Hypertension: Not so Simple
(Simplicity Trial)

Bharat Sachdeva MD
Associate Professor
LSU Health Shreveport
RESISTANT HYPERTENSION

- **Resistant Hypertension**
  - BP > 140/90 mmHg
  - 3 or more medications
    - Adequately dosed
    - Includes a diuretic agent

- **Prevalence**
  - 2/3 require ≥ 2 meds to achieve target BP
  - Framingham Heart Study, REACH, and NHANES (30-50%) achieve target BP

Cushman et al, J Clin Htn 2002; 4: 393-404
Egan et al Circulation 2011
Daugherty et al Circulation 2012; 125: 1635
De la Sierra et al Hypertension 2011; 57: 898
RESISTANT HTN – CLINICAL TRIALS

First-in-Man (AU)

Series of Pilot Studies (EU, US & AU)

SYMPLICITY HTN-2/3
Initial RCT (EU & AU)

SYMPLICITY HTN-1

VESSEX

SPYRAL

Global SYMPLICITY Registry (Approved Regions)

Pilot Studies in New Indications (Approved Regions)

SYMPLICITY CKD HF

DREAMS

EnligHTN-1

EnligHTN-2

SYMPLICITY HTN-1

PUBLISHED
SYMPPLICITY HTN-1

Change in Blood Pressure (mmHg)

6 MONTHS (N=144) 1 YEAR (N=132) 2 YEARS (N=105) 3 YEARS (N=88)

-22
-10
-14
-14
-14
-32

Systolic

Diastolic
SYMPPLICITY HTN-2

CONTROL (N=51)  |  RDN (N=49)  |  TREATMENT GROUP (N=40)

6 Months

<p>| | | |</p>
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<tbody>
<tr>
<td>SBP 1</td>
<td>DBP 0</td>
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6 Months

<table>
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<tr>
<th>SBP</th>
<th>DBP</th>
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<td>-32</td>
<td>-12</td>
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36 Months

<table>
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<th>DBP</th>
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<td>-33</td>
<td>-14</td>
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Compared to baseline, p<0.01

6 month primary endpoint, p<0.0001
Global SYMPPLICITY Registry

Change in Blood Pressure (mmHg)

- **Systolic**
- **Diastolic**

* SBP≥150 among diabetics

* P≤0.001 for all comparisons

- 3 MONTHS
  - SBP≥140: -13
  - SBP≥160: -15
  - SBP≥180: -22

- 6 MONTHS
  - SBP≥140: -18
  - SBP≥160: -19
  - SBP≥180: -22

- 12 MONTHS
  - SBP≥140: -29
  - SBP≥160: -29
  - SBP≥180: -37
GLOBAL SYMPPLICITY REGISTRY

• SAFETY (N=1,158)
  – No device related complications
  – 9% had angiographic RA abnormalities without flow disturbance
  – 2 vascular complications
  – 1 RA dissection
SYMPLICITY HTN-3 Trial

Design

Screening Visit 1
- Office SBP ≥160 mm Hg
- Full doses ≥3 meds
- No med changes in past 2 weeks
- No planned med changes for 6 M

Screening Visit 2
- Office SBP ≥160 mm Hg
- 24-h ABPM SBP ≥135 mm Hg
- Documented med adherence

Sham Procedure
- Renal angiogram; Eligible subjects randomized

Renal Denervation

Primary endpoint
- Home BP & HTN med confirmation

1 M 3 M

12-60 M

2 weeks

2 weeks

• Patients, BP assessors, and study personnel all blinded to treatment status
• No changes in medications for 6 M

Primary Safety Endpoint

Performance Goal = 9.8%

P < 0.001

1.4%

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation (N=364)</th>
<th>Sham Procedure (N=171)</th>
<th>Difference [95% CI]</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAE</td>
<td>1.4% (5/361)</td>
<td>0.6% (1/171)</td>
<td>0.8% [-0.9%, 2.5%]</td>
<td>0.67</td>
</tr>
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</table>

Primary Efficacy Endpoint

Δ = -2.39 (95% CI, -6.89 to 2.12)

P=0.26*

Δ = -14.1 ± 23.9

P<0.001

Δ = -11.7 ± 25.9

P<0.001

Office SBP (mm Hg)

180 mm Hg

166 mm Hg

180 mm Hg

168 mm Hg

(N=364) (N=353)

(N=171) (N=171)

Denervation

Sham

Baseline

6 Months

*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Change in Office SBP by Tertile of Baseline Office Office SBP

