Hepatorenal Syndrome

Octreotide

and/or

Midodrine
Objectives

1) Gain an appreciation and understanding for the pathophysiology hepatorenal syndrome

2) Review the evidence for octreotide and/or midodrine for the treatment of hepatorenal syndrome

3) Apply evidence based medicine to my patient outcomes
Case#1: CM

- 60 y/o  ht: 162 cm wt: 51 kg
- Admitted to SPH Jan 5th
  - Transferred to RJH 6S Jan 5th
  - Transferred to ICU Jan 9th

HPI: found at home on the floor for an unknown length of time with a fractured right hip
CC: Pain associated with fx and immobility
Case: CM

PMHx:
- Depression
- Alcohol abuse
- Glaucoma
- COPD
- Previous history of hypertension
- Hypothyroidism
- Anemia
- Osteoporosis
  - Previous left hip fx (10 years prior)
Case: CM

Social Hx:

Widowed and lives alone in Sidney without supports
Claims to smoke 3 cigarettes/day and have 2 glasses of wine few times a week

MPTA:

Currently not taking any medications

Pharmanet hx (last filled Aug 2011)

• Escitalopram
• Levothyroxine
• Travoprost
• Risedronate
Admission to ICU

- Brought to OR for anesthesia at which time it was noted CM was not hemodynamically stable (BP 78/43, HR 102, $O_2$ 80%)
- Remained unstable despite oxygen and fluids … OR cancelled
- Detection of decompensated alcoholic liver disease
- Subsequently developed acute renal failure Jan 7/8 (SrCr 114-178)
- Pulmonary edema requiring Oxymizer Fi$O_2$ at 60%
- Ward stabilization attempted (colloids, blood transfusion)
- Jan 8: Furosemide drip, midodrine 10mg tid / octreotide 100mg sc tid
- Transferred to ICU Jan 9$^{th}$ for pressor support
# ICU Admission Lab Values

<table>
<thead>
<tr>
<th>Jan 9th</th>
<th>Na 137</th>
<th>K 3.6</th>
<th>Cl 109</th>
<th>Anion Gap 13</th>
<th>Ca 2.03</th>
<th>Mg 0.55</th>
<th>Phos 1.17</th>
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<tr>
<td><strong>Lytes</strong></td>
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<td>Hg 109</td>
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<td>Plat 127</td>
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<td>Neut 12.7</td>
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<tr>
<td><strong>LIVER</strong></td>
<td>Bili 240</td>
<td>AST 67</td>
<td>ALT 12</td>
<td>Alk Phos 145</td>
<td>GGTP 255</td>
<td>INR 1.7</td>
<td>Albumin 21</td>
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<td>Urea 10.8</td>
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<tr>
<td>eGFR 25</td>
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<td>ScCr 178</td>
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<tr>
<td>Na Urine &lt; 10</td>
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<td>U/O 0-20</td>
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<td><strong>Renal</strong></td>
<td>Ammonia 43</td>
<td>TSH 67.2</td>
<td>Procalcitonin 0.64</td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
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</tr>
</tbody>
</table>

**Child-Pugh Score = 11-12**  **One year survival = 45%**  **Two year survival = 35%**
Systems Review

**Observation:** chronically unwell, jaundiced, extremely cachectic

**Vitals:** 38.5, HR 63, MAP 67, RR 27

**CNS:** GCS 15

**Resp:** pulmonary edema, engorged pulmonary vessels, bilateral airspace opacification and interstitial infiltrates

**CV:** JVP 4-5 cm

**GI:** distended, tense, *mild ascites*

**Liver:** palpable/tender/enlarged margin with noted mild asterixis

**Renal:** oliguric

**MSK/Skin:** 2+ leg edema
Current Medications

- Octreotide 100mcg subcut tid
- Midodrine 10mg po tid
- Vasopressin iv 2 units/hr (goal MAP > 65 mmHg)
- Norepinephrine iv 0-1 mcg/kg/min (goal MAP > 65 mmHg)
- Piperacillin/tazobactam 2.25g iv q8h
- Furosemide 10-20mg/hr iv continuous
- Lactulose 30ml po tid
- Levothyroxine 112mcg po daily
- Travoprost 0.004% 1 gtt both eyes qhs
- CIWA protocol
- Hypokalemia protocol
- Multiple albumin units prn
Drug Therapy Problem

Due to alcoholic cirrhosis CM is currently at an extreme risk of mortality/morbidity secondary to type 1 HRS and would benefit from reassessment of her current drug therapy.

