

How To Manage Resistant Hypertension

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Definition

- Resistant HT (RH) is defined as the BP of a hypertensive pt that remains elevated above goal despite the concurrent use of 3 anti-HT agents of different classes, commonly including a long-acting CCB, ACEI/ARB and a diuretic.
- All agents should be administered at max. tolerated doses and at the appropriate dosing frequency.
- Despite arbitrary with respect to the no. of meds required, RH is defined in this manner to identify pts who are at higher risk for morbid CVD events and death.

Prevalance

- On the basis of the previous cutoff of 140/90 mm Hg, the prevalence of resistant hypertension is approximately ~ 13% in the adult population.
- Multiple single-cohort studies have indicated that common risk factors for RH include older age, obesity, CKD, black race, and DM.
- Estimates suggest the prevalence would be about 4% higher with the newly recommended control target of <130/80mmHg.

Prognosis

- Observational studies using the '08 criteria have shown that pts with RH are at higher risk for poor outcomes compared with pts without RH.
- In a retrospective study of >200000 pts with incident HT, those with RH were 47% more likely to suffer the combined outcomes of death, MI, HF, CVA, or CKD over the median 3.8 yrs of FU.

- Differences in CVD events in this study were driven largely by a higher risk for the development of CKD.
- In another study of >400000 pts, compared with pts without RH, pts with RH had a 32% increased risk of developing ESRF, a 24% increased risk of an ischemic heart event, a 46% increased risk of HF, a 14% increased risk of CVA, and a 6% increased risk of death.

- BP control reduced the risk of incident CVA, CAD, or HF by 13% among those with RH compared with a 31% lower risk of these outcomes among pts without RH.
- Although BP control is associated with a lower risk for some CVD outcomes, it is possible that the benefit of BP lowering may be less in pts with RH compared with pts with non-RH.
- This is partly because of the increased co-morbidities of more prevalent cases of secondary HT (i.e. Cushing syndrome, pheochromocytoma, CKD, primary aldosteronism, etc.) in such population.

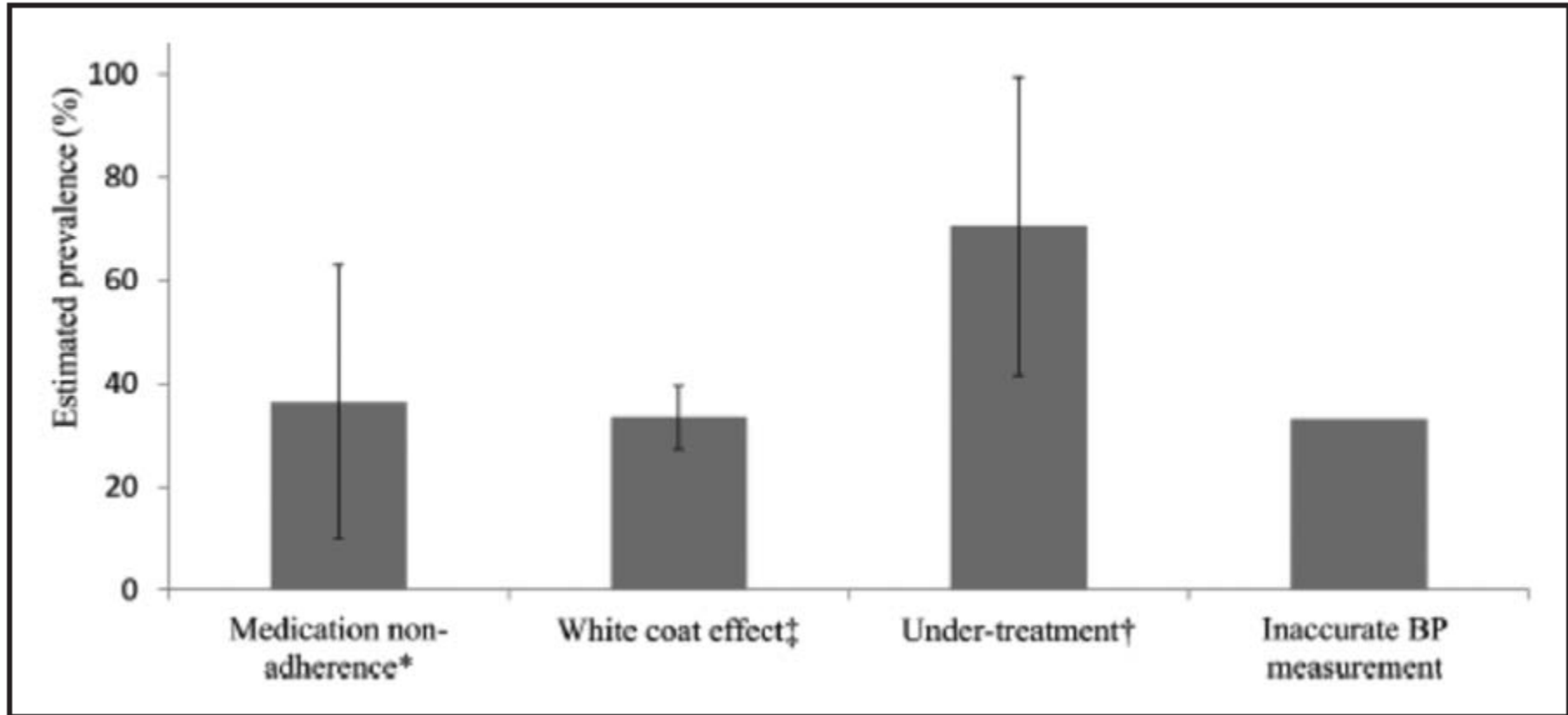
Patient Characteristics Associated With Resistant Hypertension

