Appropriate Patient Selection for Renal Denervation

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Today's Talk

Appropriate Patient Selection for RDN

- **Overview of current indication of RDN**
  - Current indication and patient selection of RDN
- **Extended indication for RDN**
  - Beyond BP lowering
- **In case of non-responders after RND**
  - Redo-RND, treatment option? Case review

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Symplicity HTN-2 Trial

Inclusion Criteria:

- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:

- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m^2 (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

Symplicity HTN-2 Investigators. The Lancet. 2010.

Resistant Hypertension
by AHA definition

- Uncontrolled Hypertension (Not at target BP), in spite of concurrent use of 3 medications of different classes including diuretics

- At target BP, but need ≥4 medications

Optimal blood pressure (<140/90mmHg, <130/80mmHg for DM)

We need "True Resistant Hypertension" !

Approach to Resistant Hypertension

Identify and reverse **contributing factor**

Smoking, Alcohol, Salt, Caffeine, Obesity, Other drugs…

Discontinue and/or minimize **interfering substance**

Screen for **Secondary HTN**

Renovascular HTN, Pheochromocytoma, Sleep apnea, Primary hyperaldosteronism…

Exclude **pseudo-resistance**

White-coat effect,
In-accurate BP measurements,
In-adequate BP regimens (Diuretics),
Poor compliance to BP medications,

Calhoun DA et al. Circulation 2008;117:e510-526

Management of resistant Hypertension; Optimizing treatment

Pharmacologic Treatment

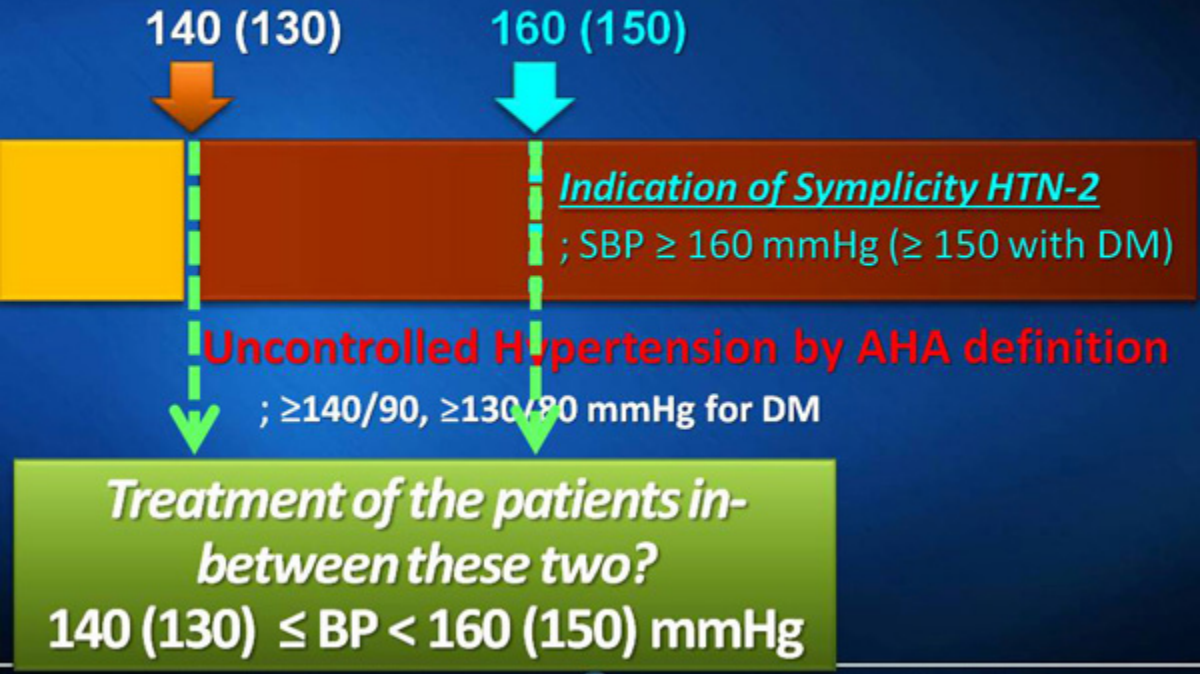
- Maximize diuretic therapy, including possible addition of mineralocorticoid receptor antagonist
- Combine agents with different mechanisms of action
- Use of loop diuretics in patients with chronic kidney disease and/or patients receiving potent vasodilators (eg, minoxidil)

Limitations of Current Pharmacologic Strategies d/t …

- Sub-optimal BP in spite of maximized therapy
- Increased Side effects due to maximized dosage of drugs

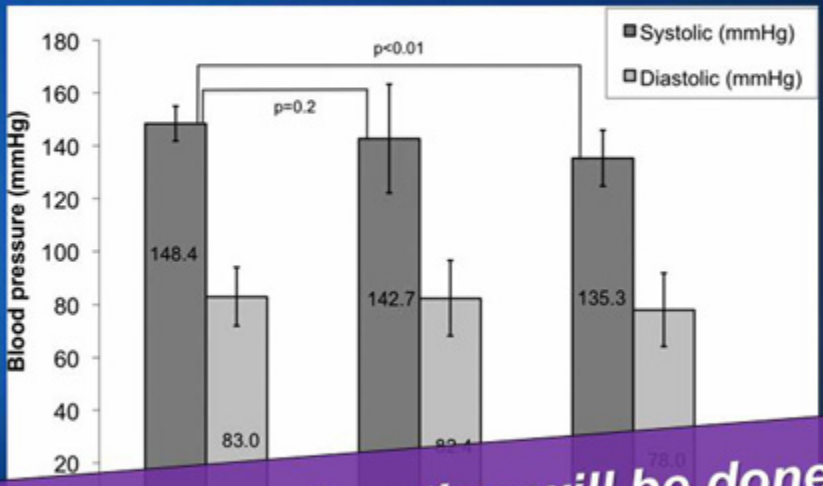
Catheter-based renal sympathetic denervation

Target BP; <140/90, <130/80 mmHg for DM



RDN and Less Severe HTN

Patients with office systolic BPs of 140–160 mm Hg despite ≥ 3 antihypertensive medications treated with CRD were included in this prospective study.



Detailed explanation will be done by Prof Choi in the next Talk…

Kaltenbach B, CCI 2013;81:335-9.

Symplicity HTN-2 Trial

Inclusion Criteria:

- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regime
- Age 18-85 years

RDN in renal insufficiency?

Exclusion Criteria:

- Hemodynamically or anat… significant renal artery abnormalities or prior renal artery inter…tion
- eGFR < 45 mL/min/1.73m^2 (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

Symplicity HTN-2 Investigators. The Lancet. 2010.