Medical problems ongoing…
• Septic shock
• Hepatic encephalopathy
• Alcohol/nicotine withdrawal
• Pain
• Hypothyroidism
• Depression
• Increased IOP
• Osteoporosis
PICO Goals of Therapy

Health Care Team

• Provide evidenced based therapy to address and improve hepatorenal syndrome
  → Decrease associated morbidity and mortality
• Reduce/minimize any ADR with therapy
• Optimize hemodynamic support

Patient

• Respect patient wishes for end of life care (Ø dialysis, intubation)
• Symptom supports
HRS

“reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure… characterized by marked reduction in GFR and renal plasma flow”

Hallmark → intense renal vasoconstriction with peripheral arterial vasodilatation

Type 1: rapid progression of renal failure (doubling of SrCr within less than 2 weeks) without identified precipitating factor.

Type 2: spontaneous steady renal failure mainly attributed to refractory ascites

Type 3/4: mentioned in literature

Wadei et al. 2006
**HRS**

**Incidence:**
- \( \approx 5\text{-}10\% \) hospitalized cirrhotics with ascites
  - HRS 18\% within 1 year, 40\% by 5

**Risk Factors:**
- Advanced ascites (diuretic resistant)
- Large volume paracentesis
- Spontaneous bacterial peritonitis

**Precipitating events:**
- *bacterial infections*, variceal hemorrhage, surgery, acute alcoholic hepatitis (25\%)
Prognosis

Salerno et al. 2008
Pathophysiology

Advanced cirrhosis

Splanchnic arterial vasodilation

Impaired cardiac output

Ineffective blood volume in the systemic circulation

Activation of vasoconstrictor systems

Impaired renal perfusion with hepatorenal syndrome

Hasper et al. 2011
Pathophysiology

CIRRHOSIS

Elevated splanchnic nitric oxide

Portal hypertension

SBP, bacterial infections, LVP, Alcoholic hepatitis

Splanchnic Arterial Vasodilation

Arterial underfilling

Decreased total systemic vascular resistance

Decreased effective arterial blood volume

Sodium and water retention

Increase in plasma volume

Stimulation of vasoconstrictors: RAAS, SNS, AVP

Central hypovolemia & impaired cardiac function

Fall in cardiac output

Development of severe renal vasoconstriction

Hepatorenal Syndrome

Wadei et al. 2006
HRS: Diagnostic Criteria

Important to rule out causes of renal disease

**Major Criteria**
- Low GFR, as indicated by serum creatinine >1.5 mg/dl or 24-h creatinine clearance <40 ml/min
- Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs
- No sustained improvement in renal function (decrease in serum creatinine to ≤1.5 mg/dl or increase in creatinine clearance to ≥40 ml/min) after diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander
- Proteinuria <500 mg/d and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

**Additional Criteria**
- Urine volume <500 ml/d
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells <50/high-power field
- Serum sodium concentration <130 mEq/L

Wadei et al. 2006
HRS: Treatment

Diagnosis of Hepatorenal Syndrome

Evaluation for Liver Transplantation → Vasoconstrictors and Albumin (Intravenous albumin: 40 g/day)

Terlipressin:
0.5 mg IV every 4 hours; may increase dose to 1 mg/4h and then up to 2 mg/4h or 2 - 12 mg/day intravenous continuous infusion

Midodrine & Octreotide:
Midodrine: 2.5-7.5 mg p.o. t.i.d with an increase to 12.5 mg t.i.d daily if needed & Octreotide: 100 ug s.c. t.i.d. with an increase to 200 ug t.i.d. if needed

Noradrenaline:
0.5-3 mg/hr continuous IV infusion

Duration of therapy: between 5 - 15 days
Consider TIPS in patients with Child-Pugh score <12 not responding to vasoconstrictors

GOAL: Reduction of serum creatinine < 1.5 mg/dL

132 mmol/L

Cardenas et al. 2006
**PICO**

**Patient:** with hepatorenal syndrome secondary to alcoholic hepatitis

**Intervention:** octreotide and/or midodrine

**Comparator:** placebo

**Outcome:**
1) prolong survival
2) restore renal function and hemodynamic stability
Literature Search

Search Terms:
- Hepatorenal syndrome
- Octreotide
- Midodrine

Databases: PubMed, Medline, IPA, Cochrane, Embase

Limits: Evidence hierarchies
- Systematic/meta-analyses > RCT > Cohort > Case-control > Cross sectional > Case reports.
Octreotide in Hepatorenal Syndrome: A Randomized Double-Blind, Placebo-Controlled, Crossover Study.

