Catheter-Based Denervation for Heart Failure

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular,Boston Scientific Corporation, Medtronic CardioVascular
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Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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Efferent Renal Nerve Activation in Heart Failure

- Majority of patients with decompensated heart failure have some degree of renal impairment
- Renal sympathetic efferent activation causes renin release, sodium and water retention, and reduced renal blood flow

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

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Efferent Renal Nerve Activation in Heart Failure

- Hypersympathetic activity is preferentially disproportionate to the kidney and heart
  - Disproportionate increase in renal sympathetic activity reduces GFR and prevents natriuresis
- Angiotensin II may directly mediate central sympathetic activity, initially as a response to decreased cardiac output and later in a positive feedback cycle
- Hypersympathetic activity in HF may stem from reduced aortic and carotid baroreceptor activity
- Increased renal norepinephrine spillover predicts decreased survival and need for transplantation, independent of LVEF and GFR

Contribution of Renal Afferent Nerve Activation in Heart Failure

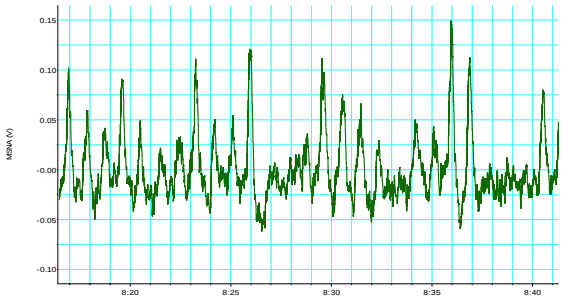
- Renal afferent activation increases sympathetic tone (renorenal reflex), inducing
  - Renal vasoconstriction
  - Renin secretion
  - Sodium and water retention
  - Increased sympathetic tone to other organs with dense sympathetic innervation (eg, cardiac)
- Afferent activity may be stimulated by proximal tubule adenosine secretion

Proof of Principle: Therapeutic Renal Denervation and Reduction of Central Sympathetic Nerve Activity

Baseline

MSNA: 46 burst/min
BP: 155/95 mmHg

baseline MSNA: 46 burst/min

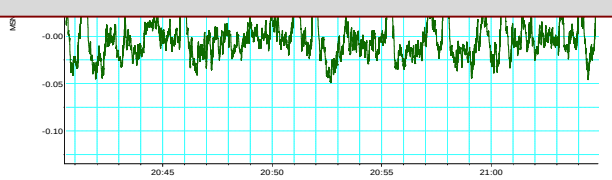


No impact on flight/fight "epinephrine" response

No blunting of baroreceptor function

Preserve central sympathetic homeostatic mechanisms

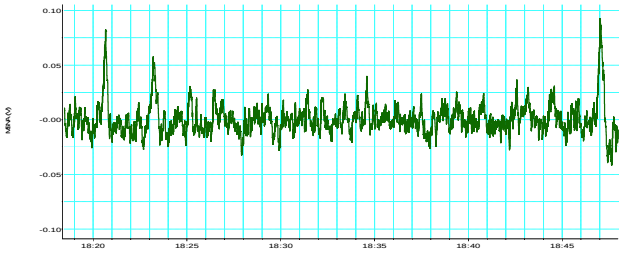
MSN
BP: 133/78 mmHg (↓22/17 mmHg)



12 Month Follow-up

MSNA: 21 burst/min (↓~54%)
BP: 132/75 mmHg (↓23/20 mmHg)

12 Months FU MSNA: 21 burst/min



Schlaich et al. *J Htn*. 2009; 27 (suppl 4):s437.