Renal Denervation in Moderate to Severe CKD

Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

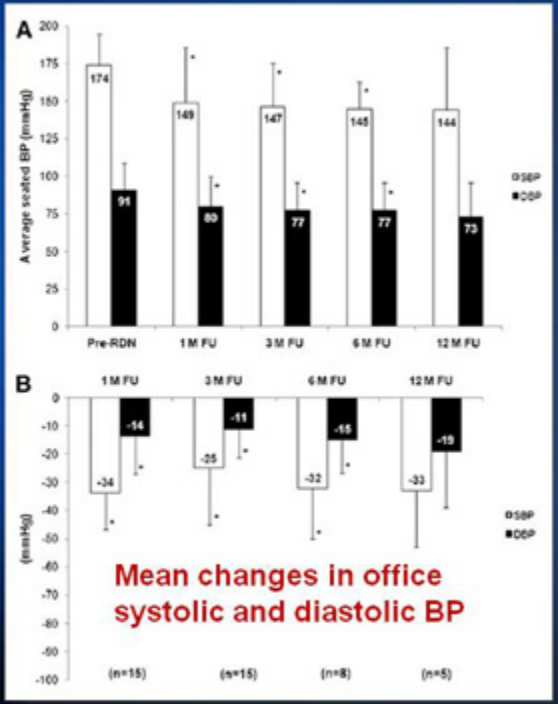
*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

ABSTRACT

Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) < 45 ml/min per 1.73 m^2 is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3–4 CKD (mean eGFR, 31 ml/min per 1.73 m^2). We used CO_2 angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO_2 angiography. Mean baseline BP ± SD was 174±22/91±16 mmHg despite the use of 5.6±1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were −34/−14, −25/−11, −32/−15, and −33/−19 mmHg, respectively. Night-time ambulatory BP significantly decreased ($P<0.05$), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3–4 CKD and resistant hypertension.

J Am Soc Nephrol. 2012;23:1250-7.

Outcomes of CKD patients after RDN



- Estimated GFR remained unchanged after the procedure, irrespective of the use of CO2 angiography (n=6).
- The main results are as follows:
  (1) selective, bilateral RDN is safe and effective in patients with stage 3–4 CKD;
  (2) bilateral renal denervation is not associated with acute or short-term deterioration of renal function.
- RDN for ESRD is on-going.

RDN for resistant hypertension with ESRD?

Renal Denervation in a Hypertensive Patient With End-Stage Renal Disease and Small Arteries: A Direction for Future Research

Christian Ott, MD;[1] Axel Schmid, MD;[2] Tilmann Ditting, MD;[1] Paul A. Sobotka, MD;[3,4] Roland Veelken, MD;[1] Michael Uder, MD;[2] and Roland E. Schmieder, MD[1]

From the Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany;[1] the Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany;[2] The Ohio State University, Columbus, OH;[3] and Coridea-NC1, New York, NY[4]

Sympathetic overactivity plays a crucial pathogenetic role in the maintenance and aggravation of arterial hypertension in patients with end-stage renal disease (ESRD). Renal denervation has been shown to be effective and safe in reducing blood pressure (BP) in patients with treatment-resistant hypertension; however, there are only case reports in hypertensive patients with ESRD and data are lacking about possibility of renal denervation in small renal arteries. A woman with uncontrolled treatment-resistant hypertension on chronic hemodialysis underwent bilateral native kidney, catheter-based renal denervation. Both native renal arteries were <4 mm. After 6 months without any change of antihypertensive medication or hemodialysis parameters, the authors observed a remarkable BP reduction of 38/30 mm Hg (from baseline 172/100 mm Hg to 134/70 mm Hg) as evaluated by 24-hour ambulatory BP monitoring. The authors report that renal denervation seems to be effective in controlling hypertension in patients with ESRD, even in cases of small renal arteries.
J Clin Hypertens (Greenwich). 2012;14:799–801.

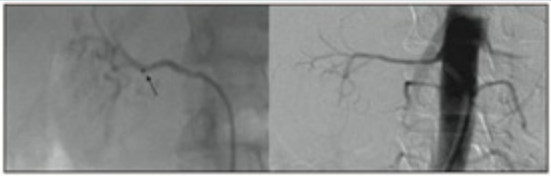


FIGURE. Left panel: Angiography of the right renal artery (diameter 2.6 mm) with positioned Symplicity catheter (tip marked with arrow; Medtronic Ardian Inc, Palo Alto, CA) at the first point of radiofrequency ablation. Right panel: Angiography of the right renal artery after renal denervation.

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Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease

Markus P. Schlaich [a,b,c,*], Bradley Bart [d], Dagmara Hering [a,e], Anthony Walton [b], Petra Marusic [a], Felix Mahfoud [f], Michael Böhm [f], Elisabeth A. Lambert [a,c], Henry Krum [g], Paul A. Sobotka [h,i], Roland E. Schmieder [j], Carolina Ika-Sari [a], Nina Eikelis [a], Nora Straznicky [a], Gavin W. Lambert [a,c], Murray D. Esler [a]

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ABSTRACT

Background and objectives: Sympathetic activation is a hallmark of ESRD and adversely affects cardiovascular prognosis. Efferent sympathetic outflow and afferent neural signalling from the failing native kidneys are key mediators and can be targeted by renal denervation (RDN). Whether this is feasible and effective in ESRD is not known.

Design, setting, participants and measurements: In an initial safety and proof-of-concept study we attempted to perform RDN in 12 patients with ESRD and uncontrolled blood pressure (BP). Standardized BP measurements were obtained in all patients on dialysis free days at baseline and follow up. Measures of renal noradrenaline spillover and muscle sympathetic nerve activity were available from 5 patients at baseline and from 2 patients at 12 month follow up and beyond.

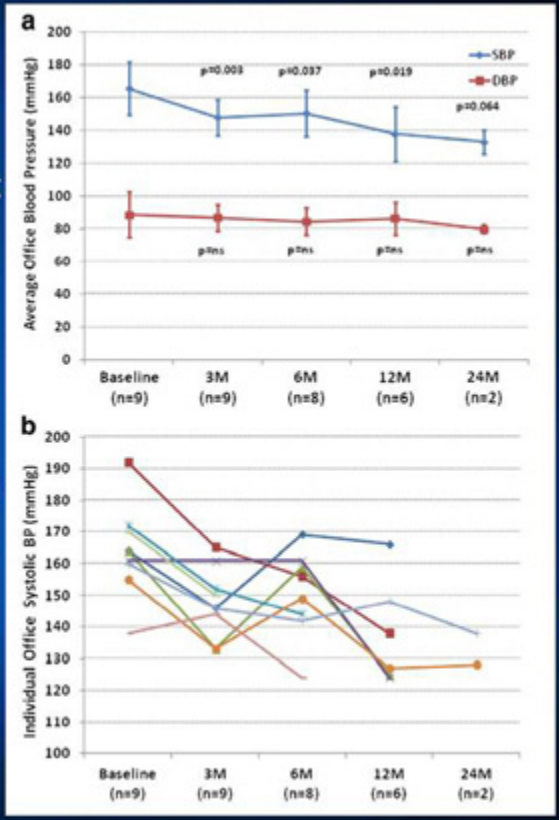
Results: Average office BP was 170.8 ± 16.9/89.2 ± 12.1 mm Hg despite the use of 3.8 ± 1.4 antihypertensive drugs. All 5 patients in whom muscle sympathetic nerve activity and noradrenaline spillover was assessed at baseline displayed substantially elevated levels. Three out of 12 patients could not undergo RDN due to atrophic renal arteries. Compared to baseline, office systolic BP was significantly reduced at 3, 6, and 12 months after RDN (from 166 ± 16.0 to 148 ± 11, 150 ± 14, and138 ± 17 mm Hg, respectively), whereas no change was evident in the 3 non-treated patients. Sympathetic nerve activity was substantially reduced in 2 patients who underwent repeat assessment.