- Older age
- High baseline BP
- Obesity
- Excessive dietary salt ingestion
- CKD
- DM
- LVH
- Black race
- Male sex

Pseudo-resistance

- Poor BP Technique
- Poor Adherence
- White-Coat Effect (WCE)
- Treatment Inertia

Estimated prevalence of each of the causes of pseudo-resistant HT



- Inaccurate BP measurement
 - Inaccurate measurement of BP can result in the appearance of Rx resistance.
 - 2 of the most common mistakes—measuring the BP before letting the pt sit quietly and use of too small a cuff—will result in falsely high BP readings.
 - Although the degree to which inaccurate measurement of BP results in falsely labeling pts as having uncontrolled HT is unknown, assessments of office BP measurement technique suggest that it is likely a common clinical problem.

- Poor/Non - adherence

- Poor adherence to anti-HT therapy is a major cause of lack of BP control.
- Retrospective analyses indicate that approximately 40% of pts with newly Dx HT will discontinue their anti-HT meds during the 1st year of Rx.
- During 5 to 10 yrs of FU, less than 40% of pts may persist with their prescribed anti-HT Rx (bear in mind that in US, considerable amount of pts will need to pay for their meds and can be expensive).

- While poor adherence is common at the primary care level, it may be less common among pts who are seen by specialists.
- Lack of BP control is distinct from treatment resistance.
- For an anti-HT regimen to have failed, it has to have been taken correctly. This distinction is clinically important as pts with poorly controlled HT 2nd to lack of adherence need not be subjected to the evaluations and continued manipulations in Rx regimens that are undertaken for pts with true Rx resistance.

- White-Coat Effect (WCE)
 - Studies indicate that a significant WCE (when clinic BPs are persistently elevated while out-of office values are normal or significantly lower) is as common in pts with resistant HT as in the more general HT population, with a prevalence in the range of 20% to 30%.
 - Also, as with more general HT pts, those with RH on the basis of a “white coat” phenomenon manifest less severe target organ damage and appear to be at less CV risk compared with those pts with persistent HT during ambulatory monitoring.
 - There is no consensus regarding the need for Rx or the type of FU required in this group of pts.

- Treatment Inertia/Under-treatment
 - Suboptimal anti-HT therapy accounts for a large subset of pts not achieving BP targets.
 - During 2007 to 2010, only 49.6% of pts with RH identified in a community-based practice network in the US were prescribed an optimal antihypertensive regimen.
 - > 90% of the ~84200 patients with RH were appropriately prescribed a diuretic; however, anti-HT meds were administered at <50% of their maximally recommended dose in 42.1% of pts with uncontrolled RH.

- Recent findings from the NHANES (National Health and Nutrition Examination Survey) of ~ 13 400 hypertensive adults demonstrate that BMI ≥ 30 kg/m² approx. doubles the risk for RH.
- In ~ 14500 patients with RH in the Spanish Ambulatory BP Monitoring Registry, a BMI ≥ 30 kg/m² was also an independent risk factor for RH (odds ratio, 1.62; 95% CI, 1.32–1.99).

Lifestyle Factors

- Obesity
- Dietary Salt
- Alcohol
- Physical inactivity

Drug-Related Causes

- Nonsteroidal antiinflammatory agents, including COX-2 inhibitors
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
- Steroid
- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds (e.g. 麻黃)

Secondary Causes

- Common
 - Obstructive sleep apnea
 - Renal parenchymal disease
 - Primary aldosteronism
 - Renal artery stenosis
- Uncommon
 - Pheochromocytoma
 - Cushing's disease
 - Hyperparathyroidism
 - Aortic coarctation
 - Intracranial tumor

Management of RH

- Lifestyle Interventions
 - *Weight Loss*
 - *Dietary Salt Restriction*
 - *DASH Diet*
 - *Exercise*

Pharmacological Treatment of RH

- *General Principles*
 - Once all identifiable forms of HT, particularly endocrine causes, have been excluded and contributions from the WCE are considered, therapeutic approaches for improved BP control in RH can begin.
 - Three mechanistically complementary anti-HT agents, commonly including a long-acting CCB (amlodipine, felodipine, long-acting nifedipine), ACEI or ARB, and a diuretic, should be prescribed with stress on drugs compliance.

- HCTZ does not induce a predictable natriuresis below an GFR of 45 mL/min, but chlorthalidone (only available as combination anti-HT drugs in HK) induces natriuresis down to an GFR of 30 mL/min.
- Thiazide or thiazide-like diuretics are appropriate down to an GFR of 25 to 30 mL/min.
- Shorter-acting diuretic agents such as bumetanide or furosemide have no significant anti-HT effects.
- These 3 separate pharmacological classes of anti-HT agents must be given at max. tolerated doses such as amlodipine 10 mg, chlorthalidone 25 mg, and one of the ACE inhibitors or ARBs at maximal dose.
- Suboptimal medication regimens are common in pts with hypertension resistant to anti-HT therapy.

