence cerebral resistance vessels from the outside (i.e., from the lumen side) as they do not penetrate the blood-brain barrier. However, human cerebral arteries clearly demonstrate α and β receptors over the endothelial layer with almost the same density as that of the smooth muscle layer (Nakai et al., 1986). Both the adrenergic and cholinergic nerve terminals in the adventitia reach the superficial layer of the smooth muscle cells of the tunica media of the pial arteries, and approach the cell membrane (Owman et al., 1974), and even though most cerebral adrenergic terminals are located along the adventitia of pial arteries (Nelson and Rennels, 1970), noradrenaline, released from the terminals, directly affect the smooth muscle via adrenergic receptors, even if they were located at the inner most layer of vascular walls (Nakai et al., 1986; Sandor, 1999). Moreover, it is important to note that there are muscarinic receptors (M_2 and M_5 subtypes) known to be present on cerebrovascular endothelium itself (Elhousseiny et al., 1999), and M_5 receptors in particular are thought to mediate vasodilation in the cerebral circulation via perivascular acetylcholine release (Elhousseiny and Hamel, 2000). In fact, current evidence does indicate that circulating amines and analogues affect cerebral vascular tone (Purkayastha and Raven, 2011). Therefore, the data cited above provide evidence that both sympathetic and parasympathetic autonomic system play a clear role in cerebral autoregulation in humans.

4.2. Cerebral vasoreactivity

Available data on autonomic control of cerebral vasoreactivity is rather limited and inferential. During ganglionic blockade in humans, cerebrovascular reactivity is reported to increase by almost 50%, and changes in arterial pressure, and those in partial pressure of CO_2 , demonstrate a strong positive correlation that is absent prior to blockade (Jordan et al., 2000). These observations suggest that the sympathetic system may restrain cerebral blood flow responses to CO_2 (thus, cerebral vasoreactivity). This is also supported by earlier data from animals: Harper and Glass (Harper and Glass, 1965) lowered arterial pressure in dogs, by controlled hemorrhage, and reported a blunted cerebral vasoreactivity. Since lowered arterial pressure is expected to yield elevated sympathetic outflow, this result is consistent with a sympathetic restraint on CO_2 -mediated vasodilation. On the other hand, cerebral vasoreactivity remains unchanged in response to alpha-adrenergic agonist (ephedrine) (Moppett et al., 2004) or alpha/ beta-adrenergic antagonists (labetalol) (Schroeder et al., 1991). There are also reports that cerebral vasoreactivity may be diminished in individuals with Alzheimer's disease, a hallmark of which is cholinergic dysfunction (Di Marco et al., 2015). However, while there is evidence of autonomic (mostly sympathetic) dysfunction in mild to moderate Alzheimer's disease (Jensen-Dahm et al., 2015), it is not clear whether diminished cerebral vasoreactivity is related to impaired central and/or autonomic cholinergic/sympathetic dysfunction. Thus, the specifics of the role autonomic control plays in cerebral vasoreactivity remain largely unknown.

4.3. Neurovascular coupling

While autonomic control of the vasculature may also play a role in neurovascular coupling, the evidence for this role is equivocal. It is generally thought that increased intracellular calcium in astrocytes, in response to neural activity (Aguado et al., 2002; Cornell-Bell et al.,

1990), leads to the formation and release of vasoactive signals (e.g., nitric oxide, endothelin, prostaglandins) that can alter the regional vascular tone at the level of parenchymal arteries (Chisari et al., 2004; Fellin and Carmignoto, 2004; Zonta et al., 2003). However, the pial arteries operate as the main site of global flow control, as they exhibit the greatest resistance to flow. Evidence indicates that under normal circumstances, downstream functional hyperemia elicits vasodilation in upstream pial arteries (main targets of autonomic nerve fibers) via intramural vascular signaling, ensuring that pial and parenchymal vessels act in concert to meet metabolic demand (Dietrich et al., 1996). Thus, any impairment in autonomic mechanisms that regulate pial arterial responses may impact neurovascular responses, and vice versa. Indeed, some data suggest that neurovascular coupling may be impaired as a consequence of sustained hypertension (Calcinaghi et al., 2013), marked by peripheral sympathetic overactivity, which may lead to a reduced ability of pial vessels to dilate. Furthermore, one study demonstrated that neurovascular coupling in response to a visual task was impaired in individuals with autonomic dysfunction, and that it worsens during orthostatic stress in the same individuals (Azevedo et al., 2011). It should be noted, however, that neurovascular coupling in Parkinson's disease patients does not appear to be different from that in healthy control subjects, despite a ~30% lower peripheral acetylcholinesterase activity (Rosengarten et al., 2010), indicating that the potential autonomic mechanism is unlikely to involve cholinergic pathways. Thus, inferential evidence suggests that sympathetic, but not cholinergic autonomic control, may modulate neurovascular coupling, although there is no direct evidence.