Conclusions: RDN is feasible in patients with ESRD and associated with a sustained reduction in systolic office BP. Atrophic renal arteries may pose a problem for application of this technology in some patients with ESRD.

RDN for ESRD

- Three out of 12 patients could not renal arteries.

- Compared to baseline, office systolic BP was significantly reduced at 3, 6, and 12 months after RDN (from **166** ±16.0 to **148** ±11, **150** ±14, and **138**±17 mmHg, respectively).



Symplicity HTN-2 Trial

Inclusion Criteria:

- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years
- **Mild resistant hypertension may be added in the inclusion criteria.**

- *Some case-reports regarding these…*
- *Await further data.*

Exclusion Criteria:

- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- ~~eGFR < 45 mL/min/1.73m^2 (MDRD formula)~~ *Be excluded from exclusion criteria.*
- Type 1 diabetes mellitus
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

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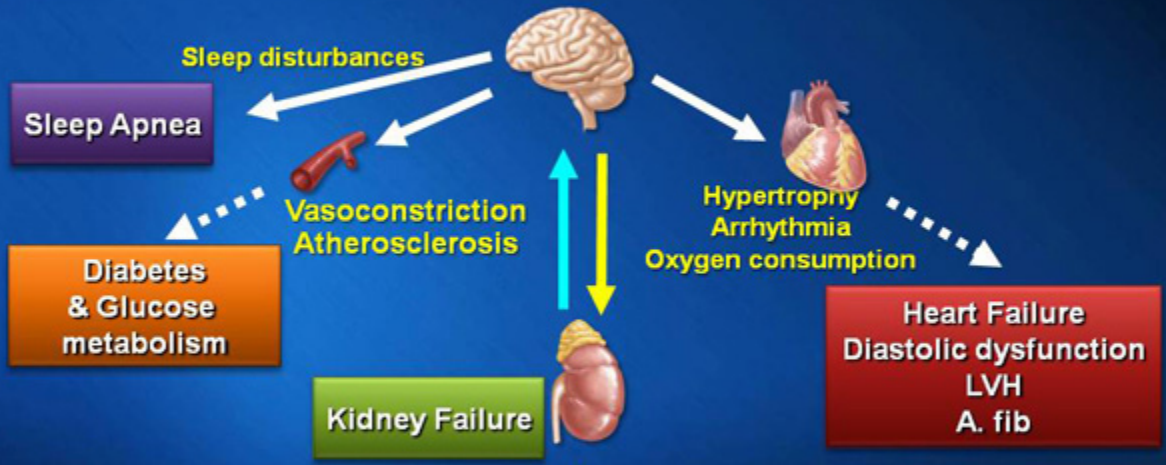
Chronic activation of renal nerves is common in multiple conditions.



RAAS = renin-angiotensin-aldosterone system.

1. Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.
2. Blankestijn PJ, et al. *Nephrol Dial Transplant*. 2011;26:2732-2734.

1. RDN for the patients with advanced heart failure

- **Background**

- Sympathetic over-activation, one of pathologic features of HF.
- **Due to the part of concerns about potential concomitant deleterious BP reductions**

  → A similar role for RDN in CHF remains unstudied.

First-in-man safety evaluation of renal denervation for chronic systolic heart failure: Primary outcome from REACH-Pilot study

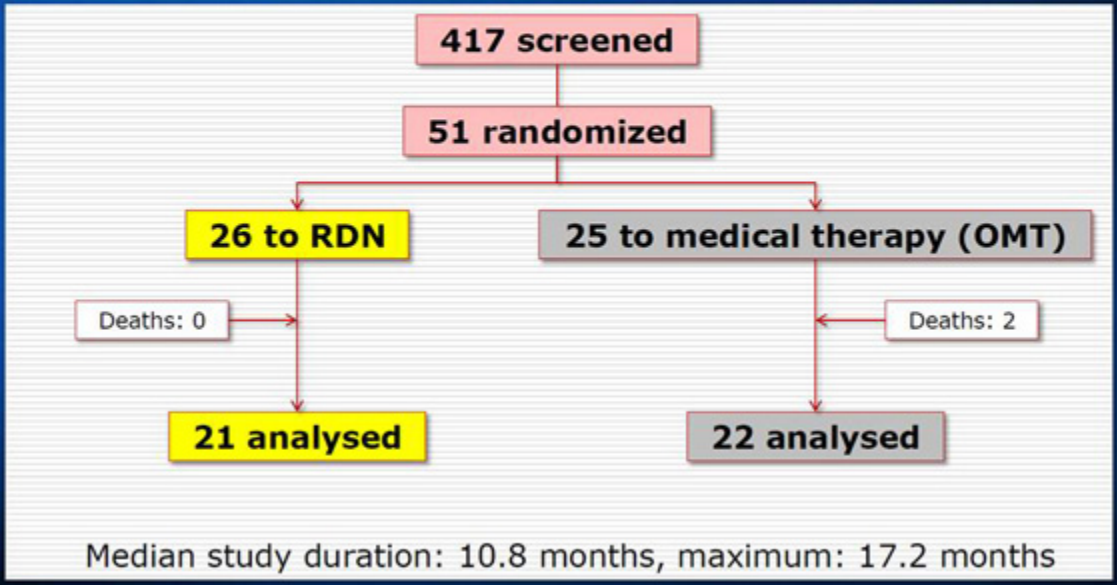
Justin E. Davies [a,*], Charlotte H. Manisty [a], Ricardo Petraco [a], Anthony J. Barron [a], Beth Unsworth [a], Jamil Mayet [a], Mohamad Hamady [a], Alun D. Hughes [a], Peter S. Sever [a], Paul A. Sobotka [b], Darrel P. Francis [a]

- Method: 7 patients (mean age 69 years) c ch' systolic HF (mean BP = 112/65 mm Hg)
- Results:
  - No significant hemodynamic disturbances during post RDN.
  - Over 6 months, non-significant trend to BP reduction (Δsystolic −7.1±6.9 mm Hg, p=0.35; Δdiastolic −0.6±4.0 mm Hg, p=0.88).
  - No hypotensive or syncopal episodes, no deterioration of renal function.
  - All patients described themselves as symptomatically improved.
  - 6-min walk distance at 6 months was significantly increased (Δ=27.1±9.7 m, p=0.03).