Management of Resistant Hypertension

Step 1

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence

+

Ensure low sodium diet (<2400 mg/d)
Maximize lifestyle interventions:

- ≥6 hours uninterrupted sleep
- Overall dietary pattern
- Weight loss
- Exercise

+

Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function.

BP not at target



Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

BP not at target



Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target



Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.

Step 4

Check heart rate: unless <70 beats/min, **add β-blocker** (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

BP still not at target



Step 5

Add hydralazine*** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).

BP still not at target



Step 6

Substitute minoxidil**** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies—www.clinicaltrials.gov.

Specific Therapeutic Regimens

- Because most cases of RH are linked to either volume excess, especially in CKD, or high sympathetic tone, establishment of the pathogenesis will optimally facilitate the choice of the 4th drug.

- Diuretic choices are important because volume excess and failure to adhere to low Na diets are very common causes of RH.
- The diuretics with the greatest evidence base for reducing CV outcomes are the thiazide-like diuretics chlorthalidone and indapamide.
- Comparative studies show an additional SBP reduction of 7 to 8 mm Hg simply by switching from HCTZ to the same daily dose of chlorthalidone.

Specific Clinical Issues Associated With Treatment Resistance

Issue Associated With Treatment Resistance	Management Consideration(s)
Volume control, edema resolution	Thiazide→chlorthalidone→loop diuretic
Heart rate control inadequate	β -Blocker, α,β -blocker, verapamil, diltiazem
Renin and aldosterone levels low	Low-salt diet, avoid nighttime shift work, amiloride
Renin low, aldosterone normal to high normal	Mineralocorticoid receptor antagonist
Would split dosing of medications improve control?	Evaluate BP pattern according to home and ambulatory BP monitoring
Medication adherence questionable	Initiate indirect or direct methods to detect nonadherence; if nonadherence is documented (partial or complete), discuss frankly, nonjudgmentally with patient and family
Pattern of BP response to medications outside clinician visit times unknown	Identify meal effects on BP, duration of medication effect, relationship of BP to side effects using out-of-office BP monitoring
Sleep disordered breathing; significant anxiety associated with highly variable hypertension	Initiate nondrug strategies concurrently with or separately from antihypertensive drug therapy

The 4th drug

- Recent reports document the efficacy of mineralocorticoid receptor blockade to improve BP in pts with RH.
- In pts who are not overtly volume overloaded but who have evidence of low salt sensitivity of BP – (salt sensitivity - sustain increases in BP with salt loading and decreases with salt depletion), mineralocorticoid receptor antagonists (spironolactone or eplerenone) are more successful than α - or β -blockers.

- Spironolactone has the advantage of QD administration and can be initiated at doses of as little as 12.5 - 25 mg daily.
- However, the use of spironolactone as a 4th drug is limited by tolerability issues in some pts, incl. the development of hyperkalemia in those with CKD with an GFR <45 mL/min or baseline serum K >4.5 mmol/L.

- With prolonged use at higher doses, gynecomastia and erectile dysfunction in men and menstrual irregularities in women may limit the use of spironolactone.
- In such cases, eplerenone may be used useful but because of its shorter $\frac{1}{2}$ life compared with spironolactone, eplerenone should be given bd for optimal effect.

- The choice of ARB may also be important. Studies comparing various ARBs demonstrate clear advantages of certain agents in BP reduction over others.
- Specifically, 24-hour ABPM studies demonstrate that azilsartan provides on average an additional 4 to 8 mm Hg further SBP reduction over other ARBs (eg, valsartan and olmesartan) or the ACE inhibitor ramipril.

The 5th drug

- The choice of a 5th drug (rather uncommon) depends on sympathetic drive as assessed in part by heart rate.
- In 2 post hoc analyses from large outcome trials, pts with HR >80 bpm had higher mortality.
- Thus, agents such as β -blockers or, if medically contraindicated, central α -2 agonists such as transdermal clonidine or guanfacine should be considered (however, both are not available in HK).

In HF pts with RH

- The addition of hydralazine (HDZ) should be considered and combined with nitrates in cases of HF.
- Nitrates are preferred in this setting because they help restore Ca cycling and cardiac contractile performance and control superoxide production in isolated cardiomyocytes.
- Moreover, hydralazine reduces nitrate tolerance in this setting.
- Note that hydralazine causes increased sympathetic tone and Na retention and therefore should be used in the presence of background appropriate diuretic and β -blocker therapy.
- Total daily doses of HDZ should be <150 mg to avoid drug-induced SLE.

Minoxidil (not available in HK)

- Lastly, minoxidil (2.5-10mg) may be tried if HDZ fails.
- Minoxidil is not well tolerated.
- It induces hirsutism, which in women can lead to discontinuation of the agent.
- Minoxidil must be given a minimum of bd and causes profound Na retention with fluid retention and increased sympathetic tone.
- Thus, a loop diuretic and β -blocker are required in virtually all cases.
- In this setting, however, minoxidil lowers BP effectively in most cases.

Device-Based Treatment of RH

- *Renal Nerve Ablation*
- *Carotid Baroreceptor Activation Therapy*

Renal Nerve Ablation

- Early studies (~2010-2013) in this field were quite promising and showed large reductions of clinic BP in pts failing to be controlled with 4 or 5 anti-HT drugs.
- However, these studies were uncontrolled, and most did not study ambulatory BP as the primary end point.