**P:** 19 cirrhotic patients with hepatorenal syndrome type 1/2

**I:** octreotide 50mcg/h x 96 hours

**C:** placebo infusion x 96 hours

- Both groups received albumin 50g/day

**O:** improvement in renal fxn between first and last day of placebo or octreotide infusions

- Defined as 20% decrease in SrCr

**T:** duration of 8 days (4 placebo arm, 4 treatment arm)
# Results

## Table 2. Effects of Placebo and Octreotide on Hemodynamics, Renal Function, and Hormones in Patients of Group 1 With Placebo First

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Placebo (day 4)</th>
<th>Octreotide (day 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>82.9 ± 52</td>
<td>79 ± 4.3</td>
<td>83.4 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>215 ± 32</td>
<td>222 ± 41</td>
<td>270 ± 54</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>23.6 ± 5.8</td>
<td>32.7 ± 17.5</td>
<td>14.5 ± 7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium (mEq/d)</td>
<td>7.1 ± 1.6</td>
<td>6.8 ± 2.5</td>
<td>12.3 ± 8.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mesenteric artery resistance index (%)</td>
<td>88.4 ± 2.0</td>
<td>86.6 ± 2.1</td>
<td>86.8 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Renal artery resistance index (%)</td>
<td>79.9 ± 1.7</td>
<td>80.6 ± 1.8</td>
<td>77.7 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>5.7 ± 1.0</td>
<td>6.1 ± 1.2</td>
<td>4.5 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>3,706 ± 2,132</td>
<td>5,925 ± 4,344</td>
<td>5,147 ± 3,471</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucagon (pmol/L)</td>
<td>207 ± 94</td>
<td>212 ± 116</td>
<td>227 ± 123</td>
<td>NS</td>
</tr>
</tbody>
</table>

## Table 3. Effects of Octreotide and Placebo on Hemodynamics, Renal Function, and Hormones in Patients of Group 2 With Octreotide First

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Octreotide (day 4)</th>
<th>Placebo (day 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>76 ± 3.2</td>
<td>86 ± 2.5</td>
<td>81.2 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>208 ± 16</td>
<td>194 ± 34</td>
<td>204 ± 47</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>17.7 ± 6.4</td>
<td>25.3 ± 8.8</td>
<td>30.7 ± 11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium (mEq/d)</td>
<td>7.8 ± 3.6</td>
<td>7.7 ± 2.7</td>
<td>15.1 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mesenteric artery resistance index (%)</td>
<td>84.6 ± 1.3</td>
<td>84 ± 0.9</td>
<td>86.0 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Renal artery resistance index (%)</td>
<td>77.7 ± 2.7</td>
<td>78.1 ± 2.0</td>
<td>79.1 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>11.2 ± 2.8</td>
<td>4.7 ± 1.2</td>
<td>7.9 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>2,193 ± 675</td>
<td>1,166 ± 607</td>
<td>1,698 ± 647</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucagon (pmol/L)</td>
<td>93 ± 33.5</td>
<td>41 ± 4.9</td>
<td>62 ± 6.1</td>
<td>NS</td>
</tr>
</tbody>
</table>
Results

Fig. 1. Individual changes of serum creatinine after placebo and octreotide in patients of group 1 (placebo first) and group 2 (octreotide first). ○, Patients with HRS Type 1; ●, patients with HRS type 2.

Fig. 2. Individual changes of plasma renin activity after placebo and octreotide in patients of group 1 (placebo first) and group 2 (octreotide first). ○, Patients with HRS type 1; ●, patients with HRS type 2.
Limitations

- Size ($n=19$); only 5 pts had type 1 hepatorenal syndrome
- Patients were used as own control with crossover design
- No mention of allocation concealment
- Patient population (young, generally healthy)
- Short duration of therapy
- Low dose of octreotide
- Surrogate endpoint
- Octreotide dosage (50mcg/hr) chosen based on previous experience in variceal bleeding without ADR
- Duration selected because previous pilot study showed benefit from octreotide in HRS after 48 hrs
Discussion:

• Trend in a decrease of plasma renin activity after octreotide infusion

Authors conclusion…

“This study demonstrates unequivocally that octreotide infusions did not have any beneficial effects in cirrhotic patients with HRS”
Acute Effects of the Oral Administration of Midodrine, an alpha-Adrenergic Agonist, on Renal Hemodynamics and Renal Function in Cirrhotic Patients With Ascites