Int J Cardiol 2012 in-press

The effect of renal denervation in patients with advanced heart failure:

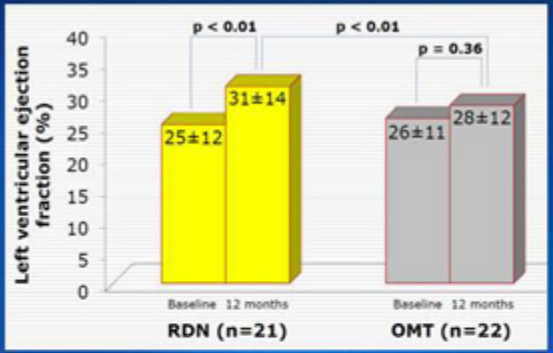
OLOMOUC I Study



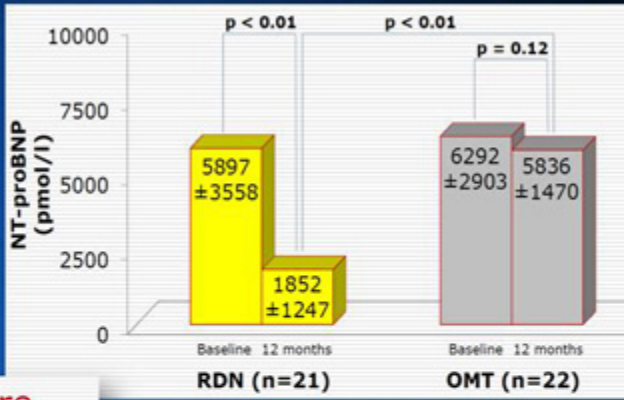
Median study duration: 10.8 months, maximum: 17.2 months

M. Taborsky, et al. presented at 2012 ESC

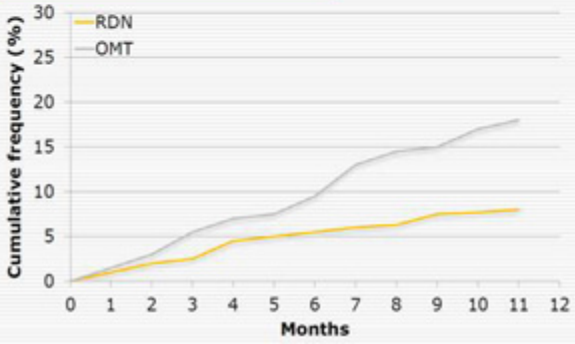
Change in LVEF



Change in NT-proBNP

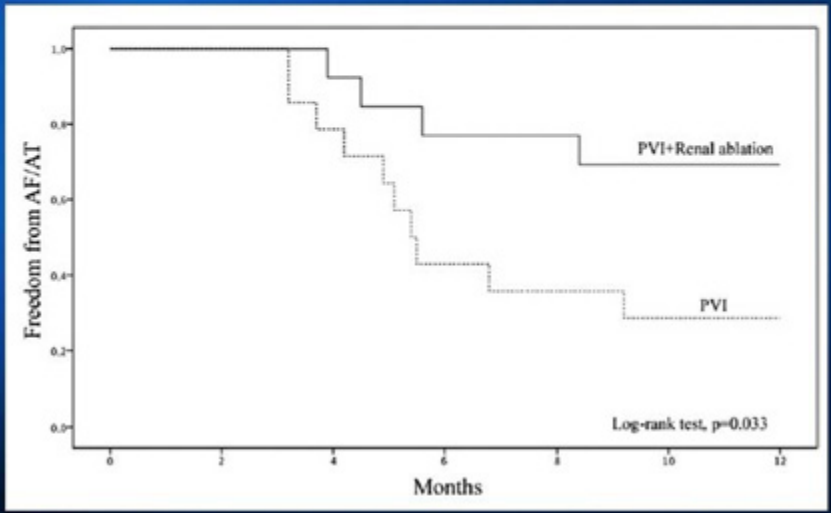


Hospitalization for heart failure



2. RDN and AF (PVI)

- Incidence of AF Recurrences in Patients With and Without RDN: The group that underwent both pulmonary vein isolation (PVI) and renal artery ablation has a significantly reduced AF recurrence rate over time compared with the control PVI-only group.



Poushkalov et al., *JACC* 2012

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SEVERANCE

Redo-RDN; Is this another treatment option for non-responders after first RDN ?

CASE

Patient history

YWK 5871613

- F/31
- C.C: Uncontrolled Blood pressure (SBP >200mmHg)
- Height / BWt: 165cm / 89.6kg (BMI 32.9kg/m^2)
- P.Hx:
  - Preeclampsia [5yrs and 3yrs ago];
    - one 5-year-old boy and abortion 3 yrs ago
  - Diabetes Mellitus (1yrs on regular PO medication
- ROS: Headache (+), Nausea/Vomiting (+/+), Blurred vision (+)
- Lab :

CBC	8300 / 11.6 / 384 K (/μL)
Electrolyte	140 / 3.9 / 97 / 24
BUN / Cr	22 / 1.07 (mg/dL)
AST / ALT	22 / 20 (IU/L)
T.pro / alb	7.5 / 4.3 (g/dL)
T3 / fT4 / TSH	1.11 / 1.18 / 1.35 (ng/mL/ ng/mL/μIU/mL)

Laboratory findings

• Renin / Aldosterone	8.21 (ng/mL/hr)/ 16.23 (ng/mL) (NL; 1.31-3.95) / (NL; 3.8-30.68)
• PAC / PRA	1.98
• 24hr Urine Metanephrine	144 μg/day (0-300)
VMA	5.98 mg/day (0-8.0)
• Overnight Dexamethasone suppression test	0.9 ug/dL (NL <1.8 ug/dL)
• 24hrs Urine cortisol	85.3 ug/day (20.0 ~ 90.0)

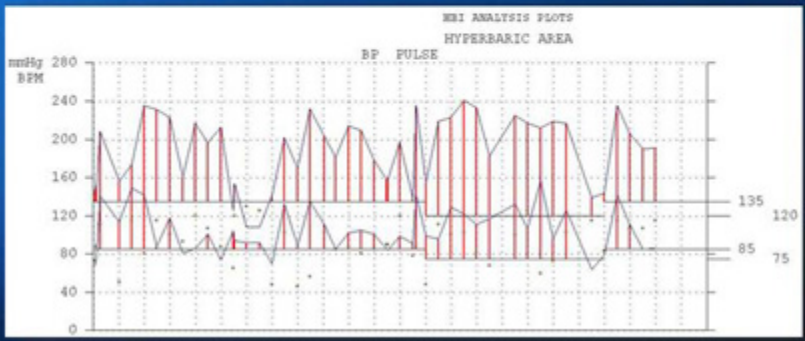
 # All values, within normal range.