- The first sham-controlled prospective randomized study in the field of renal ablation therapy, SYMPPLICITY HTN-3 (2014), showed little to no effect of renal denervation therapy in a severely drug treatment-resistant population.

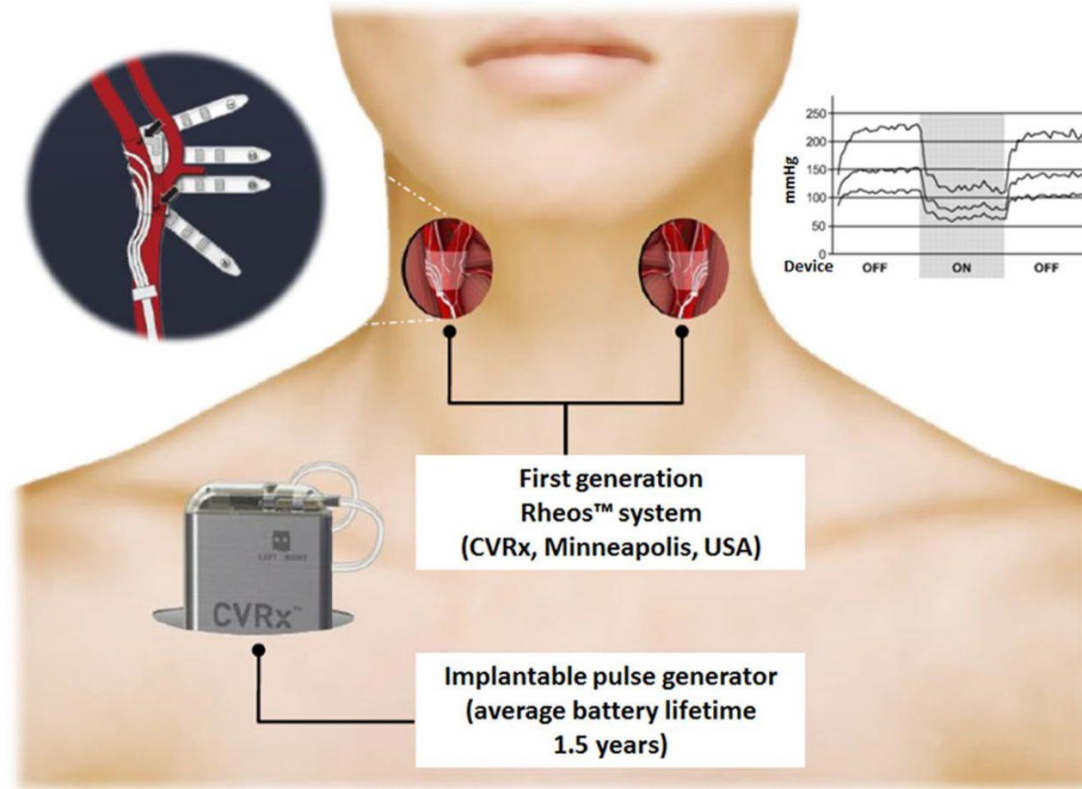
- The methodological concerns arising from SYMPPLICITY HTN-3 have led to several new catheters and new trial designs to evaluate the efficacy of more extensive renal enervation.
- Several studies are ongoing, but there are no conclusions at present.

Carotid Baroreceptor Activation Therapy

- Carotid baroreceptor activation therapy is a system that consists of baroreflex activation leads placed adjacent to the carotid sinus, an implantable pulse generator, and an external programming system.
- This modality electronically activates baroreceptors that signal the brain to orchestrate a multisystemic response for disorders associated with sympathetic overactivity such as HT, HF, and arrhythmias.

- Consequences of carotid sinus stimulation include reduced sympathetic nervous system activity and enhanced vagal activity.
- Hence, the HR slows, allowing greater LV filling time and reducing cardiac workload and energy demands.
- In addition, arterial dilation occurs, reducing cardiac afterload and improving renal blood flow, which augments natriuresis.
- The degree of stimulation can be titrated in \approx 4-minute periods to meet individual pt hemodynamic requirements.

First-generation baroreflex activation therapy device (Rheos, CVRx)



- The first results from a large randomized trial in 322 participants with RH failed to meet the primary end point of the trial, a composite of 5 individual efficacy (mostly echocardiographic measurements) and safety end points.