While the autonomic nervous system plays a clear role in cerebral autoregulation, its involvement in cerebral vasoreactivity and neurovascular coupling remains equivocal. Inferential evidence does suggest that autonomic sympathetic, and perhaps to a lesser extent, cholinergic nervous control is involved in vasoreactivity and neurovascular coupling, but direct evidence is limited.

5. Cerebrovascular dysfunction in individuals with chronic SCI

5.1. Cerebral autoregulation

We have previously shown, in able-bodied individuals, that although local (e.g., myogenic) control may be the largest determinant of the arterial pressure - cerebral blood flow relationship, these locally-mediated effects occur mostly outside the arterial pressure range within which autoregulation is most active. That is, locally-mediated control of arterial pressure - cerebral blood flow relation is mostly effective in controlling what is commonly thought as the "pressure-passive" responses. This is in contrast to autonomic (especially sympathetic) influences, which are largely responsible for cerebral blood flow control in the pressure range of active autoregulation (Hamner and Tan, 2014).

Therefore, it is expected that after SCI, the disruption of sympathetic control of cerebral vasculature impairs cerebral autoregulation. In fact, inferential evidence based on the ability of cerebrovasculature to maintain blood flow in response to orthostatic challenge indicates involvement of sympathetic nervous control: in individuals with high thoracic (T5) or cervical injuries (C4-C7), cerebral blood flow appears to be compromised in the vertebrobasilar/posterior cerebral artery (Phillips et al., 2014a), but not in the middle

cerebral artery (Handrakis et al., 2009; Phillips et al., 2014a). This pattern parallels the pattern of sympathetic innervation of these two arterial beds: the former bed receives fibers largely from the stellate ganglion at C6–7 level, whereas the latter bed is innervated mostly by fibers arising from the superior cervical ganglion at the C2–3 level (see Section 2).

Unfortunately, there are only a few studies that directly explored the impact of SCI on cerebral autoregulatory function, and these studies provide equivocal results. Earlier research reported that long-term regulation of global cerebral perfusion is intact after SCI (in both tetra- and paraplegic patients) (Gonzalez et al., 1991), although regional cerebral autoregulation appears to be impaired after SCI to an extent that is related to the severity and level of injury (Yamamoto et al., 1980). Two more recent studies reported altered cerebral autoregulation after high-level cervical SCI, but their results are hard to reconcile.

Sahota et al. (Sahota et al., 2012) reported that transfer function gain relation (a measure of change in cerebral blood flow per unit change in arterial pressure; higher gain indicates less effective autoregulation) between spontaneous slow frequency (0.05–0.15 Hz) arterial pressure - cerebral blood flow fluctuations is approximately ~ 40% higher in individuals with SCI above T5 level compared to able-bodied controls, and that individuals with anatomically complete injuries show higher gain relations compared to those with incomplete injuries. Furthermore, the magnitude of difference in gain is consistent with the change in transfer function gain observed after sympathetic blockade in healthy individuals (Hamner et al., 2010). These observations indicate impaired cerebral autoregulation after SCI, possibly due to disrupted sympathetic control of cerebrovasculature.

On the other hand, Wilson et al. (Wilson et al., 2010) reported that coherence (a measure of how linearly the fluctuations in arterial pressure are transmitted to cerebral circulation; higher coherence indicates less effective autoregulation) between slow frequency (0.02–0.07 Hz) arterial pressure - cerebral blood flow fluctuations was significantly *lower* in individuals with cervical SCI compared to able-bodied controls, without any difference in gain relations. Lower coherence would seem to imply that cerebral autoregulation is *improved* after SCI. One might argue that this apparent improvement may be the result of the reciprocal relation between the effectiveness of cerebral autoregulatory and cardiac baroreflex function reported in able-bodied individuals (Tzeng et al., 2010). However, this relation appears to be fully absent in individuals with declines in both functions (e.g., due to advanced age) (Aengevaeren et al., 2013). Thus, while the mechanisms of impairment due to the natural aging process vs. SCI may be very different, there is no a priori reason to expect a reciprocal relation between baroreflex and autoregulatory function after SCI.

