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PERSPECTIVE

A potential widespread and important role for sleep-disordered breathing in pressure injury development and delayed healing among those with spinal cord injury

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Abstract

Soft tissue pressure injuries commonly occur in those with spinal cord injury. They add an immeasurable medical, emotional, and social burden to those who suffer a spinal cord injury and ultimately can cause death due to sepsis when they ulcerate and become infected. Hence it is notable that (i) obstructive sleep apnea and other forms of sleep-disordered breathing are highly prevalent among those with spinal cord injury; (ii) several of the pathophysiologic consequences of sleep-disordered breathing, including hypoxemia, ischemia, oxidative stress, and endothelial dysfunction, would be expected to increase susceptibility to pressure injuries, worsen their severity, and slow or prevent their healing; and (iii) there is emerging clinical evidence that sleep-disordered breathing can have a significant role in the pathogenesis of other types of chronic wounds and that treatment of sleep-disordered breathing can aid in the healing of these wounds. These findings raise the possibility that sleep-disordered breathing may have a widespread and important role in the development, severity, and persistence of pressure injuries in those with spinal cord injury and that treatment of sleep-disordered breathing may be an effective adjunct in their prevention and healing. Studies to determine if there is a functional relationship between sleep-disordered breathing and pressure injuries in individuals with spinal cord injury are warranted.

The development of a pressure injury is initiated when external pressure on the skin compresses the underlying capillaries and compromises perfusion for a sufficient duration to cause ischemic injury in the surrounding soft tissue. This most readily occurs in soft tissue overlying bony prominences because the unyielding resistance provided by bone increases the compressive effects of the external pressure. Both the intensity and duration of the pressure are determinants of extent of the initial ischemic injury. Shear forces generated by the sliding of underlying tissue layers when the skin is held in fixed position by external friction augment the ischemic effect of the compressive forces by stretching and thereby narrowing blood vessels that are parallel to the skin surface and bending, torquing, and pinching blood vessels that are perpendicular to the skin surface [1]. In addition, whenever the external pressure is relieved after a period of tissue ischemia, the resulting restoration of blood flow causes hypoxia–reoxygenation injury, in which reactive oxygen species generated by the reoxygenation of hypoxic tissue react with various biomolecules causing oxidative tissue injury [2]. The ischemic and oxidative injuries together cause the soft tissue necrosis that manifests clinically as an ulcerated pressure injury.

Several comorbid conditions such as obesity, tobacco use, vascular occlusive disease, hypotension, malnutrition, diabetes, and anemia, are thought to increase susceptibility to pressure injuries or delay their healing through a variety of mechanisms [3]. For example, vascular occlusive disease decreases perfusion, which adds to the ischemic effects of soft tissue compression and shear; a deficiency of a required nutrient can delay or prevent pressure injury healing; and anemia can exacerbate the hypoxic tissue injury that occurs secondary to decreased tissue perfusion.

A condition that has not been generally recognized as having a role in pressure injuries among individuals with spinal cord injury is sleep-disordered breathing. However,

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sleep-disordered breathing is highly prevalent among those with spinal cord injury and it has several pathophysiologic consequences that would be expected to increase susceptibility to, worsen the severity of, and delay or prevent the healing of pressure injuries.

The prevalence of sleep-disordered breathing among those with spinal cord injury ranges from 27 to 82%, depending upon the diagnostic method and criteria used. The prevalence varies depending on the level and completeness of the lesion with 93% of individuals who have a neurologically complete cervical spinal cord injury suffering from sleep-disordered breathing. The high prevalence of sleep-disordered breathing in spinal cord injury has been attributed to many factors, including a high rate of obesity, neuromuscular weakness, abnormal chest wall mechanics, impaired cough, altered genioglossus reflex, and airway edema due to the cephalad shift of lower extremity stasis fluid that occurs in the supine position, and the widespread use of antispasticity medications that depress the respiratory drive [4].

Sleep-disordered breathing has several acute effects that could have a role in pressure injuries. The hypoxemia that occurs secondary to apneas and hypopneas could worsen the soft tissue hypoxic effects of pressure and shear. The increase in negative intrathoracic pressure generated by inspiration against a partially or completely collapsed upper airway (i.e., analogous to Muller's maneuver) in obstructive sleep apnea alters cardiac filling and left ventricular afterload in a manner that decreases cardiac output [5]. This could worsen the decrease in soft tissue perfusion that is brought about by pressure and sheer. In addition, because it increases sympathetic activity, sleep-disordered breathing causes vasoconstriction [5], which could further compromise soft tissue perfusion. The hypoxemia and decreased perfusion that occur as a consequence of sleep-disordered breathing could clearly increase susceptibility to pressure- and shear-induced soft tissue injury, increase pressure injury severity, and delay or prevent healing.

With the return of normal respiration between apneic and hypopneic events, the tissue reoxygenation that occurs can generate a level of reactive oxygen species that exceeds the antioxidant capacity, a condition referred to as oxidative stress. The excess reactive oxygen species can damage lipids, carbohydrates, proteins, and nucleic acids [6]. The repetitive hypoxia/reoxygenation cycles that occur in sleep-disordered breathing can therefore cause oxidative injury that adds to the ischemic and oxidative soft tissue injury induced by pressure and shear forces. In this context it is notable that ongoing oxidative stress is thought to be an etiologic feature of chronic pressure injuries [2]. It is possible that the oxidative stress that occurs as a consequence of sleep-disordered breathing slows or prevents healing of certain pressure injuries.