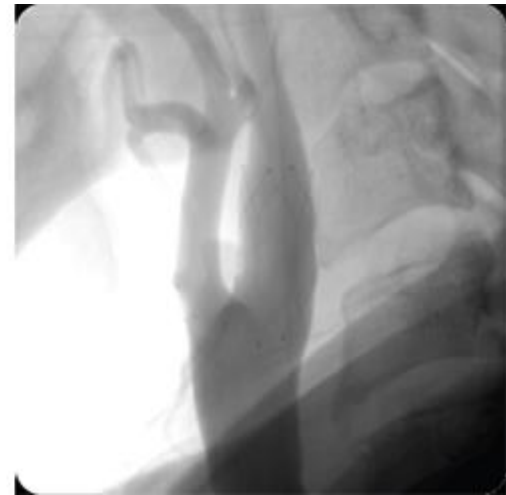
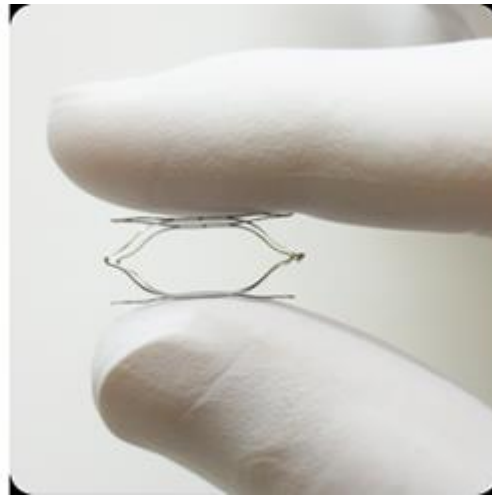
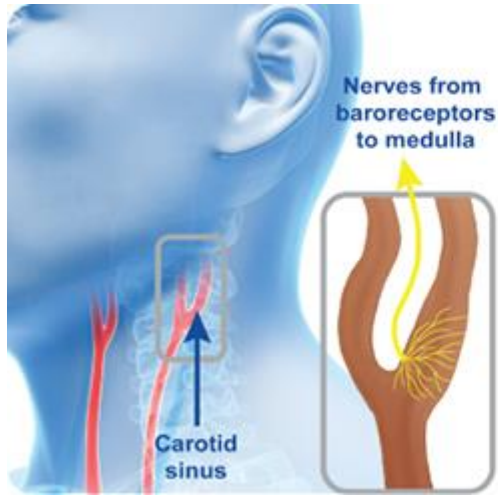
Journal of the American College of Cardiology
Improved Cardiac Structure and Function With Chronic Treatment
Using an Implantable Device in Resistant Hypertension

[Volume 57, Issue 17, April 2011](#)

DOI: 10.1016/j.jacc.2010.11.048

- It was a very small study that included 34 pts only.
- SBP - 179.6 +/- 4.3mmHg (baseline), dropped 23.6 +/- 5.4 mmHg (at 3 mths) and dropped 25.7 +/- 5.7mmHg (at 12 mths).
- DBP – 104.4 +/- 3.0mmHg (baseline), dropped 11.7 +/- 3.4 mmHg (at 3 mths) and dropped 12.9 +/- 4.3mmHg (at 12 mths).
- The device was considered safe and efficacious long term in RH.
- This has led to refinements of the device and further research with single-sided catheters and a new Rheos system.

- The Mobius HD carotid bulb expansion device is a small endovascular implantable device that works by stretching the carotid artery at the bulb and activates baroreceptors to lower BP.
- Studies in Europe, CALM-FIM_EUR (Controlling and Lowering Blood Pressure With the MOBIUSHD), which was completed, and in the United States, CALM-FIM_US, which is ongoing, should provide results in 1 to 2 years.



Case Presentation

- A 65 yrs male is referred for Mx of resistant HT.
- He has a Hx of HT for 10 yrs and a Hx of DM for 5 yrs.
- He does not have known CAD or CVA.
- His seated office BP is 168/94 mm Hg (with similar readings in both arms), he is not orthostatic, his HR is 50 bpm.

- Physical examination
 - Unremarkable except mild arteriolar narrowing in his retina vessels on fundoscopy (without any exudates or hemorrhage)
 - He does not have peripheral edema or vascular bruit
 - BMI ~32

- On review of his medical records, his BP in other physician office visits were ~165-175/ 92-95 mm Hg over the last yr.
- His current anti-HT meds incl.-
 - HCTZ 25 mg daily,
 - Valsartan 320 mg daily,
 - Amlodipine 10 mg daily
 - Atenolol 100 mg daily
 - Of note, he has been taking OTC Ibuprofen bd over the past 5 mths for knee pain.

- Baseline blood tests
 - CBC - N
 - K - 4.0 mmol/l
 - Urea – 5 mmol/L
 - Cr – 88 μ mol/L
 - TSH – N
 - Urine analysis shows no proteinuria

- He reports compliance with his meds regimen, and does not report any specific intolerances that he attributes to meds, but does note that he feels fatigued, and has excessive daytime sleepiness.

- Which of the following leads to pseudo-resistance (or false resistance)?
 - Obesity
 - Excessive Na intake
 - Excess alcohol intake
 - Inaccurate measurement of BP
 - Taking meds that can interfere with BP control

- Pseudo-resistance or false resistance can be due to:
 - 1) Inaccurate measurement of BP (including incorrect technique of measurement, incorrect cuff size, and measuring BP before the pt is seated quietly),
 - 2) Poor pt adherence to BP meds (which can be due to side effects, cost, or poor understanding of regimen)
 - 3) WCE (clinic BPs that are persistently elevated while out-of-office values are normal or significantly lower).

All the others noted above can contribute to true RH.

- The pt states that he checks BPs at home occasionally using his friend's BP monitor, and reports that he sometimes gets readings that are "much lower" than in the doctor's office.
- Given the reported discrepancy in blood pressure readings, 24-hr ABPM is planned.

- Which of the following statements fits the definition of “white coat hypertension”?
 - Office BP ~ 168/94mmHg and average BP on ABPM ~ 140/90mmHg
 - Office BP ~ 158/92mmHg and average BP on ABPM ~ 135/85mmHg
 - Office BP ~ 149/94mmHg and average BP on ABPM ~ 124/78mmHg

- White coat HT is defined as the presence of elevated office BP reading ($>140/90$ mm Hg), but a normal average 24-hr BP reading ($<130/80$ mm Hg) in a pt not receiving anti-HT meds.
- A white coat “effect” denotes rise in BP that occurs in the medical environment, and may be present in anyone treated for HT, regardless of the no. of anti-HT meds.
- Consensus guidelines suggest that an office BP that is greater than 20/10 mm Hg higher than the average awake (daytime) ABPM would constitute a clinically significant white coat effect.

