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1. Introduction

Acute spinal cord injury (SCI) is most commonly traumatic in origin but may also result from degenerative spine disease, ischemia, demyelination, inflammation, or rapidly expanding neoplastic, hemorrhagic, or pyogenic masses (Ghezzi et al, 2001). In the United States, traumatic SCI with or without bony injury has an annual incidence of 28 to 55 per million, with an average of 10,000 new cases a year and a prevalence of 200,000 (Sekhon & Fehlings, 2001). The average age at the time of injury is 32 years and the male/female ratio is 4:1. More than half (55%) of traumatic SCI involves the cervical cord. The most common causes of SCI are traffic accidents (motor vehicle, bicycle, pedestrian) (40%– 50%), assault (10%–25%), work-related injuries (10%–25%), and sports/recreation-related injuries (10%–25%) (Cheung et al, 2002; Surkhin et al, 2000). In traumatic cervical SCI, 3-month mortality is 20% to 21%. The independent predictors of mortality are level of cord injury, Glasgow Coma Scale, respiratory failure, and age. Principal causes of death are respiratory disorders, cardiovascular disorders, pulmonary embolism, infections, and suicide (Claxton et al, 1998; DeVivo et al, 1999, Yeo et al, 1998). Cardiovascular disorders are responsible for 40.5% of deaths, being the most common cause of mortality in patients with SCI (Garshick et al, 2005).

2. Cardiovascular instability

Cardiovascular instability is a frequent complication of SCI, especially when the upper thoracic or cervical cord is involved (Figure 1). Peripheral sympathetic denervation results in arteriolar dilation and pooling of blood in the venous compartment, while interruption of cardiac sympathetic innervation (T1–T4) promotes bradycardia (Figure 2) and reduces myocardial contractility. The autonomic nervous system modulates cardiac electrophysiology, and, consequently, autonomic dysfunction can lead to ventricular arrhythmias. Concomitantly, parasympathetic input to the heart (from the vagus nerve, cranial nerve [CN] X) remains intact and may frequently result in bradycardia, especially with cervical SCI. Less commonly, cardiac arrest has been documented. Bradycardia is often precipitated by tracheal stimulation (for example, during suctioning) and hypoxia (Mathias et al, 1976; Piepmeier et al, 1985). Reflex bradycardia and cardiac arrest occur due to a vago-vagal reflex. Under normal circumstances, this reflex is opposed by
sympathetic activity. As a compensatory response to hypoxia, a pulmonary–vagal reflex occurs, designed to increase respiratory rate and pulmonary inflation. However, in patients with SCI, compensatory sympathetic activity is eliminated, leaving parasympathetic activity unopposed, leading to severe bradycardia and potentially cardiac arrest. Studies of cardiovascular abnormalities after SCI show that as many as 100% of patients with motor complete cervical injuries (American Spinal Injury Association [ASIA] grades A and B) develop bradycardia, 68% are hypotensive, 35% require pressors, and 16% have primary cardiac arrest. Of persons with motor incomplete cervical injuries (ASIA grades C and D), 35-71% develop bradycardia, but few have hypotension or require pressors. Among patients with thoracolumbar injuries, 13-35% have bradycardia (Lehmann et al, 1987; Wirth et al, 2007). Bradycardia is more frequently encountered in the acute phase, and is more severe in the first 2-6 weeks after trauma (Krassioukov et al, 2007; McKinley et al, 2006). Cardiovascular dysfunctions improve in time. The reasons are not well understood, but synaptic reorganization or hyperresponsiveness of alpha receptors may play a role (Gondim et al, 2004).

Fig. 1. Spinal cord and level of injury.
Cardiovascular control in acute and chronic SCI has been investigated by measuring the response to a variety of cardiovascular markers (blood pressure, heart rate, and plasma levels of norepinephrine and epinephrine) before, during and after application of noxious stimuli below the level of the lesion. In acute SCI, noxious stimuli (e.g., bladder stimulation) caused minimal changes in heart rate and plasma norepinephrine and epinephrine levels. In chronic SCI, noxious stimuli induced bradycardia and elevation in plasma norepinephrine but not in epinephrine levels. Resting plasma norepinephrine and epinephrine levels in both the acute and chronic SCI were lower than in normal subjects (Mathias et al., 1979).

The tilt test has been used to evaluate and delineate alterations in sympathetic cardiovascular compensation, which reflect the degree of autonomic dysfunction. Autonomic and cardiovascular responses to tilt test are blunted in persons with quadriplegia or paraplegia (Welch et al., 2005). Such tests could be used to noninvasively assess autonomic dysfunction in persons with SCI, determine the degree of sympathetic disruption, and assess the risk of developing cardiac arrhythmias, especially bradycardia. However, there are very few studies on these bedside tests upon which to solidly base conclusions and recommendations.