25 patients with cirrhosis and ascites received a single dose of 15mg of midodrine. Systemic and renal hemodynamics were measured before and after administration to observe the effects. An observational study was conducted on 8 out of 25 patients, evaluating the effectiveness of an oral vasoconstrictor agent. The patients were followed for 6 hours after administration.
Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline Values</th>
<th>Period 1 (0-3 hours after M)</th>
<th>Period 2 (3-6 hours after M)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>77.0 ± 1.3</td>
<td>81.3 ± 2.0</td>
<td>80.2 ± 2.6</td>
<td>&lt;.025</td>
<td>NS</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>86 ± 2</td>
<td>77 ± 2</td>
<td>75 ± 2</td>
<td>&lt;.025</td>
<td>&lt;.005</td>
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<td>CI (mL · min⁻¹ · m² BSA)</td>
<td>4,167.4 ± 316.7</td>
<td>3,836.3 ± 299.1</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>SVR (dyn · sec · cm⁻⁵)</td>
<td>885.5 ± 65.0</td>
<td>1,039.5 ± 102.3</td>
<td>984.1 ± 90.6</td>
<td>&lt;.05</td>
<td>NS</td>
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<tr>
<td>LFBF (mL · min⁻¹ · dL⁻¹ tissue)</td>
<td>2.96 ± 0.30</td>
<td>3.4 ± 0.44</td>
<td>NS</td>
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<tr>
<td>LLBF (mL · min⁻¹ · dL⁻¹ tissue)</td>
<td>2.94 ± 0.31</td>
<td>3.20 ± 0.52</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFR (mm Hg · mL⁻¹ · min · dL tissue)</td>
<td>27.39 ± 3.05</td>
<td>26.09 ± 4.13</td>
<td>25.22 ± 4.23</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LLR (mm Hg · mL⁻¹ · min · dL tissue)</td>
<td>27.65 ± 3.27</td>
<td>28.71 ± 4.75</td>
<td>27.35 ± 4.16</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Data expressed as means ± SE.
Abbreviations: M, midodrine; NS, not significant; BSA, body surface area.
*Comparison between Period 1 values and baseline values.
†Comparison between Period 2 values and baseline values.

Statistical differences in....

MAP = mean arterial pressure
HR = heart rate
CI = cardiac index
SVR = systemic vascular resistance


Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline Values</th>
<th>Period 1 (0-3 hr after M)</th>
<th>Period 2 (3-6 hr after M)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF (mL · min⁻¹)</td>
<td>200.9 ± 39.9</td>
<td>232.2 ± 48.6</td>
<td>245.3 ± 44.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RBF (mL · min⁻¹)</td>
<td>282.7 ± 54.5</td>
<td>325.0 ± 70.3</td>
<td>343.5 ± 64.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RVR (mm Hg · mL⁻¹ · min)</td>
<td>37.65 ± 8.98</td>
<td>32.82 ± 5.61</td>
<td>31.41 ± 8.00</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (mL · min⁻¹)</td>
<td>39.0 ± 6.4</td>
<td>48.4 ± 10.4</td>
<td>45.1 ± 7.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UNaV (μEq · min⁻¹)</td>
<td>16.1 ± 5.1</td>
<td>18.1 ± 5.2</td>
<td>17.9 ± 6.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEna (%)</td>
<td>0.47 ± 0.18</td>
<td>0.51 ± 0.23</td>
<td>0.54 ± 0.26</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Clₐ (mL · min⁻¹)</td>
<td>4.8 ± 0.5</td>
<td>6.0 ± 1.8</td>
<td>5.2 ± 1.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEl (%)</td>
<td>15.5 ± 3.0</td>
<td>15.7 ± 4.9</td>
<td>11.4 ± 1.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng · mL⁻¹ · h)</td>
<td>20.70 ± 4.82</td>
<td>15.87 ± 3.70</td>
<td>&lt;.0025</td>
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</tr>
<tr>
<td>PA (pg · mL⁻¹)</td>
<td>573.2 ± 141.5</td>
<td>520.5 ± 116.0</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH (pg · mL⁻¹)</td>
<td>3.2 ± 0.3</td>
<td>3.2 ± 0.3</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP (pg · mL⁻¹)</td>
<td>60.7 ± 14.9</td>
<td>65.9 ± 18.6</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOx (μmol · L⁻¹)</td>
<td>63.1 ± 15.7</td>
<td>45.1 ± 10.5</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data expressed as means ± SE. PRA values in healthy subjects = 2.3 ± 0.4 (ng · mL⁻¹ · h⁻¹). PA values in healthy subjects = 55 ± 10 (pg · mL⁻¹). ADH values in healthy subjects = 1.5 ± 0.5 (pg · mL⁻¹). ANP values in healthy subjects = 42 ± 5 (pg · mL⁻¹). NOx values in healthy subjects = 25.9 ± 2.5 (μmol · L⁻¹).

Abbreviations: M, midodrine; NS, not significant.

*Comparison between Period 1 and baseline values.
†Comparison between Period 2 and baseline values.

Statistical differences in....

PRA = plasma renin activity
Limitations

• Size (n=25); only 8 pts had type 2 HRS
• No type 1 HRS studied
• Prospective observational trial
• Patient population (young)
• Short duration of therapy
• Surrogate endpoints
• Dose of midodrine based on an increase of at least 5 mmHg in MAP
• Applicability to patient
• 1 dose only!
Discussion:

• Midodrine (15mg) and its associated alpha-1 vasoconstriction mechanism of action is associated with a statistically significant increase in MAP, CO, SVR and a decrease in PRA in type 2 HRS patients. Application to practice and patient outcomes is unclear.

