Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Nieshoff et al. 2004; USA PEDro=6 RCT N=4	**Population:** Chronic motor complete tetraplegia **Treatment:** Midodrine 5mg, 10 mg, or placebo (unmarked capsule), double blind, placebo-controlled cross-over design. **Outcome Measures:** Measure of cardiovascular parameters during wheelchair ergometer test.	1. Midodrine, 10 mg elevated systolic blood pressure during exercise in 3 participants. Peak systolic BPs ranged from 90 to 126 mmHg under baseline and placebo conditions, 114-148 after 5 mg of midodrine, and 104 to 200 mmHg after 10 mg. 2. Two participants showed reduced perceived exertion and increased VO_2 following midodrine 10 mg. 3. No adverse effects of midodrine were noted.
Phillips et al. 2014a Canada Prospective controlled trial N=16	**Population:** 8 persons with SCI (1 female) and 8 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 30 (11) years DOI: 7 subjects <1 year post injury, 1 subject >1 year post injury All motor complete cervical spinal cord injuries AIS grade A: 6; AIS grade B: 2 **Treatment:** Subjects tested supine and during upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine. **Outcome Measures:** Beat-by-beat BP and HR, common carotid artery (CCA) diameter. Calculated arterial distensibility and arterial stiffness (β-stiffness index)	1. Systolic BP was lower in SCI while supine vs. AB; BP, CCA diameter and diameter difference were reduced in SCI while upright vs. AB; β-stiffness index was elevated in SCI when upright (+12%) and relative decrease in baroreflex sensitivity (BRS) was greater in SCI vs. AB 2. Negative relationship between BRS and β-stiffness in SCI; no relationship in AB 3. Midodrine led to increased BP and decreased HR in both supine and upright positions; no change in BRS or CCA parameters 4. Reduced BRS is closely related to increased arterial stiffness in the SCI population
Phillips et al. 2014b Canada Prospective controlled trial N=20	**Population:** 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 29 (10) years DOI: 8 subjects <1 year post injury, 2 subject >1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** Subjects tested supine and during progressive upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine. **Outcome Measures:** beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	1. Coherence increased in SCI between BP-MCAv and BP-PCAv by 35% and 22% respectively compared to AB. 2. SCI BP-PCAv gain was reduced 30% compared to AB. 3. The acute (0–30 s after tilt) MCAv and PCAv responses were similar between groups. 4. In SCI, midodrine led to improved PCAv responses 30 – 60 s following tilt (10+/- 3% vs. 4+/- 2% decline) 5. In SCI, midodrine led to a 59% improvement in orthostatic tolerance
Phillips et al. 2014c Canada Prospective controlled trial	**Population:** 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI:	1. At rest: mean BP was lower in SCI (70±10 versus 92±14 mm Hg); PCAv conductance was higher in SCI (0.56±0.13 versus 0.39±0.15

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N=20	Mean (SD) age: 29 (10) years DOI: 8 subjects <1 year post injury, 2 subject >1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** Visual and verbal fluency task to assess neurovascular coupling (NVC). SCI group had 2 sessions, one with midodrine and one without. AB group had one session without midodrine. **Outcome Measures:** beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	cm/second/mm Hg) 2. AB had a 20% increase in PCAv during cognition while this response was absent in SCI 3. With midodrine, NVC was improved by 70% in SCI, and cognitive function improved by 13% 4. Improvements in BP were related to improvements in cognitive function in those with SCI
La Fountaine et al. 2013; USA Prospective controlled trial N=27	**Population:** Study 1: 7 tetraplegic subjects (38±10 years; 2 complete AIS A injury), 6 age-matched neurologically intact controls (32±8 years). Study 2: 7 tetraplegic subjects (41±9 years; 1 complete AIS A injury), 7 age-matched neurologically intact controls (33±9). **Treatment:** Study 1: open-label trial with intravenous administration of L-NAME at specific doses (0, 1, 2, or 4 $mg \cdot kg^{-1}$) in the supine position. Study 2: orthostatic challenge (head-up tilt) with or without L-NAME (0, 1, or 2 $mg \cdot kg^{-1}$), controls completed a single visit (0 $mg \cdot kg^{-1}$). **Outcomes Measures**: Study 1: Digital ECGs obtained at baseline, immediately after infusion (60 min) and 1 hour post-infusion (120 min). Study 2: Digital ECGs obtained at baseline, 60 min, and at 2 10 min post-infusion time points after head-up tilt.	1. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change heart rate, PQ, QT or QTC (heart-corrected QT) intervals at rest or during head-up tilt in subjects with tetraplegia or controls. 2. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change resting heart rate, PQ, QT or QTC intervals in those with tetraplegia or controls. 3. L-NAME administration does not appear to affect cardiac rate or conduction.