3. Treatment

3.1 Pharmacotherapy

Although bradycardia after cervical SCI usually resolves within 6 to 8 weeks after injury, it may progress to complete heart block and cardiac arrest. As such, the acute management and maintenance of cardiovascular stability in these patients may range from a practical clinical chore to a potentially lifesaving responsibility. There is limited data available regarding the optimal and best treatment available for symptomatic bradycardia in this patient population (Table 1). All data on therapeutic management of bradycardia secondary to cervical spinal cord injury is based on case reports, case series and observational studies.

Atropine, an anticholinergic agent, is generally recommended as the first-line agent for bradycardia after cervical spinal cord injury. Atropine improves conduction through the atrioventricular (AV) node by reducing vagal tone through muscarinic receptor blockade. The dose ranges from 0.4 to 0.6 mg, administered intravenously every 4 hours for short-term therapy (Abd & Braun, 1989; Pansoori & Leesar, 2004; Piepmeier et al., 1985; Sadaka et al., 1979).
2010; Sakamoto et al, 2007; Schulz-Stubner, 2005; Weant et al, 2007; Whitman et al, 2008; Winslow et al, 1986). Atropine should be kept readily available at the bedside at all times with this patient population, as acute episodes of bradycardia and hypotension may occur suddenly and without warning in the immediate few hours and days following injury.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Route of administration</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>IV</td>
<td>reduces vagal tone by muscarinic receptor blockade</td>
</tr>
<tr>
<td>Dopamine</td>
<td>IV infusion</td>
<td>Beta\textsubscript{1} receptors on the heart</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>IV infusion</td>
<td>Beta\textsubscript{1} receptors on the heart</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>IV</td>
<td>inhibition of PDE enzyme thus increasing c-AMP with subsequent rise in catecholamines</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Enteral or parenteral</td>
<td>inhibition of PDE enzyme thus increasing c-AMP with subsequent rise in catecholamines</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Enteral</td>
<td>postganglionic parasympathetic acetylcholine receptor blocker</td>
</tr>
<tr>
<td>Permanent Pacemaker</td>
<td>invasive</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Therapeutic modalities for bradycardia secondary to cervical SCI.

Another frequently utilized category of intravenous medications includes sympathomimetic agents such as Dopamine or Epinephrine which increase heart rate through action on Beta\textsubscript{1} receptors in the heart. Continuous infusions of dopamine at a rate of 2 to 10 mcg/kg/min or epinephrine at a rate of 0.01 to 0.1 mcg/kg/min has been used in the acute setting (Abd & Braun, 1989; Piepmeier et al, 1985; Sadaka et al, 2010; Winslow et al, 1986). Complications include tachyarrhythmias, angina pain, palpitations, vasoconstriction, nausea, vomiting and headache.

When intermittent boluses of atropine or continuous infusions of sympathomimetic drugs have failed to prevent recurrent symptomatic bradycardia, or reverse high or complete heart block, permanent pacemaker placement has often been used as the next therapeutic alternative (Franga et al, 2006; Ruiz-Arango et al, 2006). Cardiac pacemaker implantation is advocated for patients with high cervical spinal cord injuries with persistent bradycardia.
not responding to medical management (Giloff et al, 1991). However, specific criteria for placement of a pacemaker are not well defined. The reported number of SCI patients requiring a pacemaker varies from 9 to 17% (Abd & Braun, 1989; Lehmann et al, 1987). Complications of permanent pacemakers include infection, lead malfunction, death during attempted insertion, and death associated with failure to capture. The methylxanthine agents, including aminophylline and theophylline, have been used effectively for the management of refractory symptomatic bradycardia when other agents have failed (Pansoori & Leesar, 2004; Sadaka et al, 2010; Sakamoto et al, 2007; Schulz-Stubner, 2005; Weant et al, 2007; Whitman et al, 2008). In addition, there are recent reports of methylxanthines used specifically as a successful first line treatment for bradycardia associated with cervical spinal cord injury. None of the patients in the case series needed a pacemaker placement and none of the patients developed drug related side effects (Sadaka et al, 2010). The proposed mechanism for the chronotropic effect of these drugs is via inhibition of phosphodiesterase (PDE) enzyme thus increasing the cyclic adenosine monophosphate with subsequent rise in catecholamines. A clear benefit of these agents is that they may be administered on a fixed schedule as an enteral preparation. An oral (or intravenous) loading dose between 200 and 300 mg was administered in most cases with maintenance doses starting at 100 mg three times daily and continued for up to 12 weeks. Drug serum levels were variable and differed widely among patients. The effective dose of theophylline resulted in serum levels that were below the therapeutic range defined in the literature (10-20 mcg/ml), and of course below the toxic range (>25 mcg/ml). Since no therapeutic index for symptomatic bradycardia has been established, the methylxanthine dose was titrated according to clinical response. The main side effects of these agents are nausea, vomiting, tremor, headache, and seizures. However, no adverse effects were noted in any of the reports. Nonetheless, until more experience is gained with this modality, careful attention should be made to monitor drug levels and avoid toxicity. Methylxanthine has also been associated with diaphragmatic strengthening in animal models, another potential beneficial effect to consider in spinal cord injury patients (Whitman et al, 2008).