Definitions of HT according to office, ambulatory, and home BP levels

Category	SBP (mmHg)		DBP (mmHg)
Office BP ^a	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

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2018 ESC/ESH Guidelines for the management of arterial hypertension

- The patient's 24 hr average BP on ABPM is 155/94 mm Hg, with a daytime (awake) average BP ~ 158/98 mm Hg and a nighttime (sleep) average BP ~ 142/85 mm Hg.
- His prior evaluation included renal Dopplers that did not suggest of hemodynamically significant renal artery stenosis.
- Plasma renin activity, plasma aldosterone and serum metanephrines were normal as well.
- Electrocardiogram shows LVH.

- Which of the following tests for secondary causes could be considered in this pt?
 - 24-hr urine for aldosterone suppression after Na load
 - 24-hr urine VMA
 - 24-hr urine metanephrines
 - Sleep study
 - CT angiogram of renal arteries

- The pt is obese, and has symptoms of excessive daytime sleepiness, suggesting OSA, which has been associated with RH.
- A sleep study would be a reasonable consideration in this pt.
- His electrolyte levels are normal and he has normal plasma renin activity and aldosterone levels, therefore, the likelihood of primary aldosteronism would be low – a 24-hr urine for aldosterone suppression after Na load is done as a confirmatory step only if there is suspicion of primary aldosteronism.
- The pt does not manifest any symptoms concerning for pheochromocytoma, and his normal serum metanephrines makes the likelihood of pheochromocytoma low. 24 hr urine VMA should no longer be considered for the workup of pheochromocytoma as it has poor diagnostic sensitivity and specificity.
- Normal renal Dopplers as well as normal renin and aldosterone levels make the diagnosis of hemodynamically significant renal artery stenosis very unlikely, and a CT angiogram would be unnecessary.

- You have a long discussion on lifestyle changes with the pt.
- He is very clear that he does not add any salt to his food because he knows this is “bad for high BP”.
- On further review of his diet, he eats out at least x 3/week, and his meals at home include processed meats and canned soups for lunch and dinner.
- He does not drink alcohol on week-days, but gets together with friends while in Mainland, and usually has a ½ bottle of Chinese white wine.
- He does not engage in any regular physical activity.

- Which of the following lifestyle modifications is the MOST accurate recommendation in the Hx of HT?
 - Low Na DASH diet, reduce dietary Na intake < 2.4g/day
 - Alcohol intake limited to < 3 drinks per day
 - Physical activity weekly
 - Weight loss to achieve a BMI < 29

- The DASH diet emphasizes higher intake of vegetables, fruits, and whole grains, and is low in saturated fat and cholesterol.
- It has been shown to decrease BP by an average of 8-14 mm Hg.
- A low Na DASH diet was shown to lower BP more significantly compared to a high Na DASH diet.
- The recommended Na intake of less than 2.4 g/d.
- Alcohol intake should be limited to no more than 2 drinks/day in men, and not more than 1 drink/day in women and lighter-weight persons.
- Binge-drinking should be avoided.
- Regular aerobic physical activity of at least 30 mins/day on most days of the week is recommended.
- Weight loss is recommended to maintain a BMI of 18.5-24.9 kg/m²

DASH diet



Source: National Heart, Lung and Blood Institute

The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to help lower blood pressure and prevent heart disease, stroke, diabetes and even some forms of cancer. It focuses on eating more fresh fruits and vegetables.

This is a guide to how much of each food group you should eat every day, based on eating 2,000 calories per day.

UKHealthCare.
Gill Heart Institute

- Which of the following statements is TRUE?
 - Betablockers no longer have a role in the Rx of HT
 - Add ACEI to this pt's regimen to achieve max. renin-angiotensin blockade
 - Chlorthalidone had a longer $\frac{1}{2}$ life and better night time BP control compared HCTZ

- Chlorthalidone has a longer $\frac{1}{2}$ life (45-60 hours) than HCTZ (16-24 hours), as well as a larger vol. of distribution.
- Chlorthalidone is x 1.5-2 times as potent as HCTZ, resulting in greater reductions in SBP , particularly during the night-time.
- While beta blockers are no longer recommended as part of first-line therapy for hypertension without compelling indications (like HF or CAD), they can still be considered as part of additional therapy for HT after other recommended classes of meds (ACEI/ARB, CCBs, thiazide-type diuretics) have been tried.
- Vasodilating beta blockers (bisoprolol , carvedilol, metoprolol succinate SR, and nebivolol) should be preferred.
- ACEIs should not be combined with ARBs due to the risk of hyperK⁺ and renal failure.

- In addition to reinforcing lifestyle changes and advising avoidance of NSAIDs, his HCTZ was changed to chlorthalidone, atenolol to carvedilol.
- His office BP after 8 wks is 149/92 mm Hg with a HR of 55 bpm.
- His sleep study indicates presence of OSA, and he is currently on nocturnal CPAP therapy.
- His symptoms of fatigue have improved.

