# Orthostatic Blood Pressure and Arterial Stiffness in Persons with Spinal Cord Injury: The Effect of the Renin-Angiotensin-Aldosterone System

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## ABSTRACT:

**Background:** Approximately 17,000 new spinal cord injury (SCI) occur each year in the United States. With advances in acute medical care, longevity has increased in persons with SCI; however, morbidity due to cardiovascular disease (CVD) occurs at an earlier age compared to the general population. Additionally, individuals with chronic SCI are at a heightened risk of CVD due to autonomic nervous system (ANS), physical inactivity and increased inflammatory processes. Arterial stiffness (AS) is recognized as an independent risk factor for CVD, and pulse wave velocity (PWV) has proven to be a valid tool to predict and track structural arterial changes that reflect arteriosclerosis. In persons with SCI an increase in AS has been noted when compared to the uninjured population; however, possible contributors to this increase are not yet fully understood.

After a SCI, sympathetic control in the regions below the lesion level are severely disrupted; however, parasympathetic function is preserved. Due to the dissociation between the two systems, those with lesions above T6 experience low resting BP and further decreases in BP when changing postures (OH). Decreased plasma norepinephrine (NE) has been noted in individuals with cervical lesions when compared to individuals with thoracic injuries and controls. Additionally, lower levels of NE have been found to be associated with an increased incidence of OH in persons with SCI. As a consequence, individuals with high-level injuries have a heightened reliance on RAAS to maintain and stabilize BP.

A mechanism for increased AS in the uninjured population is over activation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II (ANG II), a hormone produced through RAAS, modulates vascular stiffness by reducing elastin, promotes collagen formation and increases oxidative stress. Due to decentralized cardiovascular autonomic control, individuals with SCI have a heightened reliance on RAAS to maintain and stabilize blood pressure (BP), especially during an orthostatic challenge. **Participants:** A total of 33 subjects, 22 individuals with SCI and 11 age-matched uninjured controls. **Objectives:** To study the hazardous effects of a highly activated RAAS on vasculature, the participant will be placed on a tilt table in the supine position and progressively tilted (30º, 45 º and 60 º for 10 minutes at each angle of tilt). PWV will be measured during supine and hormonal assessments (active plasma renin) will be assessed at supine and 60 degree tilt to determine if RAAS specific hormones contribute to increased AS in each cohort. The study aims are: 1) To investigate the influence of orthostatic change of BP and NE responses to orthostasis; and 2) To determine if increased reliance on the RAAS for orthostatic BP regulation contributes to differences in supine AS in individuals with SCI.

## SPECIFIC AIMS:

**Aim 1:** ***To investigate the influence of orthostatic change in BP on plasma renin responses to HUT.***

***Hypothesis 1A:*** There will be an inverse relationship between the change in BP and change in plasma renin from supine rest to 60°HUT in individuals with high-level SCI.

***Hypothesis 1B:*** There will be no relationship between the change in BP and change in plasma renin from supine rest to 60° HUT in persons with low-level SCI and uninjured controls.

**Aim 2:** ***To investigate the influence of orthostatic change in BP and NE on the RAAS responses to HUT.***

***Hypothesis 2A:*** There will be a linear relationship between the change in orthostatic BP and change in plasma NE concentration from supine rest to 60° HUT.

***Hypothesis 2B:*** Plasma renin activity will be inversely related to plasma NE concentrations during HUT in persons with SCI.

**Aim 3:** ***To determine if increased reliance on the RAAS for orthostatic BP regulation contributes to differences in supine AS.***

***Hypothesis 3A:*** There will be significant group differences for change in plasma renin during HUT, in that plasma renin will be significantly increased during HUT in participants with high-level SCI, but will remain unchanged in individuals with low-level SCI and uninjured controls.

***Hypothesis 3B:*** Change in plasma renin during the HUT maneuver will be directly associated with supine PWV in individuals with high-level SCI.

***Hypothesis 3C:*** There will be no relationship between the change in plasma renin during the HUT maneuver and supine PWV in persons with low-level SCI and uninjured controls.

## REVIEW OF LITERATURE:

After a SCI, descending sympathetic preganglionlic neurons are disrupted causing loss of supraspinal regulation of cardiovascular function[1, 2],which results in numerous clinical issues. The level of the spinal lesion greatly influences the amount of cardiovascular regulation dysfunction after SCI. In individuals with injuries below T6, the sympathetic and parasympathetic control of the heart and splanchnic bed are intact, both of which are essential for short- and long- term BP regulation [2]. On the other hand, individuals with higher-level injuries, the parasympathetic control remains integral, while sympathetic autonomic control is lost (Krasioukov, 2009). This results in persistent hypotension and severe drops in BP when moving to the upright position (OH) [1, 3-7].