Denervation

Control

N=124
N=54

N=107
N=61

N=119
N=54

<170 mm Hg
-6.6
P=0.57

170 – 184 mm Hg
-13.8
P=0.29

>184 mm Hg
-19.7
P=0.13

## Results: Pre-specified Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Difference (95% CI) mm Hg</th>
<th>P Value</th>
<th>Interaction P Value</th>
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<tr>
<td></td>
<td>Denervation</td>
<td>Sham</td>
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<tr>
<td>All patients</td>
<td>353</td>
<td>171</td>
<td>-2.39 (-6.89 – 2.12)</td>
<td>0.26 *</td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>169</td>
<td>68</td>
<td>-4.53 (-11.51 – 2.46)</td>
<td>0.20</td>
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<tr>
<td>No</td>
<td>181</td>
<td>101</td>
<td>-3.46 (-9.55 – 2.62)</td>
<td>0.26</td>
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<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>208</td>
<td>108</td>
<td>-2.30 (-7.63 – 3.03)</td>
<td>0.40</td>
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<tr>
<td>Female</td>
<td>142</td>
<td>61</td>
<td>-6.64 (-14.94 – 1.65)</td>
<td>0.12</td>
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<td>African American</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>85</td>
<td>49</td>
<td>2.25 (-7.27 – 11.78)</td>
<td>0.64</td>
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<tr>
<td>No</td>
<td>264</td>
<td>120</td>
<td>-6.63 (-11.81 – 1.44)</td>
<td>0.01</td>
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<tr>
<td>BMI</td>
<td></td>
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<tr>
<td>&lt;30 kg/m²</td>
<td>91</td>
<td>42</td>
<td>-2.77 (-11.47 – 5.93)</td>
<td>0.53</td>
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<tr>
<td>≥30 kg/m²</td>
<td>259</td>
<td>126</td>
<td>-4.36 (-9.76 – 1.03)</td>
<td>0.11</td>
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<tr>
<td>On AA at baseline</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>76</td>
<td>47</td>
<td>-8.05 (-17.63 – 1.52)</td>
<td>0.10</td>
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<tr>
<td>No</td>
<td>274</td>
<td>122</td>
<td>-3.24 (-8.42 – 1.93)</td>
<td>0.22</td>
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<tr>
<td>eGFR</td>
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<tr>
<td>&lt;60 ml/min/1.73 m²</td>
<td>68</td>
<td>38</td>
<td>0.54 (-8.29 – 9.37)</td>
<td>0.90</td>
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<tr>
<td>≥80 ml/min/1.73 m²</td>
<td>282</td>
<td>131</td>
<td>-5.22 (-10.51 – 0.06)</td>
<td>0.05</td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>&lt;65 yr</td>
<td>246</td>
<td>128</td>
<td>-5.73 (-11.06 – 0.40)</td>
<td>0.04</td>
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<tr>
<td>≥65 yr</td>
<td>104</td>
<td>41</td>
<td>0.09 (-8.80 – 8.99)</td>
<td>0.99</td>
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<tr>
<td>Any medication change</td>
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<tr>
<td>Yes</td>
<td>132</td>
<td>70</td>
<td>-5.41 (-13.49 – 2.67)</td>
<td>0.19</td>
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<tr>
<td>No</td>
<td>218</td>
<td>99</td>
<td>-3.44 (-8.83 – 1.96)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*P value for superiority with margin of 5 mm Hg*  
What Happened?

- Drug adherence
- Medication changes
- 6 months follow up
- Was complete ablation achieved?
- Operator learning

Despite widespread clinical use, little is known regarding the translation of RDN to sympathetic activity

THE EFFECT OF RENAL DENERVATION ON THE LEVEL OF ARTERIAL BLOOD PRESSURE AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

BY IRVINE H. PAGE AND GEORGE J. HEUER

(From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Department of Surgery, New York Hospital, New York)

(Received for publication September 12, 1934)
SYMPATHETIC NERVOUS SYSTEM
RELATIONSHIP WITH HYPERTENSION

• The majority of patients with resistant hypertension and no secondary cause have elevated SNS activity.

• Surgical interventions
  – Techniques: radical sympathectomy and splanchnicectomy.
  – Employed in 1920-40s for treatment of malignant hypertension (100% 5 year mortality)
  – Results:
    • Improvement in blood pressure
    • Survival benefit
  – Limitations:
    • High surgical complexity
    • Significant side-effects
  – Replaced by advent of medical therapy
Renal Sympathetic Nerve Activity (RSNA)

- Anatomic location of nerves allows endovascular access for denervation.
- Endovascular ablation techniques:
  - Radiofrequency ablation
  - Ultrasound
  - Injection of neurotoxin
RSNA

• Increased RSNA
  – obesity, sleep apnea and use of BP meds

• Renal norepinephrine (NE)
  – Limitations to widespread use of measures for assessing RSNA by measuring renal NE spill

• Mineralocorticoid-induced hypertension

• Resistant HTN associated/not associated with RSNA
151 studies found for: renal denervation
Modify this search | How to Use Search Results

151 studies found, shown on map.
A similar map is available for all studies in ClinicalTrials.gov

Click on the map below to show a more detailed map (when available) or search for studies (when map not available).

