Role of Sympathetic Nervous System in Hypertension
BP = CO x PVR

SV $\times$ HR
“DEFENSE REACTION”

- Suppressed vagal activity
- Increased sympathetic activity to heart, veins, kidneys, splanchnic region, skin
- Skeletal muscle vasodilation
- Centralization of blood volume
- Rate dependent increase of C.O.
- Enhanced intestinal salt/water absorption
- Suppressed renal salt/water excretion
- Increased salt appetite
“DEFENCE REACTION”

- Long term Effects
  - Renin-angiotensin-aldosterone release with positive feedback to sympathetic NS
  - ACTH-glucocorticoid system
  - ADH system

- Metabolic effects, trophic influences, modulating membrane ionic events
Pre-synaptically \( \beta \) Receptors reinforce while the \( \alpha_2 \) receptor inhibits the release of nor-epinephrine into the synaptic cleft

\( \alpha_1 \) receptor mediates vasoconstriction

\( \alpha_2 \) also mediates vasoconstriction post-synaptically, but is part of a negative feedback loop pre-synaptically
SYMPATHETIC NERVE SYSTEM in HYPERTENSION

In young people with a family history of Htn, or young people with hypertension, studies have found them to have a hyper-dynamic circulatory system that evolves over time.
LONG TERM HEMODYNAMIC CHANGES

- Initial Hyperkinetic Circulatory State
  - Beta- increases C.O.
  - Alpha- level too active and does not allow for a reduction in PVR

- Normalized C.O. and Increased S.V.R.
  - Reduced beta- tone with age
  - Unopposed alpha tone leaves a high PVR
DOES STRESS LEAD TO HYPERTENSION?

- Long term studies are now reporting that people who tested as ‘high’ in anxiety/stress many years ago, are now more likely to be hypertensive compared to those persons who tested ‘low’ in anxiety, etc.

- Domains such as ‘demand’ and ‘control’ in the workplace, coupled with certain lifestyle issues (alcohol) also predict who is more likely to become ‘hypertensive’.
Effects of Age & Gender

- With age, especially after age 40 yrs, sympathetic nervous activity increases, especially in women.
- For each increase of 10 bursts/min in MSNA, the mean increase in MAP for men is 2.7 mmHg and 6.1 mmHg for women.
RENAL RESPONSE TO SYMPATHETIC NERVE STIMULATION

- Response increases with level of stimulation with:
  - Increased renin secretion rate
  - Decreased Na excretion with volume expansion
  - Decreased GFR and RBF
HYPERINSULINEMIA in OBESITY and the SNS

- Hyperinsulinemia leads to increased SNS activity
  - Increased cardiac output
  - Increased systemic vascular resistance
  - Increased BP
  - Increased Na reabsorption
Questions??
What classes of anti-hypertensive drugs should be considered in stage 1 or stage 2 hypertension?
CHEP Guidelines: Systolic/Diastolic Hypertension Without Compelling Indications

Target <140/90 mmHg

Lifestyle modification

Initial drug therapy

- Thiazide or thiazide-like diuretic
- ACEI
- ARB
- Long-acting CCB
- Beta-blocker*

Dual combination

Triple or quadruple therapy

A combination of two first-line drugs may be considered as initial therapy if BP ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic above target

CONSIDER
- Nonadherence
- Secondary HTN
- Interfering drugs or lifestyle

The combination of an ACEI + ARB should only be considered in selected and closely monitored people with advanced heart failure or proteinuric nephropathy

ACEI, ARB and direct renin inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

*Not indicated as first line therapy over 60 years

ACEI = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin II receptor blocker; CCB = Calcium channel blocker; CHEP Guidelines. http://www.hypertension.ca/chep-recommendations
Beta-Blocker Meta-analysis: Lindholm et al

Compared with other antihypertensives, BBs were associated with:
- 16% increase in stroke ($p = 0.009$)
- 3% increase in all-cause mortality (NS)

BUT

- Pooled end point was heterogeneous and largely driven by studies with mean age $\geq 60$ years
- No differences in MI, death or heart failure between BBs and other antihypertensives
- 14 of 18 studies used atenolol as the BB (86% of patients)
  - 4 trials used mixtures of atenolol, metoprolol, pindolol and/or propranolol (all 1st or 2nd generation BBs)