OH has a higher prevalence in individuals with cervical compared to individuals with thoracic lesions, irrespective of whether their lesion was complete or incomplete[8, 9]. According to a Consensus statement from the American Autonomic Society and American Academy of Neurology, OH is defined as a decrease in systolic BP (SBP) of 20+ mmHg and/or a fall in diastolic BP (DBP) of 10+ mmHg within 3-minutes of moving from supine to the upright position, with or without symptoms [10]. Interestingly, decreased plasma NE has been noted in individuals with cervical lesions when compared to individuals with thoracic injuries and controls [11-14]; and furthermore, there was no significant increase in NE level when individuals with tetraplegia underwent HUT [15, 16]. Additionally, lower levels of NE have been found to be associated with an increased incidence of OH in persons with SCI [17]. Individuals with

lesions below the cervical spine have normal to high levels of plasma NE concentrations [13, 14]and, as a result, are less prone to hypotension and OH [3, 18, 19].

Additionally, OH after SCI is thought to be largely related to inability to centrally regulate vascular tone [20]. The loss of the reflex vasoconstriction of the splanchnic bed and lower extremity vasculature results in venous blood pooling, which results in reduced blood volume in end-diastolic volume, leading to a decrease in cardiac output and left ventricular stroke volume [21]. In addition, due to paralysis of the lower extremities and physical inactivity, persons with SCI lose their ability to use skeletal muscle pump by activating muscle contraction. Individuals with paraplegia and uninjured controls demonstrated increased total peripheral resistance during a head-up tilt(HUT) compared to cervical injuries [22]. This suggests that the SNS was increased in controls and individuals with low-level injuries because they were able toincrease venous return in order to maintain BP.

Although many individuals with SCI demonstrate OH, symptoms associated with OH decrease over time (light-headedness, blurred vision, fatigue, weakness, etc.) [19]. Evidence demonstrates that increased dependency on the RAAS is believed to play an integral part in reducing the severity of postural hypotension and the associated symptoms [12, 16, 19, 23, 24]. Renin was shown to increase in individuals with tetraplegia during HUT, an orthostatic challenge, at a much quicker and higher rise compared to individuals with thoracic injuries and uninjured controls [12, 23, 25].

The RAAS plays an essential role in maintaining long-term BP and is an enzymatic cascade in which renin is released into the blood and acts on angiotensinogen to form angiotensin I, which forms ANG II by the angiotensin converting enzyme (ACE) [26, 27]. Despite the important benefits of the RAAS in regulating BP homeostasis, recent evidence that chronic overproduction of this system may result in remodeling and restructuring of peripheral and coronary blood vessels by augmenting the generation of reactive oxygen species, [28, 29], accompanied by an increase in oxidative stress, and production of inflammation, thrombosis and fibrosis [28]. Recent evidence has demonstrated that the use of ACE inhibitors or ANG II receptor blockers (ARBs) reduce vascular remodeling [30-32], and diminish collagen production and increase the elastin to collagen ratio [31]. A meta-analysis demonstrated that the use of ARBs and ACE inhibitors decreased the risk of myocardial infarction, stroke, cardiovascular mortality and total mortality in uninjured subjects [33], suggesting that the excessive ANG II production may lead to an increased risk of CVD.

AS has been identified as an independent risk factor for CVD [31, 34, 35] and PWV is considered to be the gold standard measurement because of its high reliability and validity [36]. Increased AS has been documented in individuals with SCI compared to age-matched uninjured controls [2, 37-41], even after matching for age, body composition and activity level [20]. It is well appreciated that the increase in AS is due to the natural aging process [42], however, we recently reported that AS was not associated with age in the SCI population, suggesting premature cardiovascular dysfunction in persons with SCI [41].

Additionally, there is evidence supporting a direct linear association between AS and LOI, with AS increasing with ascending LOI [41]. In this same study, we reported that individuals with increased AS reported experiencing OH [41], because OH may cause structural vascular adaptations secondary to persistence and episodic hypotension [43]. Interestingly, our team recently demonstrated that there was significant inverse relationship between seated SBP and AS [41]; and furthermore, Wecht et al. (2005) demonstrated that anti-hypotensive agents (Midodrine and L-NAME) reduced orthostatic dependency on the RAAS because plasma renin

and serum aldosterone levels were comparable with baseline levels. We speculate that this may be related to a reliance on RAAS for orthostatic BP maintenance, which may have detrimental effects on AS[24]. Groothuis et al. (2010) demonstrated that ANG II contributed to increased supine leg vascular resistance in individuals with thoracic injuries (T4-T12), but did not contribute to AS in controls[44]. Although increased AS has been reported in individuals with SCI, controversy abounds and additional evidence is needed to gain a better understanding of impact of morphologic and physiologic vascular adaptations that occur following SCI on orthostatic BP regulation and AS.