Medication

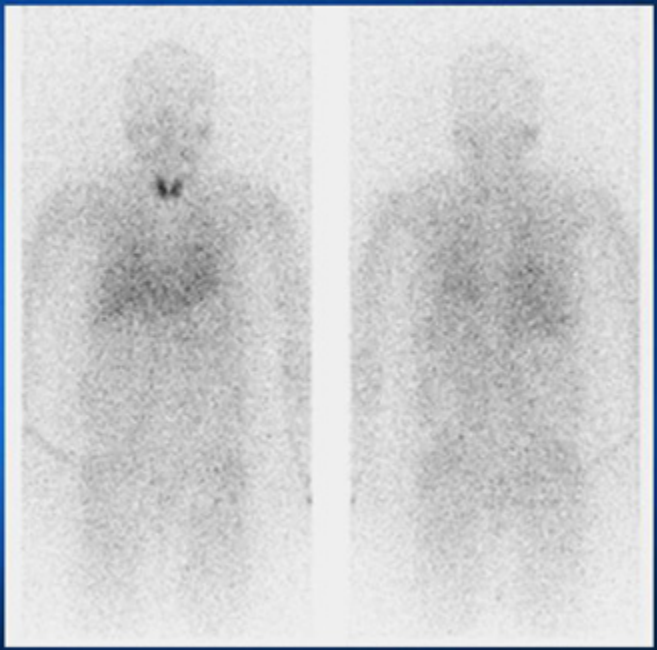
Telmisartan 80mg qd
Hygroton 25mg BID
Benidipine 4mg BID
Diltiazem 90mg BID
Propranol 40mg TID
Doxazocin 4mg BID
& IV Nicardipine infusion 2.1mg/hr

24hr BP monitoring

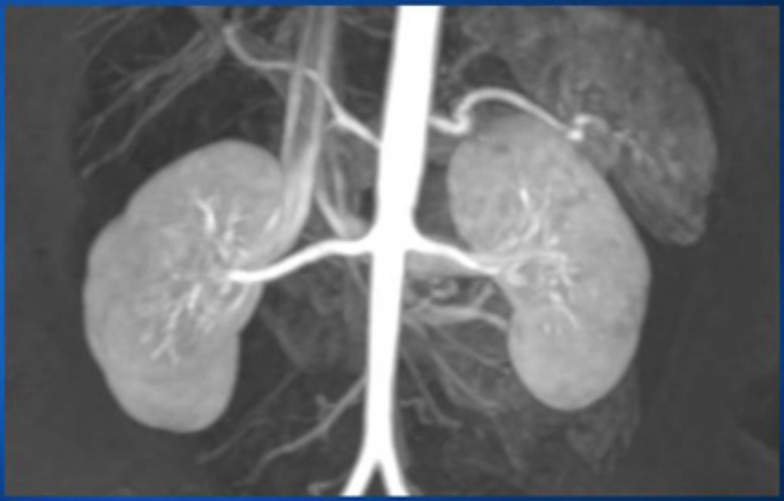
- Full mean BP
  ; 189/104 mmHg
- Awake mean BP
  ; 183/102 mmHg
- Sleep mean BP
  ; 207/113mmHg



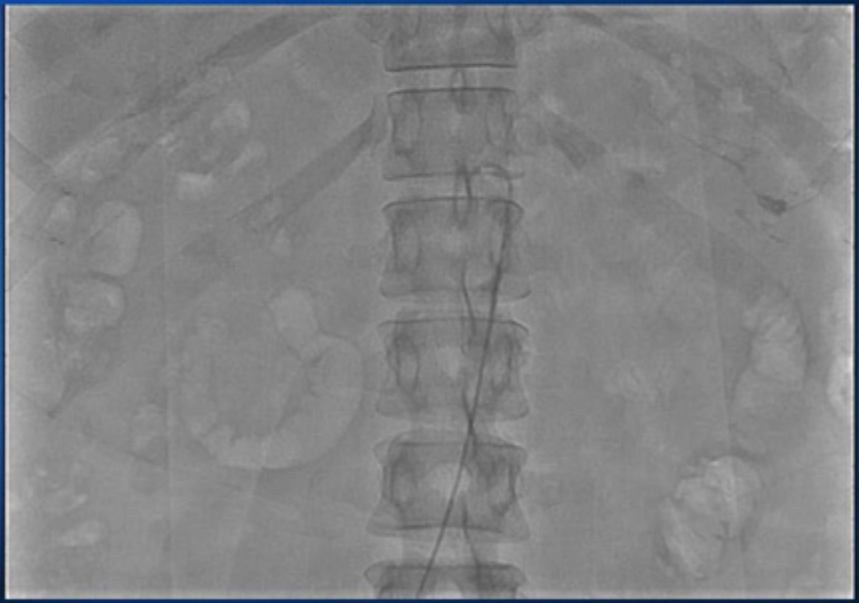
I-123 MIBG Scan



MR angio & renal



1st Renal Artery Denervation (April 2. 2012)
Renal Angiography



Renal Denervation: Right Kidney

Ablation 1

- Impedance; 270Ω
- % impedance drop; -9%
- Maximal Temp; 48.3°C

Ablation 2

- Impedance; 285Ω
- % impedance drop; -17%
- Maximal Temp; 55.3°C

Ablation 3

- Impedance; 274Ω
- % impedance drop; -15%
- Maximal Temp; 60.8°C

Ablation 4

- Impedance; 270Ω
- % impedance drop; -8%
- Maximal Temp; 47.5°C

Ablation 5

- Impedance; 257Ω
- % impedance drop; -14%
- Maximal Temp; 54.5°C

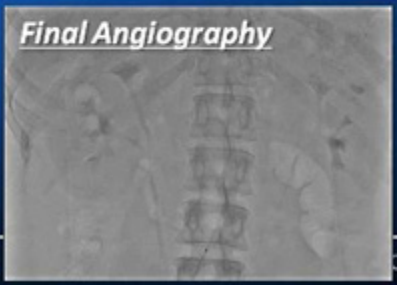
Ablation 6

- Impedance; 254Ω
- % impedance drop; -14%
- Maximal Temp; 56.5°C

Ablation 7

- Impedance; 271Ω
- % impedance drop; -17%
- Maximal Temp; 58.1°C

Final Angiography



Renal Denervation: Left Kidney

Ablation 1

- Impedance; 267Ω
- % impedance drop; -12%
- Maximal Temp; 58.3°C

Ablation 2

- Impedance; 311Ω
- % impedance drop; -15%
- Maximal Temp; 58.8°C

Ablation 3

- Impedance; 260Ω
- % impedance drop; -9%
- Maximal Temp; 46.8°C

Ablation 4

- Impedance; 272Ω
- % impedance drop; -12%
- Maximal Temp; 57.7°C

Ablation 5

- Impedance; 245Ω
- % impedance drop; -10%
- Maximal Temp; 57.1°C

Ablation 6

- Impedance; 253Ω
- % impedance drop; -10%
- Maximal Temp; 51.6°C

Blood pressure after RDN during 3 months

Medication Summary

** PO Antihypertensive agent

Telmisartan 80mg qd

Propranolol 40mg tid

Benidipine 4mg bid, Diltiazem 180mg bid

Furosemide 80mg bid, Aldactone 200mg bid

Doxazocin 4mg bid, Minoxidil 200mg bid

** IV Antihypertensive agent

Labetalol : 0.16mg/min (2012.09.24 ~)