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Wecht et al. 2013; USA Prospective controlled trial N=10	**Population:** 10 hypotensive subjects with SCI (8M; 2F); 8 tetraplegic, 1 high thoracic (T4) and 1 low thoracic (T10); age: 44±10 years; duration of injury 15±13 years. **Treatment:** Escalating dose of L-Threo-3, 4-dihydroxyphenylserine (droxidopa) (100mg, 200mg, 400mg) given over four lab visits with placebo on first visit. Each visit involved 30 min seated baseline, 30- to 60 min supine, and a 4 hour seated post-drug observation. **Outcome measures:** Blood pressure and heart rate changes from baseline to the post-drug period; orthostatic heart rate and blood pressure responses; reporting of subjective adverse effects.	1. Seated blood pressure was significantly elevated with 400mg droxidopa compared with placebo and 100mg droxidopa for 3 hours, and was elevated for 2 hours compared with 200mg droxidopa. 2. Increase in supine blood pressure was not worsened following droxidopa. 3. Expected fall in blood pressure when transferred from the supine to the seated position was prevented with droxidopa 200mg and 400mg. 4. Peak seated blood pressure reached the hypertensive range in 3 study subjects following the 400-mg dose of droxidopa (156/100, 150/94, 149/93 mmHg). These episodes occurred 100 minutes after administration of droxidopa and were resolved within 30 minutes.
Wecht et al. 2011; USA Prospective controlled trial N=7	**Population:** 5 male and 2 female healthy subjects (26-54 years old, level of injury C4-C7, duration of injury 8-37 years). **Treatment:** Subjects were studied during 3 laboratory visits: no drug, midodrine (10mg; administered orally 30 min before HUT), and L-NAME (1.0 mg/kg; infused over a 60-min period). **Outcome measures:** Heart rate, blood pressure (systolic and diastolic), mean arterial pressure (MAP), cerebral blood flow (CBF), and markers of the renin-angiotensin- aldosterone system (RAAS, plasma renin and serum aldosterone) were measured in the supine position at baseline (BL) and during a 45° HUT manoeuver.	1. L-NAME and midodrine reduced OH symptoms compared to the no-drug trial. 2. L-NAME significantly increased orthostatic MAP compared with the no drug and midodrine trials. 3. There was a trend for midodrine to increase MAP during HUT. 4. Modest suppression of renin and aldosterone responses to HUT with L-NAME and midodrine. 5. There was a significant relationship between change in MAP and change in CBF with HUT among the subjects tested (r2=0.592).
Wecht et al. 2010; USA Prospective controlled trial N=10	**Population:** 8 males, 2 females; 43±9 years; duration of injury 22±11 years; SCI C4-C7; AIS A or B **Treatment:** Midodrine (no drug, 5 mg or 10 mg) over 3 testing days. **Outcome Measures:** Blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) and middle cerebral artery mean blood flow velocity (MCA MFV) during supine and head-up tilt (HUT) of 45 min at 45°.	1. 10 mg midodrine increased supine diastolic BP and MAP, and increased systolic BP and MAP after tilt test compared to control. 2. The significant increase in systolic BP during HUT was due to an augmented response in 2 subjects with little to no change in the 8 other individuals.
Wecht et al. 2009; USA Prospective controlled trial N=12	**Population:** 5 subjects with chronic tetraplegia (1 AIS A and 4 AIS B); 7 age-, height-, and weight matched able-bodied controls. All subjects were between 19 and 53 years old. **Treatment:** SCI subjects underwent treatment of 1.0 mg/kg of L-NAME, as well as placebo control at supine rest and during head-up tilt (HUT); the control	1. Supine systolic, diastolic, and mean arterial blood pressure were significantly higher in subjects with SCI after L-NAME infusion compared to placebo 2. Orthostatic (45° HUT) MAP was significantly reduced after placebo infusion in SCI compared to controls (66±13 vs. 88±10 mmHg); 3. MAP during HUT was comparable to controls (88±10 mmHg) following L-NAME infusion in subjects with SCI (83±3 mmHg).

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	group received only placebo. **Outcome Measures:** Heart rate (continuously monitored by ECG), mean arterial blood pressure (MAP); active plasma renin and serum aldosterone concentrations.	4. Serum aldosterone levels were reduced during HUT after L-NAME infusion (120±45 pg/mL) compared to placebo (259±69 pg/mL; p<0.05) in subjects with SCI.
Wecht et al. 2008; USA Prospective controlled trial N=14	**Population**: 7 subjects with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years. **Treatment:** Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg). **Outcome Measures:** Supine heart rate (HR), mean arterial blood pressure (MAP) and plasma norepinephrine (NE) concentrations.	1. There was a heightened MAP response to escalating dose of L-NAME in subjects with tetraplegia compared to the controls. 2. HR was reduced in a dose dependent manner, and this response did not differ comparing subjects with tetraplegia to the controls. 3. Plasma NE was significantly at baseline in subjects with tetraplegia compared to the controls. 4. Following L-NAME infusion, plasma NE was reduced in a dose dependent manner in the controls, whereas plasma NE levels were un-changed following L-NAME infusion in subjects with tetraplegia.