A more likely explanation for this apparent, counter-intuitive improvement in cerebral autoregulation, in contrast to Sahota et al. (Sahota et al., 2012), is the fact that both studies assessed cerebral autoregulation from short observations of spontaneous arterial pressure - flow fluctuations. Spontaneous arterial pressure fluctuations can be extremely inconsistent and small in amplitude (Taylor et al., 1998), and the resultant spontaneous flow fluctuations are likewise expected to be inconsistent. Noise inherent in any inconsistent fluctuation may have precluded reliable assessment of cerebral autoregulation (Tan and Taylor, 2014), potentially obscuring the difference between individual with SCI and able-bodied controls. It

should also be noted that the use of transfer function to assess arterial pressure - cerebral blood flow relation is not without its limitations. An in-depth discussion of these methodological limitations is beyond the scope of this review, and we refer the reader to other recent reviews (Tan and Taylor, 2014; Tzeng et al., 2012) for methodological considerations.

Thus, while inferential data from able-bodied individuals (Hamner and Tan, 2014) suggest that cerebral autoregulation would be impaired after SCI, due to the disruption (or elimination) of sympathetic control, available data remains inconclusive; cervical injury is reported to impair (Sahota et al., 2012), not affect (Gonzalez et al., 1991), or even improve (Wilson et al., 2010) cerebral autoregulation.

5.2. Cerebral vasoreactivity

As mentioned above, whether the autonomic nervous system plays a direct role in cerebral vasoreactivity remains largely unknown. However, loss of supraspinal autonomic control may impact vascular function and structure. For example, some evidence suggests chronic stiffening of arteries (Miyatani et al., 2009; Wecht et al., 2004) and diminished endothelial function below the level of injury after SCI (Stoner et al., 2006). Although these studies focused on the peripheral vasculature, there is no reason not to expect similar adaptations in cerebral vasculature when autonomic control is disrupted.

In one of the earliest studies to explore cerebrovascular function after SCI, Eidelman et al. (Eidelman et al., 1972) used ^{133}Xe to assess cortical blood flow responses to hypocapnia in individuals with cervical (C5-C7) injuries; individuals with thoracic (T2-T4) injuries were used as controls. They reported a lack of cerebral blood flow responses to hypocapnia in individuals with cervical SCI. Interestingly, cerebrovascular responses were intact in individuals with thoracic injuries. Since sympathetic innervation of cerebral vasculature originates from cervical ganglia (described in Section 2), this observation may provide some evidence, albeit inferential, for sympathetic involvement in cerebral vasoreactivity. However, this is contradicted by another study in baboons, which showed that α -adrenergic blockade does not impact vasoreactivity to hypocapnia (Hoff et al., 1972). While these two results appear to be at odds with each other, they show that although acute blockade of sympathetic outflow does not impact vasoreactivity, its chronic absence may. Thus, although speculative, these observations may support the possibility that structural adaptations in response to disruption in sympathetic control after SCI may impair cerebral vasoreactivity. In contrast, around the same time as Eidelman et al., Nanda et al. reported (Nanda et al., 1976) that cerebrovascular responses to hypocapnia do not differ between individuals with cervical injuries and able-bodied controls (and one patient with T2-3 lesion). The reasons underlying the discrepancy between these two studies remain unclear.

Almost 4 decades later, Wilson et al. (Wilson et al., 2010) assessed cerebral blood flow and cerebrovascular resistance in response to hypo- and hypercapnia (induced by hyperventilation and inspiration of 5% CO_2 , respectively) in individuals with cervical (C5-C7) injuries. They reported similar responses of cerebral blood flow velocity to CO_2 across the hypo- and hypercapnic range to those in able-bodied controls, suggesting that cerebral vasoreactivity is not impacted by high-level SCI. However, when vasoreactivity was

assessed as using cerebrovascular resistance (instead of blood flow velocity or vascular conductance), responses to hypocapnia, but not hypercapnia, were blunted (~30%) in individuals with SCI. Wilson et al. interpreted these discrepant results as reflective of “subtle differences with the modulation of [cerebral blood flow].” However, a more likely explanation of these results is a differential arterial pressure response to hypocapnia in individuals with high-level SCI. Individuals with SCI > T3 exhibit reduced lung volumes and flow rates due to the disruption of neural innervation of respiratory muscles. Subsequently, mechanics of ventilation are impaired, which may impact arterial pressure during hyperventilation. Even though the authors reported no significant differences in mean arterial pressure at the population level, any difference in arterial pressure, however small, would impact vascular resistance (arterial pressure over blood flow).