BB = Beta-blockers; MI = Myocardial infarction; NS = Not statistically significant
CHEP Position Statement on Beta-Blockers

• Beta-blockers are equally effective at reducing cardiovascular events as other BP-lowering classes in younger patients (< 60 years)
• Beta-blockers are strongly indicated in older hypertensive patients with angina, post-myocardial infarction or with congestive heart failure
• Beta-blockers reduce cerebrovascular events to a lesser extent than other BP-lowering drugs in older patients with uncomplicated hypertension

What are the key differences among the beta-blockers?
Evolution of Beta Blockers in Canada

1st Generation
Non-Selective
Propranolol

2nd Generation
Selective
Atenolol
Metoprolol
Bisoprolol

3rd Generation
Vasodilating (alpha blockade) Non-Selective
Carvedilol*
Labetalol

Vasodilating & Selective
Nebivolol

*Not approved for Hypertension in Canada

# Selectivity of Beta-Blockers

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Selected action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha₁</td>
<td>▪ Most vascular arteries and veins&lt;br&gt;▪ Sphincters of the bladder and GI tract&lt;br&gt;▪ Penis&lt;br&gt;▪ Iris dilator</td>
<td>Smooth muscle contraction</td>
</tr>
<tr>
<td>Beta₁</td>
<td>▪ Heart muscle&lt;br&gt;▪ Salivary glands&lt;br&gt;▪ Fat cells</td>
<td>Heart muscle contraction</td>
</tr>
<tr>
<td>Beta₂</td>
<td>▪ Bronchioles of lung&lt;br&gt;▪ Arterioles of skeletal muscles, brain and lungs&lt;br&gt;▪ Bladder wall&lt;br&gt;▪ GI tract</td>
<td>Smooth muscle relaxation</td>
</tr>
</tbody>
</table>

GI = Gastrointestinal
Beta₁ Receptor Selectivity of Nebivolol (Human Myocardium)

In Canada, carvedilol is indicated for heart failure only.

Beta₁ selectivity = $K_{i}(\beta_{2}) / K_{i}(\beta_{1})$. In extensive metabolizers and at doses less than or equal to 20 mg, nebivolol is preferentially beta₁ selective. Bristow M. Am J Hypertens 2005;18(Part 2):51A-52A.
Pharmacologic Characteristics of Beta-Blockers

<table>
<thead>
<tr>
<th></th>
<th>beta1 / beta2 selectivity</th>
<th>Half-life (h)</th>
<th>Lipophilicity</th>
<th>Vasodilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonselective beta-adrenergic antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>0</td>
<td>12-24</td>
<td>Low</td>
<td>N/A</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0</td>
<td>3-4</td>
<td>High</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Selective beta-adrenergic antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>+</td>
<td>6-9</td>
<td>Low</td>
<td>N/A</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>9-12</td>
<td>Moderate</td>
<td>N/A</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++</td>
<td>3-4</td>
<td>High</td>
<td>N/A</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>+++</td>
<td>8-27</td>
<td>High</td>
<td>Endothelium-dependent, NO-mediated vasodilation</td>
</tr>
<tr>
<td><strong>Alpha1-adrenergic and beta-adrenergic antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>+</td>
<td>3-4</td>
<td>Low</td>
<td>$\alpha_1$-adrenergic blocking activity; direct $\beta_2$ vasodilatory activity</td>
</tr>
<tr>
<td>Carvedilol*</td>
<td>0</td>
<td>7-10</td>
<td>Moderate</td>
<td>$\alpha_1$-adrenergic blocking activity, vasodilation</td>
</tr>
</tbody>
</table>

*In Canada, carvedilol is indicated for heart failure only
ISA = Intrinsic sympathomimetic activity, MSA = Membrane-stabilizing activity; N/A = Not applicable; NO = Nitric oxide
Adverse Events Commonly Associated with Beta-Blockers

- Bradycardia
- Dizziness
- Vertigo
- Fatigue
- Diarrhea
- Nausea
- Erectile dysfunction
- Cold extremities

Tenormin Product Monograph, Sept 2011
Inderal Product Monograph, Sept 2012
Hemodynamics of Non-vasodilating Beta-Blockers

Beta-blockade: BP Reduction and Hemodynamic Change

The general direction of hemodynamic change described above is typical in patients receiving a beta-blocker without vasodilatory properties. The hemodynamic profile will vary based on beta-receptor selectivity and patient-specific factors.