Authors conclusion...

“midodrine only slightly improves systemic hemodynamics in patients with type 2 HRS, with no effect on renal hemodynamics and renal function”
Reversal of Type 1 Hepatorenal Syndrome With the Administration of Midodrine and Octreotide

13 cirrhotic patients with ascites and type 1 HRS
First 5 days patients received no diuretics, or other drugs with known effects on systemic and renal hemodynamics and/or renal function

On 6th day 5 pts received octreotide 100mcg sc tid (up to 200mcg) and midodrine 7.5 mg tid (up to 12.5 mg) titrated to obtain an increase in MAP of 15 mmHg.

On 6th day 8 patients received dopamine infusion 2-4 ug/kg/min

Both groups received albumin 20-40 g/day

not mentioned; observational

study lasted 20 days, patients from Jan 1996 – Jan 1998
Fig. 2. One-month survival in cirrhotic patients with HRS treated with nonpressor doses of dopamine (group A) or with midodrine and octreotide (group B). The P value compares the two groups by means of the log-rank test.
Results

Fig. 1. Individual patterns of serum creatinine in cirrhotic patients with type 1 HRS treated with nonpressor doses of dopamine (group A) or with midodrine and octreotide (group B); d 5, d 10, and d 20 signify times after the initiation of treatment.

<table>
<thead>
<tr>
<th>Serum creatinine (mg/dL)</th>
<th>Group A (n = 8)</th>
<th>Group B (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.6 ± 0.6</td>
<td>5.0 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>5.5 ± 0.8</td>
<td>4.6 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>5.1 ± 1.5</td>
<td>3.3 ± 0.7*</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.8 ± 0.1*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>
Limitations

- Size ($n=15$); only 6 pts had type 1 HRS secondary to alcohol cirrhosis
- Dopamine comparison
- Strict Na restriction
- Patient population (young, generally healthy)
- Short duration of therapy
- Exploratory study
- No explanation why a MAP increase of 15 mmHg chosen
- No allocation concealment
- Single centre
- High doses of albumin could be responsible for increased renal perfusion
Discussion:

• The combination of octreotide and midodrine plus aggressive volume expansion compared to dopamine seems to increase length of survival and improve renal perfusion.

Authors conclusion…

“In conclusion, this study shows that prolonged administration of midodrine and octreotide combined with plasma volume expansion by means of albumin is a promising therapeutic perspective in the treatment of type 1HRS”
Midodrine and Octreotide

Esrailian *et al.* (2007) conducted a retrospective chart review of 81 patients with type 1 HRS at one centre

- 60 patients received dual therapy (octreotide 100-200mcg sc tid + midodrine 5-15mg tid) – aim to increase MAP 15 mmHg
- Compared to 21 patients without therapy

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Thirty-day treatment outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment group</td>
</tr>
<tr>
<td>Reduction of creatinine</td>
<td>24/60 (40%)</td>
</tr>
<tr>
<td>Death at 30 days</td>
<td>26/60 (43%)</td>
</tr>
</tbody>
</table>
Skagen et al. (2009) conducted a retrospective cohort chart review of 162 patients with type 1 HRS at one centre

- 75 patients received dual therapy (octreotide 100-200mcg sc tid + midodrine 7.5-15mg tid) – tolerated up to a SBP < 140mmHg
- Compared to 87 patients without therapy
Midodrine and Octreotide

Wong et al. 2004

• 14 pts with type 1 HRS
  – Received medical therapy (M,O,A) until SrCr less than 135 umol/L for at least 3 days, followed by TIPS procedure if not contraindicated

• Medical therapy (14 ± 3 days)
  – SrCr: 233 ± 29 vs. 112 ± 8 umol/L (p=0.001)
  – Urinary Na: 5 ± 2 vs. 9 ± 2 mmol/d (p=0.002)
### Summary

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>Octreotide</th>
<th>Midodrine</th>
<th>Octreotide + Midodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings</td>
<td>May decrease [renin]</td>
<td>Increase MAP, CO, SVR</td>
<td>High dosages + Aggressive ablumin</td>
</tr>
<tr>
<td>Renal Function</td>
<td>No benefit shown</td>
<td>No benefit shown</td>
<td>Improvement</td>
</tr>
<tr>
<td>Mortality</td>
<td>No benefit shown</td>
<td>?</td>
<td>Prolonged survival</td>
</tr>
<tr>
<td>Overall</td>
<td>Ineffective</td>
<td>? (limited evidence)</td>
<td>Benefit</td>
</tr>
</tbody>
</table>

