Pathophysiology of Hypertension and Pain Management

Heejung Choi, MD
Assistant Professor
Anesthesiology
Northwestern McGaw Medical Center

William B. White, MD
Professor Emeritus
Calhoun Cardiology Center
University of Connecticut School of Medicine
Pathophysiology of Pain and Pharmacologic Treatment for Pain

Heejung Choi, MD
Assistant Professor, Anesthesiology
Northwestern McGaw Medical Center
The opinions expressed in this presentation (and/or slides) are solely those of the presenter and not necessarily of the American Heart Association / American Stroke Association (AHA/ASA). The AHA/ASA does not endorse any specific products or devices.

Dr. Choi has no disclosures.
• Pathophysiology of pain management including pain pathways

• Overview of pharmacologic treatment for pain
Definition of Pain

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

- International Association for the Study of Pain

Pain is always a *personal* experience.

Pathophysiology of Pain

Perception of Stimulus

1. Transduction
2. Transmission
3. Modulation
4. Perception


Rene Descartes, 1662
Perception of Stimulus

1. Transduction
   - Peripheral terminals of primary afferent neurons
2. Transmission
   - Peripheral sensory cells in dorsal root ganglion (DRG) to spinal cord
   - Spinal neurons second order neurons project to thalamus, brainstem, diencephalon
   - Brainstem and diencephalon neurons form third component to cortical sites
3. Modulation
   - Dorsal horn of spinal cord including DRG
4. Perception
   - Cortex and subcortical regions

How we fail black patients in pain

Janice A. Sabin, PhD, MSW

January 6, 2020

# Types of Pain

<table>
<thead>
<tr>
<th>Pain</th>
<th>Description</th>
<th>Onset and Course</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td>Sharp</td>
<td>Correlated with injury</td>
<td>Area of injury or trauma</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Achy, dull, stabbing</td>
<td>Progressive, affected by activity</td>
<td>Localized to the inflammation/infection</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Burning, electric, shooting</td>
<td>Insidious, progressive</td>
<td>Radiates from nerve damage</td>
</tr>
</tbody>
</table>

Types of Pain

ACUTE vs. CHRONIC

CANCER vs. NON-CANCER
Pharmacologic Treatment of Pain

- Opioids
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
  - Selective COX-2 inhibitors
  - Nonselective COX inhibitors
- Acetaminophen

- Antidepressants
  - Tricyclic antidepressants (TCAs)
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
  - Selective serotonin reuptake inhibitors (SSRIs)
- Antiepileptics
  - Calcium channel blockers
  - Sodium channel blockers
- Local anesthetics
Hypertension Pathophysiology and Non-Opioid Pain Management Considerations for Patients with Hypertension and/or Cardiovascular Disease in the Hospital

William B. White, MD
Professor Emeritus
Calhoun Cardiology Center
University of Connecticut School of Medicine
Disclosures

- Cardiovascular safety consultant (CV endpoint committees and data safety committees): Astra-Zeneca, Bristol-Myers Squibb, Cerevel, Clarion, Clexio, JAZZ, Johnson & Johnson, Millenium-Takeda, Protalix, UCB
- Educational consultant: Wolter Kluwers and UpToDate
- Speaker’s bureaus – NONE
- Stock ownership in pharmaceutical or device companies - NONE
- Patents related to lecture - None

THE OPINIONS EXPRESSED IN THIS PRESENTATION (AND/OR SLIDES) ARE SOLELY THOSE OF THE PRESENTER AND NOT NECESSARILY OF THE AMERICAN HEART ASSOCIATION / AMERICAN STROKE ASSOCIATION (AHA/ASA). THE AHA/ASA DOES NOT ENDORSE ANY SPECIFIC PRODUCTS OR DEVICES.
Blood Pressure Values

- Blood pressure is traditionally measured using an air-filled cuff around the arm (sphygmomanometer) with values expressed in millimeters of mercury (mmHg)
- Major blood pressure values derived from sphygmomanometry:
  - SBP (systolic blood pressure): maximum within-cycle pressure in the arteries
  - DBP (diastolic blood pressure): minimum within-cycle pressure in the arteries
  - PP (pulse pressure): within-cycle pressure range (PP=SBP – DBP)
  - MAP (mean arterial pressure): mean blood pressure for each cardiac cycle (MAP=1/3 PP + DBP [usually])

AMBULATORY BLOOD PRESSURE MONITORING

ABPM devices are programmed to measure the patient’s blood pressure at preset intervals throughout a 24-hour period.