Hemodynamics of Nebivolol (5 mg) vs. Atenolol (100 mg) in Patients with Hypertension

Percent change vs. baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nebivolol 5 mg qd (n = 12)</th>
<th>Atenolol 100 mg qd (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral resistance (dyne/cm⁵)</td>
<td>-13.2*</td>
<td>5.8</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>20.6*</td>
<td>3.6</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>-24.0</td>
<td>7.1*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-15</td>
<td>-7*</td>
</tr>
</tbody>
</table>

The clinical significance of these changes is unknown

*p < 0.05 nebivolol versus atenolol
Systolic/diastolic BP reductions were -19/-12 mmHg for nebivolol and -16/-7 mmHg for atenolol
Parameters measured at 2 weeks.
Adapted from Kamp O, et al. Am J Cardiol 2003;92:344-8
What new beta-blocker is available for the management of hypertension?
Nebivolol: A Novel 3rd Generation Beta-Blocker

- Indicated for the treatment of mild to moderate hypertension, to lower BP
- Cardioselective beta-blocker with vasodilating properties
- Effective as monotherapy, combination therapy, and in populations which do not typically respond to beta-blocker therapy
- Maintains cardiac output and exercise tolerance
- Associated with a low incidence of side effects

Nebivolol Monotherapy Pooled Data: Change in Blood Pressure

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Nebivolol 5 mg</th>
<th>Nebivolol 10 mg</th>
<th>Nebivolol 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BP (mmHg)</td>
<td>152.2/99.5</td>
<td>152.1/99.3</td>
<td>152.7/99.2</td>
<td>151.9/99.2</td>
</tr>
<tr>
<td>n</td>
<td>156</td>
<td>409</td>
<td>410</td>
<td>410</td>
</tr>
</tbody>
</table>

Mean change in blood pressure from baseline (mmHg):

- Baseline BP: 152.2/99.5
- Dose: Placebo, Nebivolol 5 mg, Nebivolol 10 mg, Nebivolol 20 mg

*SBP = Systolic blood pressure; DBP = Diastolic blood pressure

*p < 0.001 for all pairwise comparisons of active treatment vs. placebo

Germino FW. Clin Ther 2009;31:1946-56
### Nebivolol Monotherapy Pooled Data: Adverse Events

The most common adverse events occurring in ≥2% of patients taking nebivolol monotherapy

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=205) %</th>
<th>Nebivolol 5 mg (n=459) %</th>
<th>Nebivolol 10 mg (n=461) %</th>
<th>Nebivolol 20 mg (n=460) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.9</td>
<td>8.9</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.5</td>
<td>2.2</td>
<td>2.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.4</td>
<td>3.7</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.0</td>
<td>1.5</td>
<td>2.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.0</td>
<td>2.4</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2.4</td>
<td>2.4</td>
<td>1.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Bystolic (nebivolol tablets) Product Monograph, Forest Laboratories Canada Inc., January 2013
Effect of Nebivolol vs. Metoprolol on Erectile Function: Study Design

Effect of Nebivolol vs. Metoprolol on Erectile Function: IIEF

Brixius K et al. Clin Exper Pharmacother 2007;34:327-331

*p < 0.05 vs. baseline; † p < 0.05 vs. metoprolol
IIEF = International Index of Erectile Function

Change in score from baseline

-1.0 -0.5 0.0 0.5 1.0 1.5

Erectile function  Orgasmic function  Sexual desire  Intercourse satisfaction  Overall satisfaction

Nebivolol 5 mg
Metoprolol 100 mg
Nebivolol vs. Amlodipine: Change in BP

*$p < 0.05$ between the groups

DBP = Diastolic blood pressure; SBP = Systolic blood pressure

Nebivolol vs. Amlodipine: Tolerability

Frequency of adverse events (n)