- Which of the following would be the next best option in managing this pt?
 - No changes to his meds, see in 1 yr
 - Addition of non-dihydropyridine CCBs (e.g. verapamil)
 - Start spiro lactone
 - Refer for experimental therapy (e.g. renal denervation)

- Aldosterone antagonists like spironolactone have been shown to be beneficial in the Rx of RH when added on as a 4th agent, unrelated to plasma or urinary aldosterone levels.
- They are also particularly useful in pts who have OSA.
- The patient has normal RFT and is not hyperkalemic, and addition of spironolactone would be a reasonable next step in Mx.
- K levels should be closely monitored, because the risk of developing hyperkalemia is higher in pts who are already on renin-angiotensin blockers, elderly, diabetics, or those who CKD.
- S/Es of spironolactone incl. breast tenderness and enlargement.
- These risks are higher with higher doses and should be discussed with pts.

- Alternative aldosterone antagonists like eplerenone which do not have this S/E profile could be considered.
- Pts with RH should be followed closely until BP goal is reached; planning to see this pt back in a year when he is not at goal is not a good option.
- Addition of non-dihydropyridine CCBs like diltiazem or verapamil could be considered if pt is not bradycardic.
- The efficacy of experimental therapy including renal denervation and baroreflex activation are unclear, and medical therapy should be optimized prior to considering any experimental therapy.
- Referral to a hypertension specialist is advised if goal BP cannot be achieved with optimal medical therapy, or if there is suspicion of secondary causes of HT.

What is new and what has changed in the 2018 ESC/ESH Arterial HT Guidelines?

Changes in recommendations	
2013	2018
Diagnosis	Diagnosis
Office BP is recommended for screening and diagnosis of hypertension.	It is recommended to base the diagnosis of hypertension on: <ul style="list-style-type: none"> • Repeated office BP measurements; or • Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible.
Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high-normal BP.	Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD.
Treatment thresholds Treatment of low-risk grade 1 hypertension: Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-moderate-risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	Treatment thresholds Treatment of low-risk grade 1 hypertension: In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.
Treatment thresholds Older patients Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.	Treatment thresholds Older patients BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.
BP treatment targets	BP treatment targets
An SBP goal of <140 mmHg is recommended.	<ul style="list-style-type: none"> • It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. • In patients <65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.

BP treatment targets in older patients (65–80 years)		BP treatment targets in older patients (65–80 years)	
An SBP target of between 140–150 mmHg is recommended for older patients (65–80 years).		In older patients (≥ 65 years), it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.	
BP treatment targets in patients aged over 80 years		BP treatment targets in patients aged over 80 years	
An SBP target between 140–150 mmHg should be considered in people older than 80 years, with an initial SBP ≥ 160 mmHg, provided that they are in good physical and mental condition.		An SBP target range of 130–139 mmHg is recommended for people older than 80 years, if tolerated.	
DBP targets		DBP targets	
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.		A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.	
Initiation of drug treatment		Initiation of drug treatment	
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.		It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).	
Resistant hypertension		Resistant hypertension	
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1 blocker doxazosin should be considered if no contraindication exists.		Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin.	
Device-based therapy for hypertension		Device-based therapy for hypertension	
In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered.		Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.	
Recommendation Grading			
	Grade I	Grade IIa	Grade IIb
			Grade III

- Thank you very much!

Evaluation of RH

- Medical History
- Physical Examination
- Out-of-Clinic BP Monitoring
- Biochemical Evaluation
- Noninvasive Imaging

Medical Hx

- Documentation of the duration, severity, and behavior of the HT is important, along with adherence to medical appointments and Anti- HT Rx, clinical and adverse event responses to prior Anti-HT meds, and current prescription and OTC meds (incl. herbal meds) that may elevate BP or interfere with antihypertensive drug effects.
- The medical interview should also be directed toward identifying secondary causes of HT.

Other rarer endocrine causes of Secondary HT

Disorder	Major Clinical Findings	Physical Examination	Screening Tests	Additional/Confirmatory Tests
Hypothyroidism	Dry skin; cold intolerance; constipation; hoarseness; weight gain	Delayed ankle reflex; periorbital puffiness; coarse skin; cold skin; slow movement; goiter	High TSH; low or normal fT4	
Hyperthyroidism	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag; fine tremor of the outstretched hands; warm, moist skin	Low TSH; high or normal fT4 and T3	Radioactive iodine uptake and scan
Hypercalcemia and primary hyperparathyroidism	Hypercalcemia	Usually none	Serum calcium	Serum parathyroid hormone
Congenital adrenal hyperplasia (excess DOC)	Hypertension and hypokalemia; virilization (11- β -OH deficiency); incomplete masculinization in males and primary amenorrhea in females (17- α -OH deficiency)	Signs of virilization (11 β) or incomplete masculinization (17 α)	Hypertension and hypokalemia with low or normal aldosterone and renin	11- β -OH: elevated DOC, 11-deoxycortisol and androgens; 17- α -OH: decreased androgens and estrogen; elevated DOC and corticosterone
Other mineralocorticoid excess syndromes caused by DOC	Early-onset hypertension, hypokalemia	Arrhythmias (with hypokalemia)	Low aldosterone and renin	DOC; urinary cortisol metabolites; genetic testing
Acromegaly	Acral features; enlarging shoe, glove, or hat size; headache; visual disturbances; diabetes mellitus	Acral features; large hands and feet; frontal bossing	Serum growth hormone ≥ 1 ng/mL during oral glucose load	Elevated age- and sex-matched IGF-1 level; MRI scan of the pituitary

Physical Examination (PE)

- The PE of pts with RH should be oriented toward ascertainment of target organ damage and possible secondary causes.
- BP should be measured as described previously.
- The presence of vascular disease, incl. in the retina, and careful examination of the quality of peripheral and carotid pulses and auscultation for bruits.
- Although not specific, abdominal bruits increase the possibility that obstructive renal artery disease exists.