In summary, on one hand, an earlier study points towards an impairment in cerebral vasoreactivity to CO₂ with SCI that may potentially be due to structural vascular adaptations secondary to autonomic disruption. On the other hand, a more recent study appears to show no effect of SCI on cerebral vasoreactivity to CO₂, although its interpretation may be confounded by differential arterial pressure responses to hypocapnia. Thus, whether SCI impairs cerebral vasoreactivity remains unclear.

5.3. Neurovascular coupling

Most studies exploring the impact of SCI on cerebrovascular function do not probe neurovascular coupling. And those that do rely on different paradigms to engage neurovascular coupling, making it difficult to compare their observations.

It has been suggested that persistent hypotension subsequent to SCI (especially high-level injuries) may chronically reduce cerebral blood flow, resulting in blunted neurovascular coupling and cognitive performance. An early study supports this possibility. Jegede et al. (Jegede et al., 2010) explored the relation of memory, attention, and executive functions to arterial pressure in 20 individuals with low (< T2) and high (> C8) SCI. They reported that individuals who were hypotensive (defined as systolic blood pressure <100 mmHg for women and < 110 mmHg for men, without regard to diastolic blood pressure) had impairments in their memory, but not attention and executive function, and that 24-h systolic arterial pressure explained almost half of the variation in the memory function, even after accounting for group differences in age, level of injury, and depression score. However, conclusions of this study were also limited by the lack of cerebral blood flow measurements. Therefore, it remained unclear whether the apparent relation between hypotension and memory impairment was causal, or a parallel epiphenomena due to autonomic dysfunction (most of the hypotensive patients were those with cervical injuries).

In a follow-up study Wecht et al. (Wecht et al., 2012) reported that middle cerebral artery blood flow increased by ~ 4% in response to Stroop color task (a test of attention and cognitive flexibility) in able-bodied individuals, without any change in arterial pressure, but that this response was absent in individuals with SCI. This study also reported a modest, but statistically significant, inverse relation between task performance and the change in cerebrovascular resistance ($R^2 = 0.34$) in able-bodied individuals (but not in those with SCI). The authors interpreted this relation as suggestive of a contribution of cerebral vasodilation

to enhanced cognitive performance. Although plausible, this interpretation would imply that the impairment in cerebral blood flow responses may be due to the disruption of cholinergic cerebrovascular control, and contradicts the data suggesting that the potential autonomic mechanism underlying neurovascular coupling is unlikely to involve cholinergic pathways ((Rosengarten et al., 2010), described in Section 4). It is possible that the chronic stiffening of arteries (Miyatani et al., 2009; Wecht et al., 2004) and impaired endothelial function (Stoner et al., 2006), subsequent to loss of sympathetic control below the level of injury, may contribute to diminished vasodilatory capacity (thus, impaired neurovascular responses and cognitive function).