Colors indicate the number of studies with locations in that region

Least  |  |  | Most
Conclusion

• Renal denervation was thought to be the solution for all patients

• SIMPLICITY HTN-1 and HTN-2:
  – great magnitudes of blood pressure reduction

• SYMPLICITY HTN-3: Mixed results
  – lower blood pressure reduction
  – extent of the denervation

• Defining the right population in which to study RND is critical to moving forward
Role of Peritoneal Dialysis in the Treatment of Severe Pulmonary Hypertension

Bharat Sachdeva MD
Associate Professor
LSU Health Shreveport LA
Case

• 58 Yr Old AA Male
• History of HTN, Cocaine (2000’s), AKI on HD for 2 years 2000-2001, CKD
• Incarcerated 2010-2011
• Hypertension; 2001-2010
• BP controlled on 2-3 medications, compliance poor
Case

- Seen in Pulmonary clinic 3/2011 for SOB and DOE
  - All SEROLOGY NEGATIVE
  - SPIROMETRY: NO EVIDENCE OF AIR FLOW OBSTRUCTION
  - NO H/O HEART FAILURE OR THROMBOEMBOLIC DISORDERS
  - GFR 40-50ml/min
- RIGHT HEART CATH
  - RIGHT ATRIAL PRESSURE TO BE 13 mmHg
  - RIGHT VENTRICULAR PRESSURE 74/11 mmHg
  - PULMONARY ARTERY PRESSURE OF 74/37 mmHg
  - WEDGE PRESSURE OF 11 mmHg
  - LVEDP 8 mmHg
Diagnostic Tests

- High resolution chest CT: No ILD
- Arterial blood Gas: Normal
- Hepatitis serology: Normal
- Left heart catheterization: Normal
- Cardiopulmonary exercise study
- Bubble study negative
Ventilation Perfusion Lung Scan

PAH

CTEPH

Perf

Vent

Perf

Vent
Management  PAH

- Started on Sildenafil TID
- Amlodipine
- Lisinopril
- Asprin
PH in ESRD

• Prevalence up 48% on echo reported in literature$^{1-4}$
  – Only 10-14% had est. sPAP>45-50 mm Hg$^1$

• Largest study: 500 pts, 68 (13%) on PD
  – Mean sPAP: 47±9 mm Hg, range: 35-75 mm Hg
  – 5.9% incidence in PD patients
  – Longer duration of dialysis in PH pts, 51 vs 30 months

• Patients with PH had:
  – Higher CO$^{1-3}$
  – Worse survival$^{1,3}$

3. Issa et al, Transplantation, 2008
5. Hemnes et al, Nephrol Seminar, 2010
<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest before test is performed</td>
<td>Immediately after Test is performed</td>
</tr>
<tr>
<td>• HR: 62</td>
<td>• HR: 111</td>
</tr>
<tr>
<td>• Dyspnea: 1</td>
<td>• Dyspnea: 1</td>
</tr>
<tr>
<td>• Fatigue: 1</td>
<td>• Fatigue: 1</td>
</tr>
<tr>
<td>• SPO2: 97</td>
<td>• SPO2: 92</td>
</tr>
</tbody>
</table>

Other symptoms at end of 6MWT:
Dyspnea no Fatigue no Angina no Dizziness no Leg Pain no

# of Laps: 5 (x60meters) + final partial lap 0(m) - 0 total meters.

Total distance walked in 6 min: 300 meters.
6-MW 2013

Baseline
At rest before test is performed

- HR: 52
- Dyspnea: 1
- Fatigue: 1
- SPO2: 98

Post Test
Immediately after Test is performed

- HR: 94
- Dyspnea: 8
- Fatigue: 9
- SPO2: 98

Other symptoms at end of 6MWT:
Dyspnea yes Fatigue yes Angina no Dizziness no Leg Pain no

# of Laps: 5 (x60meters) + final partial lap 48(m) - 0 total meters.

Total distance walked in 6 min: 348 meters.
6-MW 8-2014

Baseline
At rest before test is performed

- HR: 65
- Dyspnea: 8
- Fatigue: 8
- SPO2: 91

Post Test
Immediately after Test is performed

- HR: 79
- Dyspnea: 10
- Fatigue: 9
- SPO2: 92

Other symptoms at end of 6MWT:
Dyspnea yes Fatigue yes Angina no Dizziness no Leg Pain no