Nitroprusside : 0.2mcg/kg/min (2012.09.28 ~)

**** Isosorbide dinitrate + Sildenafil** (2012.6.24-7.8) **→ Decrease of SBP up to 110mmHg**

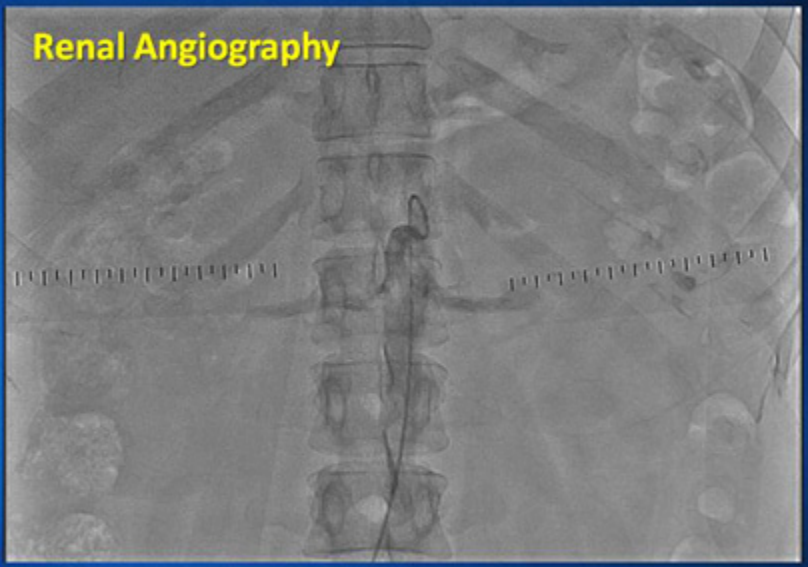
→ Re-elevation of BP 4 days later

→ Stop medication after 2 weeks

- Hospitalization for 3 months after RDN because of iv drug. → not discharge up to 6 months !
- Transfer other hospital for 2nd opinion.
  - → No changes of BP
  - → Recommend "Surgical thoraco-sympathectomy"
  - → Re-transfer our institute.
- No specific causes for 2ndary hypertension including renal, adrenal, and various hormonal deficiency SDs.
- Normal renal function

Finally, we decided to perform "Redo-RDN" considering high operation risks and possibility of incomplete denervation at prior RDN or BP reduction by a more complete sympathetic deactivation.

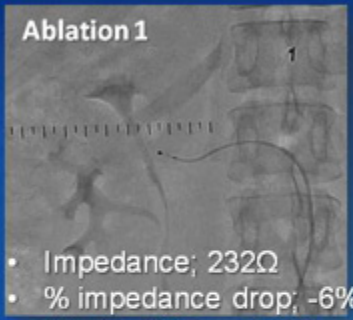
Redo-RDN (December 20, 2012)



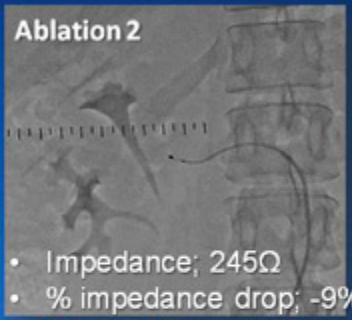
Strategy of redo-RDN

- **Increase the frequency of ablation maximally (at least more than 6), when renal anatomy permits.**

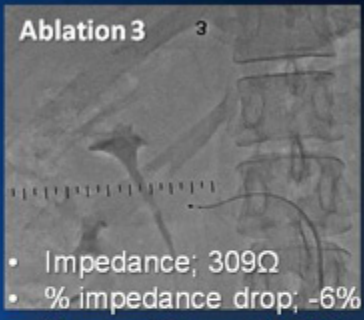
Redo-RDN: Right Kidney (# 1 – 6)



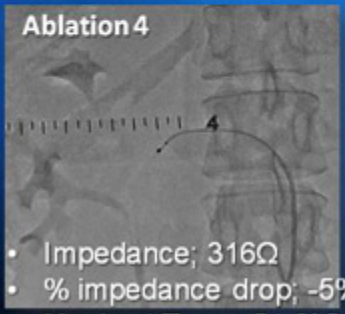
- Impedance; 232Ω
- % impedance drop; -6%
- Maximal Temp; 52°C



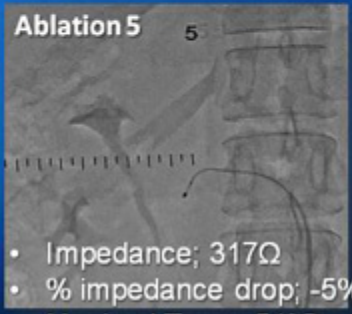
- Impedance; 245Ω
- % impedance drop; -9%
- Maximal Temp; 52.1°C



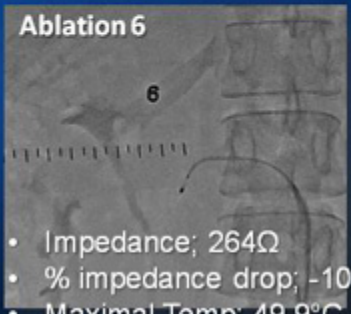
- Impedance; 309Ω
- % impedance drop; -6%
- Maximal Temp; 48.1°C



- Impedance; 316Ω
- % impedance drop; -5%
- Maximal Temp; 51.0°C

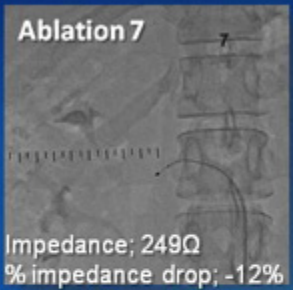


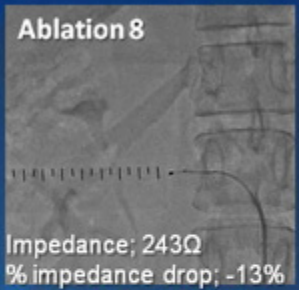
- Impedance; 317Ω
- % impedance drop; -5%
- Maximal Temp; 51°C

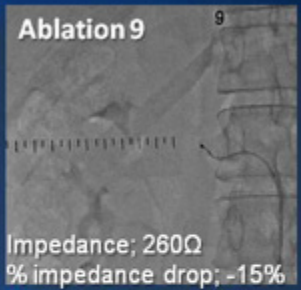


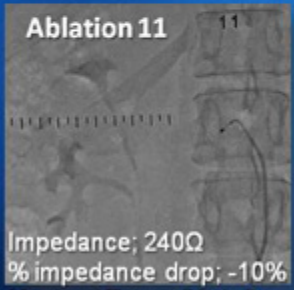
- Impedance; 264Ω
- % impedance drop; -10%
- Maximal Temp; 49.9°C