In patients requiring long-term therapy, there are case reports of successful treatment with propantheline 7.5 to 30 mg every 4 to 6 hours (Abd & Braun, 1989; Winslow et al, 1986). Propantheline competitively blocks the action of acetylcholine at postganglionic parasympathetic receptors. The main side effect reported from chronic propantheline therapy is a reduction in gastrointestinal motility due to its anticholinergic effects.

3.2 Anticipation, prevention & positioning

Bradycardia and potential for cardiac arrest should be anticipated in any patient with spinal cord injury. Bedside care providers should be alerted to the fact that life threatening events occur more frequently with high spinal cord lesions. Personnel should anticipate and document triggers for serious bradycardic episodes. Hyperoxygenation and ambu “bagging” may be helpful prior to tracheal suctioning. Prophylactic atropine administration before tracheal suction, laryngoscopy, or oral intubation has been shown to minimize severity of events (Frankel et al, 1974; Mathias, 1976;Welphy et al, 1975). Theophylline may also be started at the first indication of bradycardia. Particular attention should be paid to other potential exacerbating factors, including rapid changes in positioning, prolonged recumbency, drug adverse effects, underlying infection, and hypovolemia.
Before moving the patient out of supine position, abdominal binder, thigh-high stockings, and elastic bandages to the lower extremities can be applied. These measures decrease venous pooling in the lower extremities and splanchnic vasculature. The patient can be moved slowly, from a supine position to a relatively upright position. A tilt table can be used to slowly bring the patient to the upright position.

3.3 Rehabilitation measures
Active arm exercises can be used to maintain blood pressure while the patient is on the tilt table (Mckinley et al, 2006). Bilaterally functional electric stimulation to lower-limb muscles, quadriceps, hamstrings, tibialis anterior and gastrocnemius during tilting improves orthostatic tolerance in patients with cervical SCI. Functional electric muscle stimulation during tilting maneuver, significantly increases heart rate (Chao et al, 2005).

4. Conclusion
Spinal cord injury is a very common and devastating disease process that can occur as a consequence of motor vehicle collisions, falls or other traumatic injuries. Cardiac disorders are common consequences following SCI. Cardiovascular disturbances are the leading causes of morbidity and mortality in both acute and chronic phases of SCI. Disruption of descendent pathways from superior centers to spinal sympathetic neurons, originating into the intermediolateral nuclei of T1-L2 spinal cord segments results in a reduced overall sympathetic activity and unopposed parasympathetic activity. As a result, the most common cardiac dysrrhythmia is bradycardia. There are a few well established therapeutic modalities (Table 1) for the treatment of bradycardia associated with cervical SCI. All therapeutic options are based on anecdotal reports and small retrospective reviews. Atropine should be kept readily available at the bedside at all times. Based on recent evidence with methylxanthines, we recommend further studies to establish the role of these agents as a first line therapy in this specific patient population. Optimal dose and duration of therapy need to be established. Theophylline’s use via entral route as a first line therapy for spinal cord injury-related bradycardia can help avoid the long term use of inotropic and chronotropic infusions and their associated risks and complications, as well as prevent and/or decrease the use of cardiac pacemaker placement and its associated procedural risks and complications. We further recommend the study of xanthine derivate as prophylactic treatment for the first 2-6 weeks of the injury based on the frequency of bradycardia in patients with cervical SCI which is reported to be 100%. Currently, there are no established guidelines regarding permanent pacemaker placement in this patient population. Permanent pacemaker should still be considered in patients with refractory or recurrent bradycardia more than two weeks after the injury. In addition, the incidence of bradycardia after cervical SCI may be decreased by proper prophylactic measures, cardiac exercises and appropriate rehabilitation.

5. References

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Piepmeier JM, Lehmann KB, & Lane JG. Cardiovascular instability following acute cervical spinal cord trauma. Cent Nerv Syst Trauma. 1985; 2(3):153-60.


The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographic features, ion channel alterations, heart diseases still unknown, and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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