## SIGNIFICANCE OF RESEARCH:

Evidence has shown that PWV is increased 2-3 m/s in persons with SCI compared to able-bodied individuals [45, 46] which corresponds a staggering 40 year acceleration of age-related cardiovascular decline[47]. Evidence of causality suggests that decreases in AS, subsequent to administration of ARBs or ACE inhibitors, reduced vascular remodeling and decreased the risk of myocardioal infarction, stroke and cardiovascular mortality in the uninjured population [33]. Additionally, the effects of OH on AS have not been studied in the SCI population, even though, persistent and episodic OH have been associated with elevated risk of stroke and cognitive deficits, including memory, processing speed and executive function in the uninjured population[48-51]. Documenting the impact of the RAAS on AS in the SCI population, will provide a necessary step in initiating a change in clinical treatment of hypotension and OH, which may lead to improved regulation and preservation of cardiovascular health and longevity.

## RESEARCH DESIGN &METHODOLOGY:

***Subjects***– 22 individuals with SCI and 11 age-matched non-SCI controls will be recruited for eligibility to participate in the study. Individuals with SCI will be recruited from the Northern New Jersey SCI Model (NNJSCIS) System database, which contains over 1000 people with traumatic SCI. The control subjects will be recruited from prior study enrollment at Kessler Foundation and hospital personnel.

**Inclusion Criteria**:

- All subjects:
  - Between ages 21 and 70 years old.
- Additional Inclusion Criteria: SCI subjects:
  - Traumatic injury,
  - High-level injury: C1-T1 and Low-level injury: T6-T12,
  - Non-ambulatory,
  - American Spinal Injury Association Injury Scale (AIS) A, B or C,
  - 1+ year(s) post injury.

**Exclusion Criteria**:

- Acute illness or infection,
- Current smokers within 1 year,
- Documented history of controlled or uncontrolled hypertension or diabetes,
- Any other neurological condition other than a SCI (multiple sclerosis, Parkinson's disease),
- CVD (coronary heart disease, congestive heart failure, peripheral artery disease, stroke).

**Procedure:** All subjects will be asked to visit the Kessler Foundation (KF) laboratory for 1 day of testing. The study will take about 3 hours to complete per subject. Subjects will be asked to arrive between 8:00 am and noon at the KF testing facility after a normal breakfast and a good night sleep. Subjects will remain seated for 5-minute hemodynamic assessment. After, subjects will be transferred to the tilt table to lay supine for 10 minutes prior to another 5-minute hemodynamic assessment. Arterial stiffness, renin and NE will be collected in the supine position. Subjects will then be progressively tilted to 30°, 45° and 60 ° for 10 minutes at each angle and 5 minutes of hemodynamic assessments will be measured at each angle. At 60 °, renin and NE will be collected.

- *Cardiovascular Assessments*: While the subject is seated 3 ECG electrodes will be affixed to the chest and abdomen for continuous monitoring of HR and respiration rate (RR). Brachial BP will be monitored at 1 minute intervals using a standard adult BP cuff placed at the right upper arm, and beat-to-beat finger arteriolar BP will be continuously monitored from the right middle finger throughout testing. MAP (mmHg) will be calculated from brachial BP using the formula: [systolic BP + (2 X diastolic BP)]/3. Beat-to-beat HR, RR and BP data will be viewed in real-time and stored for subsequent analysis using customized programs created with LabView graphical software.
- *Arterial Stiffness:* aPWV (aortic pulse wave velocity) will be measured using the SphygmoCor CPV system (AtCor Medical Pty Ltd., West Ryde, NSW., Australia) at the carotid and femoral sites measured from the participant's supra-sternal notch to each artery. The aPWV measurement will be taken in two steps: a tonometry reading of site A (carotid artery) with an ECG signal simultaneously recorded captured after 10 seconds of good data, followed by a 10 second reading of site B (femoral artery) with an ECG signal.
- *Tilt table:* will be used to perform an orthostatic provocation, which will be a progressive HUT from supine position to 30º, 45 º and 60 º for 10 minutes at each angle of tilt. Adjustment of the tilt table to each angle will be accomplished in less than 5 seconds, and subjects will be questioned at each angle of tilt regarding symptoms of syncope (i.e., blurry vision, dizziness, light-headedness, or nausea). The tilt table will be padded and motorized. Restraining straps will be used on the lower extremities and trunk to ensure subject safety during higher inclinations of HUT and to avoid lower-extremity muscle contractions in the control subjects. The straps will be wide and padded for subject comfort and to insure that stimulation of sympathetic spinal reflexes was not evoked.
- *Hormonal Assessment:* Blood will be drawn from a vein in the arm or hand twice each study visit to measure plasma renin level and NE. One sample of each will be taken in the supine position after baseline hemodynamic data collection and the other will be taken when tilted to 60º. Alcohol will be used to sterilize the area. A rubber band will be placed around the arm proximal to the vein. A small needle will be inserted into the vein to

collect blood. Once the blood has been collected, the needle will be removed and the puncture site will be covered. Samples will be immediately spun, down plasma separated and stored at -80 º C for subsequent high performance liquid chromatography (HPLC) analysis of renin and NE concentrations which will be performed at the Bronx VA research lab.