High dose therapy with octreotide and midodrine in combination with aggressive intravascular fluid resuscitation has been shown to improve renal function and prolong survival in patients with type 1 HRS.
PICO

**Patient:** with hepatorenal syndrome secondary to alcoholic hepatitis

**Intervention:** octreotide and/or midodrine

**Comparator:** placebo

**Outcome:**

1) prolong survival
2) restore renal function and hemodynamic stability
**Recommendations**

1) Increase midodrine to 15mg po tid as tolerated

2) Increase octreotide to 200 mcg sc tid

3) Discuss discontinuation of furosemide or dose reduction

4) Aggressive intravascular replacement with albumin
HRS Monitoring (ICU)

**CNS:** headache, dizziness

**Resp:** pulmonary edema

**CV:** CVP and HR

**Renal/GU:** SrCr, eGFR, urea and U/O

**Fluid/lytes:** weight, urine Na
Course of Stay

<table>
<thead>
<tr>
<th>Jan 10</th>
<th>WBC</th>
<th>INR</th>
<th>Ammonia</th>
<th>SrCr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.6</td>
<td>1.7</td>
<td>72</td>
<td>199</td>
</tr>
<tr>
<td>Jan 11</td>
<td>Patient diseased; secondary to septic shock</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unfortunately, an improvement CM’s renal function was not seen with octreotide and midodrine since initiation on Jan 9th.
References:


References:


Pathophysiology

Peripheral Arterial Vasodilation
- Circulating volume decreases due to liver dysfunction and portal hypertension secondary to splanchnic blood pooling
- Therefore systemic and splanchnic vasodilation

Reduced effective blood volume causes activation
- Sympathetic nervous system
- Renin-angiotensin-aldosterone system
- Vasopressin

- Leads to renal vasoconstriction and reduced GFR
- Na retention → water retention → plasma volume expansion → ascites

Cardiac dysfunction
- Hyperdynamic circulation
  - Increase CO
  - Decreased SVR

- Hypotension
- Further vasoconstriction of renal vessels
Therapeutic Approach / Alternatives

General Measures (aggressive therapy reserved for liver transplant)
- Paracentesis
  - $>$5L $\rightarrow$ albumin

Pharmacologic Treatment
- Renal vasodilators
  - Ex. Dopamine, ACE inhibitors, prostaglandins
- Systemic Vasoconstrictors
  - Ornipressin, terlipressin, vasopressin
  - Octreotide
  - Alpha adrenergic agonists (epinephrine, norepinephrine, midodrine)

Transjugular intrahepatic portosystemic shunt (TIPS)

Renal Replacement Therapy (HD, CRRT)

Liver transplantation
Vasopressin

**MOA:** endogenous hormone that affects three vasopressin receptors $V_1$, $V_2$, $V_3$.
- $V_1$ responsible for vasoconstriction found extensively in splanchnic vasculature.

**Initially studied in HRS**
- Retrospective study by Kiser *et al.* showed
  - patients who received vasopressin alone or in combination with octreotid had a significantly greater recovery rates* than those receiving octreotide alone (42 vs 38 vs 0) respectively ($P=0.01$)
  - Patients who responded to therapy had lower mortality (23 vs 67%) ($P=0.008$)

*defined as a decrease in $SrCr$ to less than 114 mmol/L
Landmark meta-analysis by Obritsch et al showed that vasopressin in vasodilatory septic shock led to severe ischemia of the mesenteric mucosa, skin, and myocardium.

- Newer analogues (terlipressin/ornipressin) subsequently replaced vasopressin in HRS.
  - Terlipressin has greater affinity for $V_1$ receptor, longer half life and appears to have less ischemic complications.
  - Terlipressin is the most studied analogue in HRS.
  - Unfortunately it is not available in many countries including Canada and therefore is replaced by vasopressin.
Norepinephrine

**MOA**: catecholamine (strong alpha-adrenergic effect)
- Potent vasoconstrictor (venous & arterial)

**Evidence:**

Only 1 pilot prospective study that looked at NE, albumin and furosemide in HRS
- $n=12$; mean dose 13.3–5.0 mcg/min
- Duration 10–3 days

**Results:**

SrCr 358±161 to 145±78 umol/L ($P=<0.001$)

Reversal of HRS 83% (95% CI 52-98%)
Vasopressin vs. Norepinephrine

No study that directly compares vasopressin versus NE

Two studies evaluate terlipressin versus NE

1) Ottobrelli et al. 2007
   • Randomized, unblinded prospective pilot study $n=22$

2) Kumar et al. 2008
   • RCT, open label pilot trial $n=40$

Neither study showed a statistical difference in ADR

Both studies concluded that it appears NE is as efficacious as terlipressin in HRS
Vasopressin vs. Norepinephrine

Since its proposed benefit is due to vasoconstriction and less of a direct effect on renal hemodynamics, more data are needed before it can be recommended over vasopressin.