Advantages:
- Detects dipping patterns that may increase cardiovascular risk
- Elucidates subsets of hypertension (e.g., white coat hypertension (WCH), masked, borderline, and refractory hypertension)
- Multiple readings throughout the day may reveal patterns in blood pressure and periods when control is inadequate

24-hour Blood Pressure Tracing With Hypertension

**Systemic Hemodynamics**

\[
\text{MAP} = \text{CO} \times \text{SVR}
\]

- **Increased Blood Volume** (salt and water retention)
- **SNS Activation**
- **RAAS Activation**
- **Arteriolar Constriction**

CO (cardiac output)  SVR (systemic vascular resistance)  HR (heart rate)  SV (stroke volume)
SNS (sympathetic nervous system)  RAAS (renin-angiotensin-aldosterone system)

Arteriolar Hypertrophy in Hypertension (Arteriolosclerosis)

NORMAL

HYPERTENSION

Arteriolar smooth muscle hypertrophy causes

- ↑ wall thickness
- ↑ systemic vascular resistance (chronic)
- ↑ pressure-dependency of salt and water excretion (pressure natriuresis curve)

Mechanical (chronic ↑ blood pressure)
Humoral (e.g., norepinephrine, angiotensin II)

Pathogenesis of Wide Pulse Pressure

Blood Pressure Regulatory Systems

- Interactive regulatory systems integrate short-term and long-term cardiovascular and metabolic responses

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>RESPONSE TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNS</td>
<td>Seconds to minutes</td>
</tr>
<tr>
<td>RAAS</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Kidney (salt and water balance)</td>
<td>Hours to days</td>
</tr>
</tbody>
</table>

- These regulatory systems remain the major target of antihypertensive drugs

Angiotensin II Generation and Effects

Angiotensinogen → Renin

Tissue: Heart, Brain, Kidney, Arteries

Systemic: Liver

Angiotensin I → ACE

Bradykinin, Substance P, Enkephalins, Other Peptides

Angiotensin II

Inactive Fragments

Angiotensin Receptors

AT₁

AT₂

SNS activation, Arteriolar constriction, Aldosterone release, Free radical generation

Thirst, Vasopressin release, Cardiac and smooth muscle hypertrophy

ACE bypass pathways

Angiotensin converting enzyme

Salt-sensitivity

- Physiology
  - “Low renin states” (e.g., elderly) tend to be salt-sensitive but the condition also occurs in higher renin populations (e.g., obesity)
  - In research studies of salt-sensitivity, the exaggerated BP response to salt and water loading is due to increased vasoconstriction (or failure to adequately suppress vasoconstrictive systems)
- There is no routine clinical test for salt-sensitivity
- Probably about half of hypertensives are salt-sensitive
- Populations with increased salt-sensitivity:
  - Chronic kidney disease
  - Diabetics
  - African Americans
  - Elderly
  - Obese
  - Non-steroidal anti-inflammatory drug users

## SPRINT Primary Outcome and its Components

### Event Rates and Hazard Ratios

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Events</strong></td>
<td><strong>Rate, %/year</strong></td>
<td><strong>Rate, %/year</strong></td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>243</td>
<td>319</td>
</tr>
<tr>
<td>All MI</td>
<td>97</td>
<td>116</td>
</tr>
<tr>
<td>Non-MI ACS</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>All Stroke</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>All HF</td>
<td>62</td>
<td>100</td>
</tr>
<tr>
<td>CVD Death</td>
<td>37</td>
<td>65</td>
</tr>
</tbody>
</table>

### ACC/AHA Guidelines for BP Thresholds and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>BP Threshold, mm Hg</th>
<th>BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td><strong>Specific comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Heart failure</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Whelton P et al. Hypertension 2018 Table 23

30
For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

SR indicates systematic review.

### Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal &lt;130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.</td>
</tr>
</tbody>
</table>

## Causes of Secondary Hypertension With Clinical Indications

<table>
<thead>
<tr>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Renovascular disease</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Drug or alcohol induced</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma/paraganglioma</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Aortic coarctation (undiagnosed or repaired)</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Mineralocorticoid excess syndromes other than primary aldosteronism</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
</tbody>
</table>

83 y/o woman with a history of difficult to control hypertension despite a 6 – medication regimen!

• Hospital admissions for TIA, hypertensive urgency and AKI with various providers

• History of Heart Failure with preserved ejection fraction (EF of 60%)

• History of longstanding osteoarthritis of the knees and hips with chronic pain

• CKD Stage IIIB (eGFR – 23.9 ml/min/1.73m²)
  o Baseline Serum Cr ~2.0
Hospitalization due to progression of CKD

Sept 2017
BUN/Cr 96/3.9
K 5.0
BP 162/62 mmHg

9/3/17
BUN/Cr 101/5.0
K 5.4
Continuous diuresis and PO BP meds
BP 160-180/60-70 mmHg
Selective Right Renal Angiogram before and after Percutaneous Intervention

CO2 Angiography

99% Right Ostial Renal Artery Stenosis

Herculink 6.5x18mm

Pre stenting

Post stenting
Blood Pressures Following Renal Revascularization
# Kidney Function Following Revascularization

<table>
<thead>
<tr>
<th>DATE</th>
<th>Events</th>
<th>BUN (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>eGFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 2007</td>
<td></td>
<td>34</td>
<td>1.1</td>
<td>51.8</td>
</tr>
<tr>
<td>INFINITY TRIAL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aug 2017</td>
<td>Resumed OTC Naproxen</td>
<td>69</td>
<td>2.1</td>
<td>23.9</td>
</tr>
<tr>
<td>1st Sept 17</td>
<td>ARB dosed once</td>
<td>94</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>2nd Sept 17</td>
<td></td>
<td>96</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>3rd Sept 17</td>
<td></td>
<td>101</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>6th Sept 17</td>
<td>Angioplasty</td>
<td>91</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>7th Sept 17</td>
<td></td>
<td>61</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>8th Sept 17</td>
<td></td>
<td>40</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>25th Sept 17</td>
<td></td>
<td>29</td>
<td>1.2</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Potential Effects of NSAIDs on Cardiorenal Physiology

Arachidonic acid

PGE$_2$
Prostaglandin

COX-1

COX-2

NSAIDs

PGI$_2$
Prostacyclin

Sodium retention
• Peripheral edema
• ↑ Blood pressure
• ↑ Weight
• CHF (rarely)

Hyperkalemia

Acute renal failure

Effects of COX-2 Selective Inhibitors on Systolic BP in Treated Hypertensives (n = 1092)

![Graph showing change in systolic BP for ACE inhibitors, β-blockers, and CCBs with COX-2 inhibitors. Celecoxib 200 mg (n=549) and Rofecoxib 25 mg (n=543). P values: <0.001, 0.04, 0.87.]

The Effect of Aspirin Alone and of Ibuprofen Plus Aspirin on Platelet Cyclooxygenase-1

A. Platelet cyclooxygenase-1

- Catalytic site
- Serine residue at position 529
- Channel of access
- Arachidonic acid
- Platelet

B. Following aspirin

- Acetyl serine

C. With ibuprofen and aspirin

- Ibuprofen

* ns-NSAID in this model was ibuprofen
Effect of Ibuprofen on Aspirin’s Inhibition of Platelet Aggregation

P < .001.
*Ibuprofen, 400 mg; aspirin, 81 mg.
Stepped Care Approach to Pharmacologic Therapy for Musculoskeletal Symptoms With Known CV Disease or Risk Factors for Ischemic Heart Disease

- Acetaminophen, ASA, tramadol, narcotic analgesics (short term)
- Nonacetylated salicylates

Select patients at low risk of thrombotic events

Prescribe lowest dose required to control symptoms

Add ASA 81 mg and PPI to patients at increased risk of thrombotic events*
Considerations from the Rheumatology Community

- The rheumatologist has to weigh the desirable and undesirable effects of NSAIDs and decide what is best for their individual patient.
- The bottom line: There must be a balance in the benefit-risk ratio, the patient must be informed, and physicians must be knowledgeable.
- Sufficient treatment options are of critical importance in the management of pain and arthritis.
Thank You.