If blood vessels are compressed and distorted by external pressure and shear forces to an extent that causes ischemia of the surrounding soft tissue, as occurs during pressure injury development, subsequent relief of the pressure and shear would normally induce endothelium-dependent vasodilation. This results in tissue hyperemia that serves to limit soft tissue ischemic injury. Endothelium-dependent vasodilation is mediated by the release of the potent vasodilator nitric oxide from vascular endothelial cells. In those with severe sleep-disordered breathing, however, the reactive oxygen species generated by the hypoxia/reoxygenation cycles are thought to decrease nitric oxide levels, impairing endothelium-dependent vasodilation [7]. Therefore, the degree of tissue hyperemia that occurs upon relief of external pressure and shear may be blunted in those with sleep-disordered breathing, which could delay the resolution of pressure- and shear-induced ischemia. This would result in increased ischemic injury during pressure injury development.

An increase in systemic inflammatory markers has been thought to be associated with sleep-disordered breathing [8]. This is notable because protracted excessive inflammation disrupts wound healing [9] and therefore could be another functional link between sleep-disordered breathing and chronic pressure injuries. However, a relationship between sleep-disordered breathing and increased systemic inflammation has not been a consistent finding [8], so its potential to have a role in mediating an effect of sleep-disordered breathing on pressure injuries is unclear. Nevertheless, it has been proposed that increased systemic inflammation may occur in a subset of the individuals who suffer from sleep-disordered breathing [8].

It is important to point out that the pathophysiologic consequences of sleep-disordered breathing outlined above are derived from findings in nonspinal cord injured individuals. Whether these findings can be extrapolated to those with spinal cord injury is unknown as there has been a paucity of research on the effects of sleep-disordered breathing in those with spinal cord injury. It is conceivable that the pathophysiologic consequences of sleep-disordered breathing are altered by the effects of spinal cord injury. For example, the increase in negative intrathoracic pressure that occurs during apneic episodes in nonspinal cord injured may be limited by neuromuscular respiratory weakness in those with spinal cord injury, which would lessen or prevent the fall in cardiac output that occurs during obstructive apneic events. These same individuals, however, may suffer from poor respiratory mechanics and increased airway collapsibility, which could worsen the severity of apneic events and disruption in gas exchange. Similarly, those with spinal cord injury frequently suffer sympathetic nervous system impairment (typically those with lesions at T6 or higher), which could

decrease the vasoconstrictive effects of sleep-disordered breathing. On the other hand, many of these individuals suffer from hypotension, which could exacerbate the tissue hypoxia that results from sleep-disordered breathing. The balance and importance of each of these and other effects of spinal cord injury in altering the pathophysiologic consequences of sleep-disordered breathing is unknown.

The findings outlined above raise the possibility of a widespread functional role of sleep-disordered breathing in pressure injury development and persistence in individuals with spinal cord injury. The two other major categories of chronic wounds, diabetic and venous, share several underlying pathophysiologic features with pressure injuries that can occur as a consequence of sleep-disordered breathing [10]. Therefore, it should not be surprising that there is emerging clinical evidence for a role of sleep-disordered breathing in chronic wound development and persistence in general.

First, it was found that among individuals with non-healing lower extremity wounds who attended a chronic wound clinic, the prevalence of moderate or severe obstructive sleep apnea was 57%. This is 5.7–11.4-fold higher than the prevalence of obstructive sleep apnea in the general population. When those who had mild obstructive sleep apnea were included, the prevalence was 82% [11]. Conversely, among a group of individuals with type 2 diabetes, when a logistic regression analysis was performed in which obstructive sleep apnea, age, gender, ethnicity, presence of peripheral vascular disease, BMI, HbA1c, diabetes duration, and insulin treatment were the independent variables and a history of having had a diabetic foot ulcer was the dependent variable, it was found that having obstructive sleep apnea predicted a markedly increased risk of a history of diabetic foot ulcer (OR 3.34, 95% CI 1.19–9.38, $p = 0.022$) [12]. These findings are consistent with a role for sleep-disordered breathing in the pathogenesis of chronic wounds.

Indeed, in a prospective study of 94 patients with diabetic foot ulcers, a positive result on validated sleep apnea assessment tool predicted a more than twofold increase in risk of poor ulcer healing. This finding was independent of other risk factors for poor healing [13].

Finally, in a case series of three patients with diabetic foot ulcers that failed to heal despite optimal wound care who were found to also have severe obstructive sleep apnea, two agreed to treatment for obstructive sleep apnea with continuous positive airway pressure (CPAP). The wounds of the two who used CPAP healed, while there was no improvement of the wound of the third. Below the knee amputation had been considered for one of the patients who used CPAP; strikingly, however, their wound rapidly vitalized and showed significant granulation within 96 h of initiation of CPAP treatment and amputation was avoided. In the second patient who used CPAP, "a remarkable improvement was noted in ulcer quality and speed of granulation" [14].

Hence, there is both biologic plausibility and emerging clinical evidence that sleep-disordered breathing is a risk factor that can contribute to the development and persistence of pressure injuries. Because sleep-disordered breathing is highly prevalent among those with spinal cord injury, its effects may be widespread. If treatment of sleep-disordered breathing is truly effective in preventing and aiding the healing of pressure injuries, it will also decrease their complications, which include pain, cellulitis, abscess formation, osteomyelitis, the need for amputation, sepsis, death, the psychological and social stresses they cause, and their societal costs. Studies to determine if sleep-disordered breathing has a functional role in pressure injury development, severity, and delayed healing should be pursued.

Author contributions SJW conceived the work; SJW and SXC drafted and revised the paper, approved the final version and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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