**Bottom line:** evidence would support the use of a vasopressin analogue over NE for the treatment of HRS
P: 19 cirrhotic patients with hepatorenal syndrome type 1 or 2

• Inclusion
  – renal failure (<40ml/min)
  – No evidence of hypovolemia, infection, previous nephrotoxic drugs
  – CVP > 5 mmHg
  – Renal failure despite plasma volume expansion
  – Ruled out organic renal failure*

• Exclusion
  – Heart/respiratory failure
  – Arterial hypertension
  – Hepatocellular carcinoma
  – Previous treatment with \( B \)-blocker(s) for GI bleed in past 7 days

Pomier 2003
### Table 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 9) (placebo first)</th>
<th>Group 2 (n = 7) (octreotide first)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio: M/F</td>
<td>7/2</td>
<td>5/2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.8 ± 3.2</td>
<td>53.9 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>HRS type 1</td>
<td>3/9</td>
<td>2/7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>83.3 ± 4.6</td>
<td>75.7 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pugh score</td>
<td>12.3 ± 0.4</td>
<td>12.1 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>7.1 ± 0.7</td>
<td>6.3 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>134 ± 1.8</td>
<td>134 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urea (µmol/L)</td>
<td>16.5 ± 2.1</td>
<td>14.3 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>215 ± 5.2</td>
<td>196 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>22.5 ± 5.2</td>
<td>15.7 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium (mEq/d)</td>
<td>7.0 ± 1.5</td>
<td>7.6 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance indices (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenteric artery</td>
<td>88.9 ± 1.7</td>
<td>85.5 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Renal artery</td>
<td>80.8 ± 1.3</td>
<td>77.5 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>5.7 ± 1.0</td>
<td>10.5 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>3,085 ± 1,686</td>
<td>2,193 ± 675</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucagon (pmol/L)</td>
<td>228 ± 86</td>
<td>131 ± 47</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** Values are expressed as mean ± SEM.
Abbreviation: NS, not significant.
Analysis 1.1. Comparison | Terlipressin versus placebo or no intervention, Outcome | Mortality.

Review: Terlipressin for hepatorenal syndrome

Comparison: | Terlipressin versus placebo or no intervention

Outcome: | Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadengue 1998</td>
<td>0/5</td>
<td>0/4</td>
<td></td>
<td>18.6%</td>
<td>0.0 [-0.34, 0.34]</td>
</tr>
<tr>
<td>Solanki 2003</td>
<td>7/12</td>
<td>12/12</td>
<td></td>
<td>50.2%</td>
<td>-0.42 [-0.70, -0.13]</td>
</tr>
<tr>
<td>Yang 2001</td>
<td>0/8</td>
<td>3/7</td>
<td></td>
<td>31.2%</td>
<td>-0.43 [-0.80, -0.05]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>25</strong></td>
<td><strong>23</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>-0.34 [-0.56, -0.12]</strong></td>
</tr>
</tbody>
</table>

Total events: 7 (Treatment), 15 (Control)

Heterogeneity: Chi² = 4.28, df = 2 (P = 0.12); I² = 53%

Test for overall effect: Z = 3.06 (P = 0.0022)
Analysis 1.2. Comparison 1 Terlipressin versus placebo or no intervention, Outcome 2 Creatinine clearance.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin versus placebo or no intervention

Outcome: 2 Creatinine clearance

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference (IV,Fixed,95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadenge 1998</td>
<td>4</td>
<td>5</td>
<td>12.3 % 11.00 [-3.16, 25.16]</td>
<td></td>
</tr>
<tr>
<td>Solanki 2003</td>
<td>12</td>
<td>12</td>
<td>25.3 % 55.00 [45.12, 64.88]</td>
<td></td>
</tr>
<tr>
<td>Yang 2001</td>
<td>8</td>
<td>7</td>
<td>62.4 % 10.00 [3.71, 16.29]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 24 24 100.0 % 21.49 [16.53, 26.46]

Heterogeneity: Chi² = 59.12, df = 2 (P<0.00001); I² = 97%
Test for overall effect: Z = 8.48 (P < 0.00001)
## Analysis 1.3. Comparison 1: Terlipressin versus placebo or no intervention, Outcome 3 Serum creatinine.