# of Laps: 4 (x60 meters) + final partial lap 0(m) - 0 total meters.

Total distance walked in 6 min: 240 meters.
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<th>Value</th>
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<tr>
<td>RA</td>
<td>23</td>
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<tr>
<td>RV</td>
<td>86</td>
</tr>
<tr>
<td>RV Mean</td>
<td>7</td>
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<tr>
<td>PA</td>
<td>86/34</td>
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<tr>
<td>PCWP</td>
<td>21</td>
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<tr>
<td>CO/CI</td>
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<tr>
<td>SVR/SVRi</td>
<td>1667/3350</td>
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<tr>
<td>PVR/PVRi</td>
<td>562/1197</td>
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<tr>
<td>SYSTEMIC BP</td>
<td>147/95</td>
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</table>
Sildenafil

TADALIFIL

Sildenafil

Ambrisentan
Targets for current PAH-specific therapy

**Prostacyclin Pathway**
- Arachidonic Acid
  - Prostacyclin Synthase
    - Prostacyclin
      - cAMP
        - Prostacyclin Derivatives

**Endothelin Pathway**
- Big Endothelin
  - Endothelin-converting Enzyme
    - Endothelin-1
      - Endothelin Receptor Antagonists
        - Endothelin Receptor A
        - Endothelin Receptor B

**Nitric Oxide Pathway**
- Arginine
  - Nitric Oxide Synthase
  - Nitric Oxide
    - cGMP
      - Exogenous Nitric Oxide
        - Phosphodiesterase Type-5
          - Phosphodiesterase Type-5 Inhibitors

**Vasodilatation and Antiproliferation**

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<td>RA</td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>70/5</td>
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<tr>
<td>RV Mean</td>
<td></td>
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<td>70/30</td>
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<tr>
<td>CO/CI</td>
<td>6.1/2.9</td>
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<td>SVR/SVRi</td>
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<td>PVR/PVRI</td>
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<td>SYSTEMIC BP</td>
<td>147/95</td>
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Progression

- Persistent Volume Overload
- Diuretic Resistance
- Hypoxia
- Multiple Admissions
  - Oct 14 – Mar 15
Adjunctive treatments of PAH

• Salt restriction
• Diuretics
• Oxygen
• Anticoagulation
• Digoxin
• Calcium channel blockers
• Exercise
What are the Options for our patients

• Acute on Chronic Injury?
• Poor Hemodynamics
• CKD patient who has not had HD access placed during follow up
• Poor Surgical Candidate
• ??Candidate for long term dialysis
Reduction in systolic BP during hemodialysis in patients with and without HD-induced regional wall motion abnormalities

Burton J O et al. CJASN 2009;4:914-920
Change in EF at rest and during HD over 12 m in patients with fixed reductions in segmental function of >60%

Burton J O et al. CJASN 2009;4:1925-1931
Rate of Sudden Cardiac Death in Prevalent ESRD patient by Modality

Deaths per 1,000 patient years

- Hemodialysis
- Peritoneal dialysis


USRDS 2013
Probability of Sudden Cardiac Death in Incident ESRD patient by modality

![Graph showing the probability of sudden cardiac death over months after initiation for hemodialysis and peritoneal dialysis. The probability increases over time for both modalities, but hemodialysis shows a higher probability.]
Urgent Start: PD Prescription

• Lower volumes (500-1000 ml)
• Glucose concentration and Dwell time (2-4 hours); clinically determined
  – Volume, electrolytes, UF goal
• Recumbent position, drain before ambulation
• Daily exchanges, variable time
• Treatment time- during dialysis unit hours of operation, 8a to 5 p
• Labs biweekly
Urgent Start PD

CKD patient who will need RRT within **TWO WEEKS** of placement of the PD catheter

Therapy is initiated with **SUPINE/LOW VOLUME** for a period of two weeks until the Cuff is well healed

Dialysis centers are not equipped to deal with unstable Uremic patients (Volume, Hyperkalemia, Uremic.....)

Selecting the right patients is imperative to the overall success of the program
Benefits of Urgent-Start PD

• **Avoids the placement and use of a central venous catheter (CVC)**:!!
  – Infections
  – Hospitalizations
  – Loss of Central vein patency!

• Care can be provided in the outpatient setting if patient is clinically stable

• **Training starts** concurrent with dialysis

• 80% start HD dialysis using a catheter [USRDS]

• Incident HD--CVC patients have an 80% higher risk of death in the first year compared with incident PD patients [Perl Jet al.JASN 2011,22(6)]
Conclusions

PAH and CKD cause difficulty with diuresis

Fluoroscopic PD catheter insertion and Urgent Start

Modality of RRT should be individualized for each patient