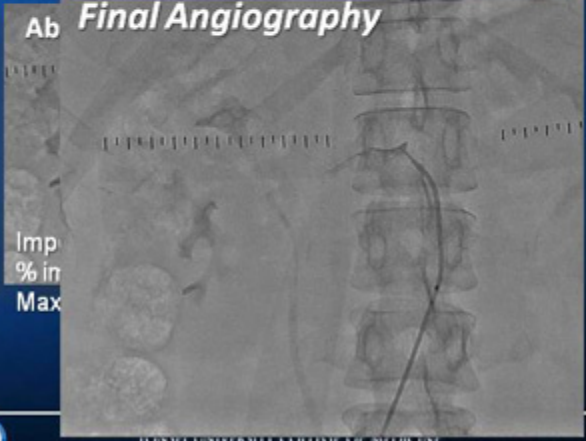
Redo-RDN: Right Kidney (#7– 12)



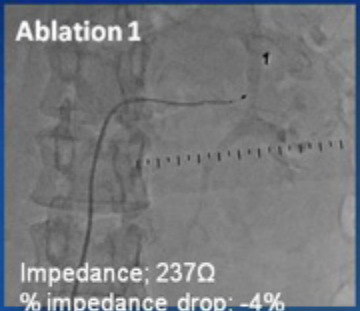


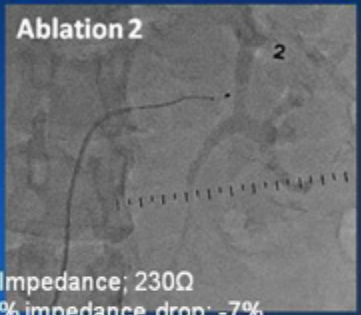


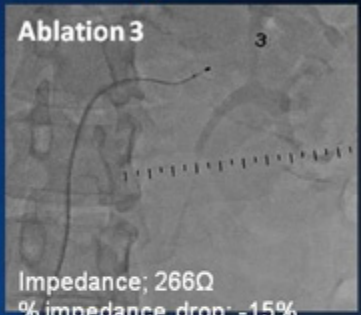


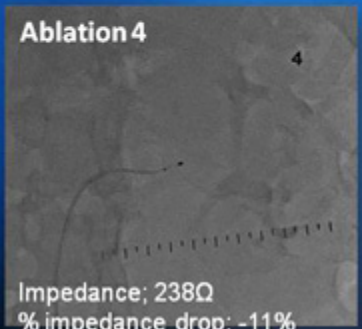


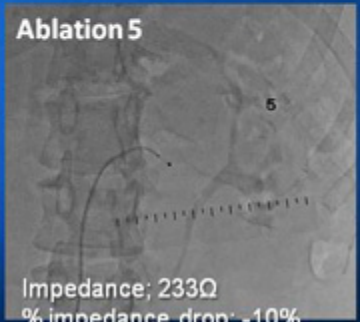
Redo-RDN: Left Kidney (# 1 – 6)

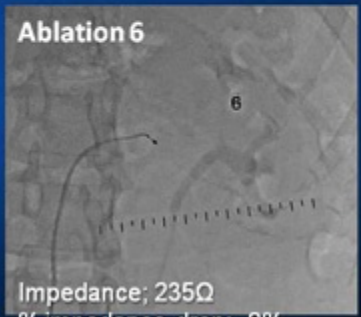




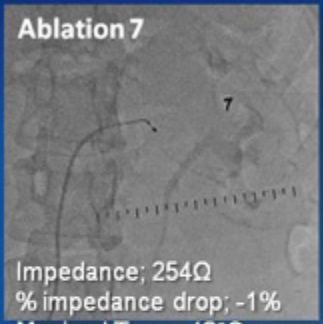


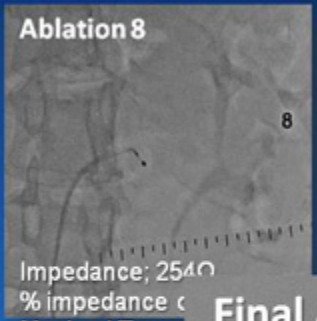


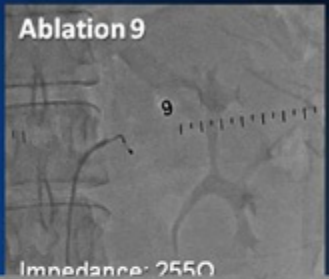


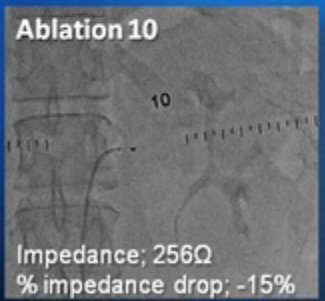


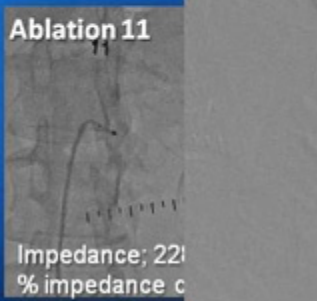
Redo-RDN: Left Kidney (# 7 – 12)