- If radial-femoral delay is detected and/or aortic coarctation is suspected then BP should be measured in both arms and in the thigh (in pts <30 yrs).
- If the thigh SBP is >10 mm Hg lower than the arm SBP while the pt is supine, imaging studies for coarctation should be performed.
- Hypercortisolism may be suspected in pts with obesity, DM, depression, and bone loss accompanied by abdominal striae, “moon” facies, and intrascapular fat deposition.

Out-of-clinic BP Monitoring

- Automated clinic BP measurements, self-measurements (home or work), and ambulatory BP monitoring (ABPM) have utility in determining whether there might be a WCE that creates the appearance of Rx resistance.
- Of these methods, ABPM is the most objective and robust means to define the WCE because it has been shown to be a stronger predictor of CVD morbidity and mortality than clinic measurements and has received recommendations for use in the Dx of HT in both the UK and US.

- A WCE (office BP above goal but ambulatory BP below goal) should be considered in pts with normal or lower self-measured BP, in those lacking target organ involvement (e.g., retinopathy, CKD, LVH), and when there are symptoms of excessive anti-HT meds.
- If a WCE is confirmed, out-of-clinic measurements (ambulatory or self-measured values if ABPM is not available) should be used to confirm the achievement of BP goals and to adjust drug therapy.

Biochemical Evaluation

- Ix of the pts with RH should include –
 - Basic biochemistry
 - Fasting glucose/lipids
 - A paired morning plasma aldosterone and aldosterone/renin ratio (PRA) to screen for primary aldosteronism
 - ECG +/- echocardiography and CTCA (strictly speaking not biochemical evaluation)

- The PRA is an effective screening test because it has a high –ve predictive value for screening of primary aldosteronism.
- Observational studies from many different countries have demonstrated a prevalence rate of primary aldosteronism of $\approx 20\%$ in pts with confirmed RH.
- This relatively high prevalence contrasts with the $\approx 8\%$ overall prevalence of primary aldosteronism in primary HT.

- A high ratio (> 20) when the serum aldosterone is >16 ng/dL and PRA is <0.6 ng/mL per hr is suggestive of primary aldosteronism, particularly in a pt taking an ACE inhibitor or ARB (these drugs elevate the PRA; hence, if renin is still suppressed, it increases the sensitivity of the ratio), but further assessments are required to confirm the Dx.

- The screening test of choice for pheochromocytoma is measurement of circulating catecholamine metabolites.
- Catechol *O*-methyl transferase releases *normetanephrine* and metanephrine from the tumors, measured as plasma free (sensitivity, 96%–100%; specificity, 89%–98%) or urinary fractionated (sensitivity, 86%–97%; specificity, 86%–95%) metanephrines.

Noninvasive Imaging

- Imaging for the evaluation of renal artery stenosis in pts with RH should be reserved for those with a high likelihood of renovascular disease-
 - Young pts in whom fibromuscular dysplasia
 - Older patients with a Hx of smoking or vascular disease who have increased risk for atherosclerosis.

- Doppler USG of the renal arteries is the usual initial test (but not useful in obese pts) and is preferred over CT or MRI angiography as a screening tool.
- Imaging of the adrenal glands by CT or MRI is indicated only if there is biochemical evidence of hormonally active tumors (aldosterone secreting tumor or phaeochromocytoma).

- Thank you very much!

Obstructive Sleep Apnea

- OSA is extremely common in pts with RH, with prevalence rates as high as 70% to 90%, and when present, OSA is often severe.
- The high occurrence of OSA in pts with RH has been attributed to increased fluid retention and accompanying upper airway edema, as suggested by studies positively relating the presence and severity of OSA to aldosterone excess and high dietary Na intake.

- Rx of pts with OSA and RH with CPAP induces significant but generally modest reductions in BP.
- In a randomized evaluation of Rx of moderate to severe OSA with CPAP vs. no CPAP in pts with RH, Rx with CPAP reduced mean 24hrs SBP and DBP by 3.1 and 3.2 mmHg, respectively (hence more like an association than causation).

- Routine evaluation by polysomnography is not indicated for all pts with RH.
- However, given the high prevalence of often severe OSA in pts with RH and the potential benefit of CPAP to enhance BP control, clinicians should vigorously screen such pts for symptoms of OSA (loud snoring, frequent nocturnal arousals, witnessed apnea, and excessive daytime sleepiness) and have a low threshold for referral for definitive dx and Rx.

Primary Aldosteronism

- Primary aldosteronism is defined as a group of disorders in which aldosterone production is inappropriately high, relatively autonomous, and independent of the renin-angiotensin system and in which aldosterone secretion is not suppressed by sodium loading.

- Obesity

- Excess body fat ranks among the most important factors responsible for the increasing prevalence of HT.
- Visceral adiposity in particular plays a fundamental role in causing high BP through a variety of mechanisms culminating in enhanced salt sensitivity, vascular dysfunction, and activation of the sympathetic nervous system and renin-angiotensin system.

- Dietary Sodium