Wecht et al. 2007; USA Prospective controlled trial N=14	**Population**: 7 subjects with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years. **Treatment:** Placebo versus L-NAME (1.0 mg/kg). **Outcome Measures:** Supine heart rate (HR), and mean arterial blood pressure (MAP).	1. Supine MAP was significantly reduced in subjects with tetraplegia compared to controls at baseline. 2. Supine HR did not differ between the groups at baseline. 3. MAP was significantly reduced in subjects with tetraplegia compared to the controls following placebo infusion. 4. Differences in MAP between subjects with tetraplegia and controls were no longer evident following L-NAME infusion.
Frisbie 2004; USA Observational N=4	**Population:** Chronic cervical complete tetraplegia; AIS A. **Treatment:** Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily). **Outcome Measures**: Severity of OH, urinary output.	1. With decreasing ephedrine dose (and OH severity), there was an increase in mean daily output of urine sodium (from 50 to 181 mEq), water (from 1.5 to 5.3 L), rate of creatinine secretion, rates of water excretion, sodium concentrations, and reduced urine osmolality.
Mukand et al. 2001; USA Case report N=1	**Population:** 21-year old male with traumatic C6 tetraplegia; AIS C, with symptomatic OH. **Treatment:** Midodrine (2.5 to 15 mg 3X/day). **Outcome Measures**: Blood pressure, symptoms of OH.	1. Gradual increase in dose of midodrine from 2.5mg to 10 mg (at 0800, 1200 and 1600 hours) resulted in resolution of symptoms of OH. Patient was able to participate fully in the rehabilitation program.
Barber et al. 2000; USA Case series N=2	**Population:** 2 cases of acute motor complete tetraplegia. **Treatment:** Fludrocortisone acetate 0.1 mg 4X/day or midodrine 10 mg 3X/day. **Outcome Measures***:* Blood pressure, heart rate, and symptoms of OH.	1. No effect of fludrocortisone on OH. 2. Fludrocortisone in both patients resulted in pitting edema of hands and lower limbs. 3. Initiation of midodrine hydrochloride resolved orthostatic symptoms in both individuals without any complications.

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Frisbie & Steele 1997; USA Observational N=231	**Population:** SCI; ephedrine (medically treated for OH) group age, 57±15 years; duration of injury 26±15 years. SCI no ephedrine group: 51±15 years, duration of injury 22±14 years. **Treatment:** Retrospective chart review of use of ephedrine (n=30), salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. **Outcome Measures**: OH symptoms, serum sodium and urine osmolality.	1. Single dose of ephedrine usually sufficient to prevent symptoms but observed that some patients failed to recognize need for repeat doses later in day. 2. Symptoms of OH were reduced consciousness (100% of subjects), strength (75%), vision (56%) and breath (53%). Precipitating factors were hot weather (77%), bowel care (33%) and meals (30%). 3. Low blood sodium found in 54% of the OH patients and 16% of those without.
Muneta et al. 1992; Japan Case report N=1	**Population:** 72-year old woman with non-traumatic SCI and paroxysmal hypotension. **Treatment:** Several weeks of salt supplement (7 then 15 g/day) was followed by L-threo-3,4-dihydroxyphenylserine (*100 mg up to 600 mg/day).* **Outcome Measures***:* Blood pressure, catecholamines (epinephrine and norepinephrine), plasma renin activity.	1. After salt supplement, a marked ↑BP, ↑ norepinephrine and ↓ basal plasma renin activity was observed in response to sitting. 2. Addition of L-threo-3,4-dihydroxyphenylserine for 2 weeks, showed elevation in catecholamines about 5 and 10 times without an apparent increase in resting BP. 3. Significant improvement in the symptoms of OH and patient was able to participate in rehabilitation program.
Senard et al. 1991; France Pre-post N=7	**Population:** 45-year-old subject with chronic complete traumatic paraplegia; 6 non-SCI male controls. **Treatment:** Clonidine (150 µg, 2X/day) and midodrine (specific alpha 1-agonist) (10 mg, 2X daily). Heart rate assessed by blinded tester. **Outcome Measures***:* Blood pressure, heart parameters, plasma catecholamine, alpha-adrenoceptor sensitivity.	1. The increase in systolic blood pressure induced by midodrine (10 mg) was significantly higher in the tetraplegic patient (change of 56 mmHg) compared to controls (change of 15 mmHg). 2. Midodrine and clonidine alone or the two drugs in combination led to an increase in resting BP and decrease severity of OH.
Groomes & Huang 1991; USA Case report N=1	**Population:** 28-year-old with chronic C5 tetraplegia. **Treatment:** Ergotamine (2 mg), daily combined with fludrocortisone (0.1- .05 mg). **Outcome Measures:** Blood pressure.	1. Following 10 days with fludrocortisone patient able to tolerate sitting. Following additional ergotamine, the patient was able to tolerate an upright position without symptoms.