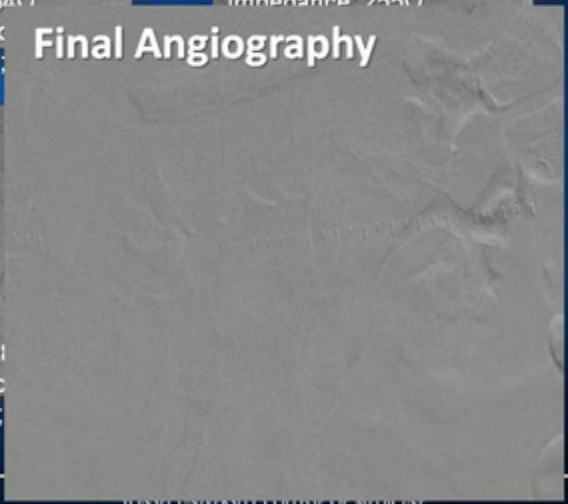










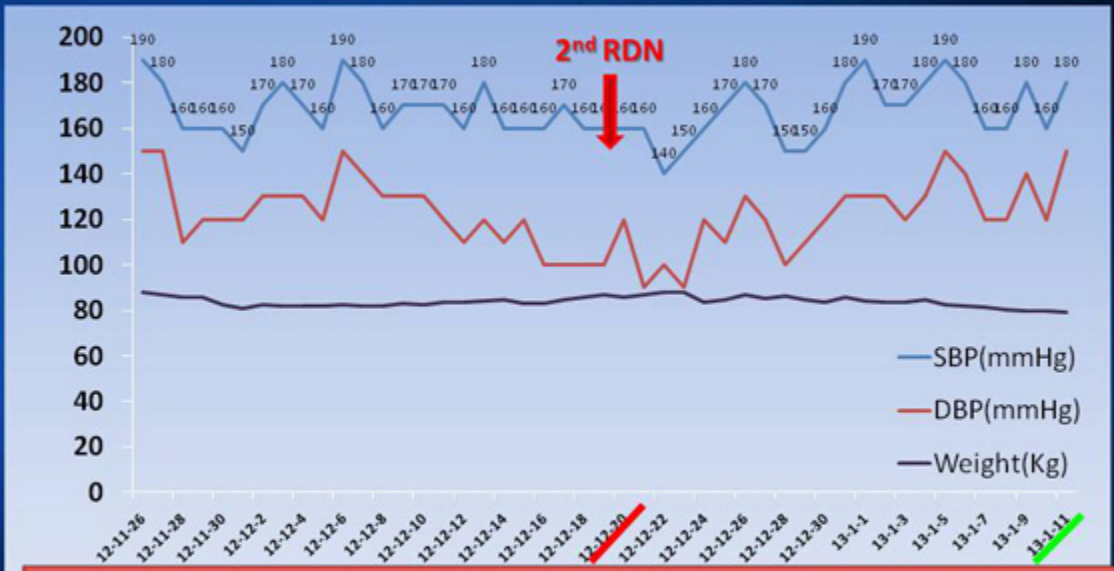


Laboratory findings after Redo-RDN

CBC	4890/9.3/360 K (/μL)
Electrolyte	143/3.7/103/25
BUN / Cr	10.5 / 0.77 (mg/dL)
eGFR	87mL/min/1.73m^2
AST / ALT	13 / 9 (IU/L)
T.pro / alb	6.2 / 3.8 (g/dL)

No vascular complication during hospital stay.

BP after Redo-RDN for 30 days

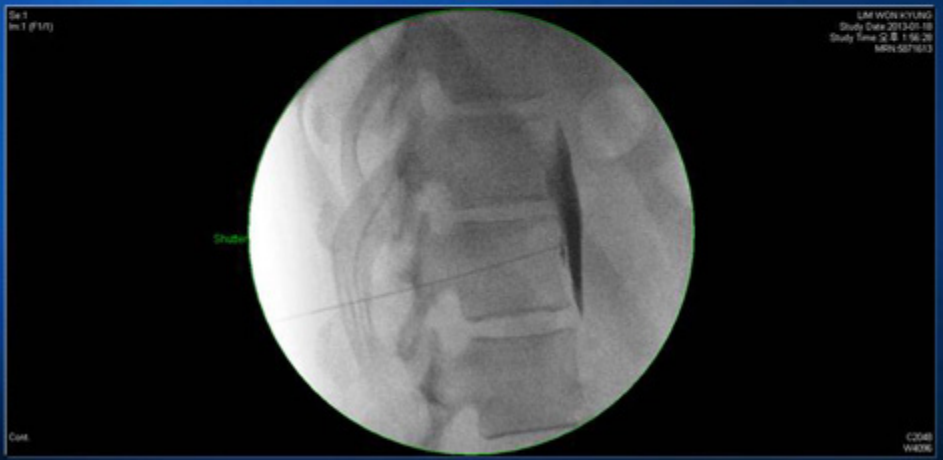


→ *We could not wait RDN effects..*

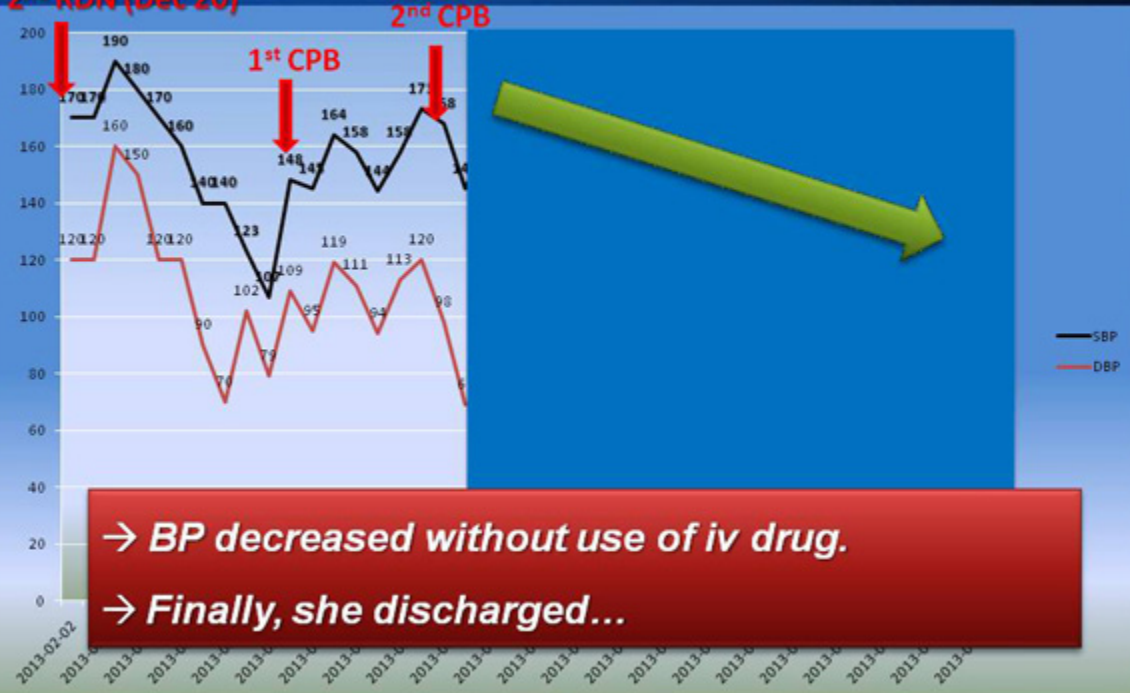
→ *We need a different method for the immediate symptomatic control*

Celiac plexus block

- 2013.1.18 1st Celiac plexus block
- 2013.1.29 2nd Celiac plexus block



Blood pressure after RDN & CPB



Current Medication

Rx> Captopril [50 mg/T] 1T tid
CARdura-XL [4 mg/T] 1T bid
Nebilet [5 mg/T] 1T bid
Norvasc [10 mg/T] 1T qd
Aldactone [25 mg/T] 2T bid

She takes medicine at home,
not at hospital …

Now, four months passed following redo-RND & 3 months passed after CPB.

Is this drop due to the effects of CPB or redo-RDN ?

- We don't know "the Real Helper", because therapeutic effects by both treatment modalities exactly overlaid.
- However, as time goes by, we will know which treatment really did the leading role for this patient.

  - The treatment effect by CPB will not last long (within 6 months).

Conclusion

Appropriate Patient Selection for RDN

- **Current indication of RDN for resistant HiBP**
  - → Indication will be expanded and exclusion criteria will be reduced.
  - → However, more important one will be the identification of true resistant hypertension with optimal medication.
- **Extended indication for RDN, beyond BP lowering**
  - → Many researches including HF and A Fib are currently underway.
- **Redo-RDN for non-responders after RND**
  - → We still need data regarding these.