**Review:** Terlipressin for hepatorenal syndrome

**Comparison:** 1 Terlipressin versus placebo or no intervention

**Outcome:** 3 Serum creatinine

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solanki 2003</td>
<td></td>
<td>12</td>
<td>88 (34)</td>
<td></td>
<td>12</td>
<td>345 (44)</td>
<td>-257.00</td>
<td>63.9%</td>
<td>-257.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 2001</td>
<td></td>
<td>8</td>
<td>103 (21)</td>
<td></td>
<td>7</td>
<td>254 (53)</td>
<td>-151.00</td>
<td>36.1%</td>
<td>-151.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td><strong>20</strong></td>
<td><strong>103 (21)</strong></td>
<td><strong>19</strong></td>
<td><strong>254 (53)</strong></td>
<td><strong>-218.75</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>-218.75</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 15.73, df = 1 (P = 0.00007); I² = 94%

Test for overall effect: Z = 17.05 (P < 0.00001)
P: 13 cirrhotic patients with ascites and type 1 HRS

- Inclusion
  - Absence of recent GI bleed, infection, hepatic encephalopathy, or other complications
  - Absence of hepatocellular carcinoma at time of the study
  - Moderate to severe ascites
  - Diagnosis of type 1 functional renal failure by International Ascites Club
  - SrCr greater than 2.0 mg/dL (177 umol/L)
  - Absence of shock, fluid loss or nephrotoxic drugs
  - No improvement in renal function following at least 5 days of diuretic withdrawal and volume expansion
  - Proteinuria less than 500 mg/d
  - Urinary sodium excretion less than 10 mEq/L
  - Ratio between urine and plasma osmolality greater than 1
**TABLE 1. Clinical Parameters, Baseline Systemic Hemodynamics, Serum Sodium Concentration, and Renal and Liver Function Tests in Patients With HRS Treated With Nonpressor Doses of Dopamine (Group A) and With Midodrine and Octreotide (Group B)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 8)</th>
<th>Group B (n = 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 3</td>
<td>62 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of cirrhosis (alcoholic, HCV, HBV)</td>
<td>3/4/1</td>
<td>2/3/0</td>
<td>NS</td>
</tr>
<tr>
<td>Time from the appearance of ascites (yr)</td>
<td>2.7 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>0/1/7</td>
<td>0/1/4</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of peripheral edema (yes/no)</td>
<td>4/4</td>
<td>2/3</td>
<td>NS</td>
</tr>
<tr>
<td>Ascites (moderate/severe)</td>
<td>3/5</td>
<td>2/3</td>
<td>NS</td>
</tr>
<tr>
<td>Encephalopathy (yes/no)</td>
<td>3/5</td>
<td>1/4</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of type 2 HRS before the onset of type 1 HRS (yes/no)</td>
<td>4/4</td>
<td>2/3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum urea (mg · dL⁻¹)</td>
<td>167 ± 32</td>
<td>208 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.6 ± 0.6</td>
<td>5.0 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>128 ± 3</td>
<td>130 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.9 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>42.8 ± 5.4</td>
<td>44.4 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>6.1 ± 2.0</td>
<td>4.3 ± 1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** P values are the comparison between patients of group A and group B (Student’s t test for unpaired data and Fisher’s exact test).

Abbreviations: NS, not significant; HCV, hepatitis C virus; HBV, hepatitis B virus.
P: 25 patients with cirrhosis and ascites

- Inclusion
  - Absence of GI bleed, encephalopathy, infection, other complications
  - Absence of conditions requiring rapid relief of ascites
  - Positive sodium balance after at least 5 days of restricted intake
  - Diagnosis of cirrhosis based on liver histology or clinical and lab findings

- First five days of inclusion patients did not receive diuretics or other drugs with known effects on systemic and renal hemodynamics and/or renal function.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 9) (placebo first)</th>
<th>Group 2 (n = 7) (octreotide first)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio: M/F</td>
<td>7/2</td>
<td>5/2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.8 ± 3.2</td>
<td>53.9 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>HRS type 1</td>
<td>3/9</td>
<td>2/7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>83.3 ± 4.6</td>
<td>75.7 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pugh score</td>
<td>12.3 ± 0.4</td>
<td>12.1 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>7.1 ± 0.7</td>
<td>6.3 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>134 ± 1.8</td>
<td>134 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urea (μmol/L)</td>
<td>16.5 ± 2.1</td>
<td>14.3 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>215 ± 5.2</td>
<td>196 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>22.5 ± 5.2</td>
<td>15.7 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium (mEq/d)</td>
<td>7.0 ± 1.5</td>
<td>7.6 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance indices (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenteric artery</td>
<td>88.9 ± 1.7</td>
<td>85.5 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Renal artery</td>
<td>80.8 ± 1.3</td>
<td>77.5 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>5.7 ± 1.0</td>
<td>10.5 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>3,085 ± 1,686</td>
<td>2,193 ± 675</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucagon (pmol/L)</td>
<td>228 ± 86</td>
<td>131 ± 47</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Values are expressed as mean ± SEM.
Abbreviation: NS, not significant.