While the reasons for impaired neurovascular function and potential role of disruption in autonomic control remain unclear, both studies appear to indicate hypotension as the main culprit of impaired neurovascular function after SCI, rather than the inability of the cerebrovasculature to respond to acute increases in metabolic demand. To further test this possibility, Phillips et al. (Phillips et al., 2014b) explored middle and posterior cerebral artery flow responses to visual stimulation (magazine reading) and verbal fluency tasks in 10 individuals with SCI (C4-T5) and 10 able-bodied controls before and after elevating systemic arterial pressure via oral midodrine (an α_1 -adrenergic agonist) administration. They reported impaired neurovascular coupling in posterior, but not in middle cerebral artery territory in individuals with SCI, and that the responses in posterior, but not middle cerebral, artery were improved after midodrine administration. Phillips et al. interpreted the latter result to be a consequence of the former (i.e., neurovascular coupling in middle cerebral artery is maintained after SCI, and thus, elevated arterial pressure has little impact). One might argue that there can be no improvement in already normal (i.e., same as able-bodied controls) responses. This may be true. It is also important to note that the use of a sympathetic agonist to elevate arterial pressure may affect interpretation of this result. While some studies reported that midodrine does not bind to cerebrovascular adrenergic receptors due to the blood-brain barrier, evidence indicates that circulating amines and analogues affect cerebral vascular tone (reviewed in (Purkayastha and Raven, 2011); also see Cerebral Autoregulation under Section 4). In fact, we have shown that systemic administration of an α_1 -adrenergic antagonist does impact the cerebrovasculature without any impact on arterial pressure. Given the dense sympathetic innervation (thus adrenergic receptor distribution) in the anterior circulation (see Section 2), it is likely that while elevated arterial pressure may improve neurovascular responses to cognitive tasks, tonic stimulation of adrenergic receptors restrains the ability of cerebral vasculature to vasodilate, potentially blunting functional hyperemia, which may have been otherwise apparent.

Despite the differences in protocols to probe neurovascular coupling (memory tasks, Stroop test, magazine reading, verbal fluency), the limited data summarized above do suggest that neurovascular function is impaired after SCI. However, it remains unclear whether this impairment is due to chronic hypotension (“limited cerebrovascular reserve” (Phillips et al., 2014b)), disruption of sympathetic and/or cholinergic control (e.g., (Wecht et al., 2012)), structural alterations (e.g., arterial stiffening (Miyatani et al., 2009; Wecht et al., 2004)), or a combination of all three.

6. Summary and outlook

Prior data, from both animals and humans, demonstrate an important role for the sympathetic and parasympathetic autonomic system in cerebral autoregulation (the ability of cerebral vasculature to buffer against arterial pressure fluctuations). Whether autonomic control plays a role in cerebral vasoreactivity (the ability to respond to changes in blood gases) and neurovascular coupling (the ability to alter regional blood flow to meet metabolic demand), and the specifics of this role, remain largely unknown, although inferential evidence suggests a modulatory role for sympathetic control. Given that spinal cord injuries above T4 level can disrupt or eliminate sympathetic and - indirectly - parasympathetic control of cerebral vasculature, it is conceivable that SCI results in cerebrovascular dysfunction (see Fig. 1), and that this dysfunction may underlie elevated risk of stroke in this population.

Available evidence does indeed link cerebrovascular dysfunction to exacerbated risk of cerebrovascular disease and stroke. In a recent cross-sectional study in older individuals with vascular risk factors, Purkayastha et al. (Purkayastha et al., 2014) reported a relatively small, but statistically significant, relation between cerebral autoregulation, small vessel ischemia, and white matter structural integrity. In a ~2 year follow-up study, Yonas et al. (Yonas et al., 1993) reported an over 10-fold increase in incidence of ischemic stroke in individuals with compromised cerebrovascular reactivity (assessed based on the change in cerebral blood flow in response to acetazolamide administration). Consistent with this finding, a separate 2-year follow-up study with 94 patients with asymptomatic carotid artery disease, Silvestrini et al. (Silvestrini et al., 2000) reported a > 3-fold increase in incidence of ischemic stroke in patients who had impaired cerebrovascular reactivity. Given these evidence, there is a direct link between cerebrovascular dysfunction and the risk of cerebrovascular disease and stroke.

However, there are only a few studies that probed cerebrovascular function in patients with chronic SCI, and the data is equivocal. Available data show that (high-level) SCI may impair, not affect, or even improve cerebral autoregulation; that cerebral vasoreactivity to hyper-, but not hypocapnia may be blunted, possibly due to structural vascular adaptations secondary to autonomic disruption; and that neurovascular coupling is impaired, although it remains unknown whether this impairment is due to chronic hypotension, autonomic dysfunction, structural adaptations, or a combination of the three. Thus, the need for future research is clear.

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Fig. 1.

Schematic depiction of the key regulatory mechanisms of cerebral blood flow and the potential impact of SCI. Dark blue lines depict cerebral blood flow responses in able bodied individuals, and dark red lines depict potential responses in individuals with SCI, consequent to disruption in autonomic control of cerebral vasculature. Light red and light blue shaded areas indicate regions of over- and under-perfusion, respectively. Boxes designate hypothetical cognitive tasks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)