- Nebivolol 2.5-5 mg/day (n = 81)
- Amlodipine 5-10 mg/day (n = 87)

*p = 0.0358 vs. nebivolol
Nebivolol: Contraindications

- Severe bradycardia (generally < 50 bpm before start of therapy)
- Cardiogenic shock
- Decompensated heart failure
- Second or third degree atrioventricular block
- Sick sinus syndrome or sinoatrial block
- Severe hepatic impairment (Child-Pugh >B)
- Severe peripheral arterial circulatory disorders
- Hypersensitivity to any component of this product

bpm = beats per minute
Summary: Beta-blockers in Hypertension

- Beta-blockers are equally effective at reducing CV events as other BP-lowering classes in younger patients (< 60 years)
  
- Beta-blockers are recommended as a first-line option for patients (with uncomplicated hypertension <60 years of age), as add-on therapy, and for hypertensive patients with angina, post-MI or congestive HF (CHEP 2013)
  
- Beta-blockers are a heterogeneous class
  
- Outcomes seen in older clinical trials seem to be more of a drug effect than a class effect
  
- Newer vasodilatory beta-blockers such as nebivolol are promising

BP = Blood pressure; CV = Cardiovascular; HF = Heart failure; MI = Myocardial infarction
NeuroModulation or Denervation for Hypertension Management
Breathing Control Device - RESPERATE
The CVRx® Rheos System

- Implantable Pulse Generator
- Baroreflex Activation Leads
- Programming System
Ability to Personalize and Control the Therapy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Volt</th>
<th>2 Volts</th>
<th>3 Volts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>71</td>
<td>56</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>210 / 96</td>
<td>168 / 73</td>
<td>156 / 72</td>
<td>144 / 66</td>
</tr>
</tbody>
</table>
Renal Nerves and the SNS

Afferent Renal Sympathetics

The kidney is a source of central sympathetic drive in hypertension, heart failure, chronic kidney disease, and ESRD

Efferent Sympathetic Activation

Patients cannot develop and/or maintain elevated BP without renal involvement

↑ Vasoconstriction
↓ RBF/GFR
↑ Renin
↑ Na+/Volume
↑ HR
↑ Contractility
Renal Sympathetic Innervation

**Increased afferent signalling from the kidney to central integrative brain structures**
- Adenosine
- Acidosis
- Oxidative stress
- Inflammation
- Endothelial factors
- Angiotensin II
- Ischaemia

**Kidney norepinephrine spillover**

**Renal injury/renal ischaemia**
- Sodium and water retention
- Reduced renal blood flow
- Activation of the RAAS
- Proteinuria
- Glomerulosclerosis

**Whole body norepinephrine spillover**

**Increased efferent sympathetic outflow to the kidney and other organs**
- Remodelling
- Hypertrophy
- Arrhythmias
- Ischaemia
- Apoptosis

**Medial hyperplasia**
- Decreased arterial compliance
- Endothelial dysfunction
Placement
Renal Sympathetic Nerves as Therapeutic Target

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
Ablation Catheter has electrodes on Multiple sites along Sides of the Catheter
Blood-pressure changes (mm Hg) in resistant hypertension patients with and without renal denervation

<table>
<thead>
<tr>
<th>Time mo</th>
<th>Renal denervtn (n=45)</th>
<th>Nontreated (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-14/-10</td>
<td>+3/-2</td>
</tr>
<tr>
<td>3</td>
<td>-21/-10</td>
<td>+2/+3</td>
</tr>
<tr>
<td>6</td>
<td>-22/-11</td>
<td>+14/+9</td>
</tr>
<tr>
<td>9</td>
<td>-24/-11</td>
<td>+26/+17</td>
</tr>
<tr>
<td>12</td>
<td>-27/-17</td>
<td>—</td>
</tr>
</tbody>
</table>

Krum H et al. Lancet 2009
Conclusions

- The SNS plays an important role in the development and maintenance of htn
- Beta-blockers, particularly vasodilating beta-blockers, can be useful in lowering BP
- Medical devices for SNS denervation should be considered investigational until there is a better understanding of adverse effects.
Questions??