Table 1. Protocol Timeline

| Time Point | Seated | Seated | Supine | 30° Tilt | 45° Tilt | 60° Tilt |
|---|---|---|---|---|---|---|
| Time (min) | 0-10 | 10-15 | 15-50 | 50-60 | 60-70 | 70-80 |
| Heart Rate | Instrumentation | X | X | X | X | X |
| Breathing Rate | | X | X | X | X | X |
| Blood Pressure | | X | X | X | X | X |
| Blood Draw | | | X | | | X |
| Arterial Stiffness | | | X | | | |

## RISKS AND DISCOMFORTS:

1. *Heart Rate, Arterial Stiffness and Blood Pressure:* These are non-invasive procedures that involve minimal risk; however some subjects may experience discomfort when the ECG electrodes are removed from the skin and when the blood pressure cuffs are inflated.
2. *Blood Draws:* Subject may experience some discomfort when the needle is being place in the arm vein. Expected risks may include bruise or infection at the site of skin puncture, temporary faintness and rarely temporary loss of consciousness.
3. *Tilt table:* Subjects may feel dizzy, lightheaded or nauseous letting the staff passively reposition the subject from lying down to 30, 45 and 60-degree tilt. A staff member will be supporting the subject during this tilt, but if he or she feels uncomfortable, the staff will stop the test at any time.

## DATA ANALYSIS:

**Aim 1:** ***To investigate the influence of orthostatic change in BP on plasma renin responses to HUT.***

*Hypothesis 1A:* There will be an inverse relationship between the change in BP and change in plasma renin from supine rest to 60° HUT in individuals with high-level SCI.

*Hypothesis 1B:* There will be no relationship between the change in BP and change in plasma renin from supine rest to 60° HUT in persons with low-level SCI and uninjured controls.

**Statistical Analysis:** To determine the relationship between change in BP and change in plasma rennin, we will use Pearson's correlation coefficient or Spearman's correlation coefficient with alpha. The independent variable is change in SBP from supine rest to 60° HUT and the dependent variable is change in renin from supine rest to 60° HUT. The alpha level will be set at 0.05.

**Aim 2:** ***To investigate the influence of orthostatic change in BP and NE on the RAAS responses to HUT.***

*Hypothesis 2A:* There will be a linear relationship between the change in orthostatic BP and change in plasma NE concentration from supine rest to 60° HUT.

*Hypothesis 2B:* Plasma renin activity will be inversely related to plasma NE concentrations during HUT in persons with SCI.

**Statistical Analysis:** To determine the relationship between change in BP and NE, we will use Pearson's correlation coefficient or Spearman's correlation coefficient with alpha. The independent variable is change in SBP from supine rest to 60° HUT and the dependent variable is change in NE from supine rest to 60° HUT. The alpha level will be set at 0.05.

**Aim 3:** ***To determine if increased reliance on the RAAS for orthostatic BP regulation contributes to differences in supine AS.***

*Hypothesis 3A:* There will be significant group differences for change in plasma renin during HUT, in that plasma renin will be significantly increased during HUT in participants with high-level SCI, but will remain unchanged in individuals with low-level SCI and uninjured controls.

**Statistical Analysis:** Differences in change in plasma renin during HUT between groups will be analyzed using univariate group by ANOVA, with the interaction effect being the statistical effect of interest. The alpha level will be set at 0.05. The G*Power calculations indicate that with a total sample size of 33, there will be a power = 0.8.13 to detect the effect size.

*Hypothesis 3B:* Change in plasma renin during the HUT maneuver will be directly associated with supine PWV in individuals with high-level SCI.

*Hypothesis 3C:* There will be no relationship between the change in plasma renin during the HUT maneuver and supine PWV in persons with low-level SCI and uninjured controls.

**Statistical Analysis:** To determine the relationship between change in plasma renin and supine PWV, we will use Pearson's correlation coefficient or Spearman's correlation coefficient with alpha. The independent variable is change in renin from supine rest to 60° HUT and the dependent variable is PWV during supine rest. The alpha level will be set at 0.05.

**STUDY COMPENSATION:**
Subjects will receive $100 for their participation.

**PUBLICATION OF RESEARCH:**
It is anticipated that the observations made in this study will be presented at National meetings and will be submitted for publication in peer-reviewed journals, including those in the fields of Spinal Cord Medicine.

**COST ANALYSIS:**
Kessler Foundation will be not responsible for any costs associated with this project. This protocol will be funded by the NJ Commission on Spinal Cord Research (CSCR18FEL010).

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