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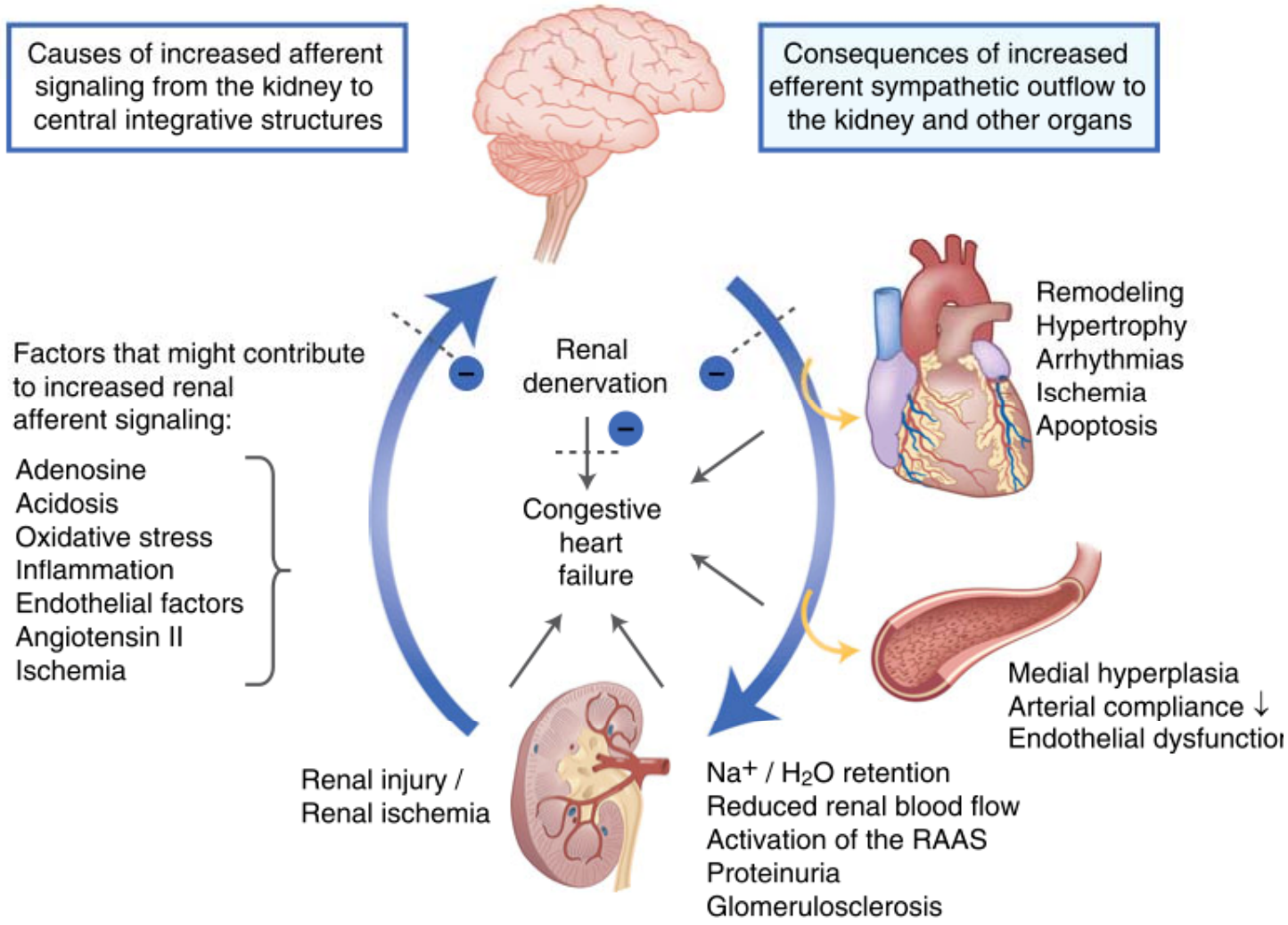
Effects of Increased Sympathetic Tone in Heart Failure on Renal, Cardiac and Peripheral Vasculature



Sobotka et al. Curr Cardiol Rep 2012

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Pilot Study in Heart Failure with Reduced LVEF

- 40 patients at up to 5 international centers
- Inclusion Criteria:
  - Heart Failure patients NYHA Class II or III
  - Renal Impairment Left Ventricular Ejection Function <40%
  - GFR 30 to 75 mL/min/1.73m2
  - Optimal stable medical therapy

- Exclusion Criteria:
  - Renal artery anatomy must be eligible for treatment as determined by Angiography, and
  - History of prior renal artery intervention
  - Single functioning kidney.
  - Myocardial Infarction, unstable angina pectoris or cerebrovascular Accident within 3 months
  - Systolic BP <110mmHg

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Pilot Study in Heart Failure with Reduced LVEF
Study Assessments

- Left ventricular function by echocardiography at baseline, 6 and 12 months
- Renal function (GFR) at baseline, 1/3/6/12 months
- Subgroup analyses (N=10)
  - Right heart catheterization measures at baseline, 6 and 12 months
  - Renal spillover
  - Heart rate variability
  - MSNA
  - Renal blood flow
  - Holter monitoring for arrhythmias

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REACH Pilot Study

FIM evaluation of safety of chronic severe stable heart failure

PI's: Justin Davies & Darrel Francis, Imperial College London

Primary aim: Evaluation of safety of renal denervation in chronic severe stable heart failure

Secondary aims: Technical feasibility of performing denervation in heart failure

Protocol: 7/7 patients, single center, non-blinded safety study
Stable CHF, on maximum medical therapy +/- CRT +/- ICD
Bilateral denervation
7 Day hospital admission with intensive monitoring of hemodynamics and biochemistry
2-4 weekly review for 6 months

Follow-up: 6 months

Study-close: February 2012

Reports: August 2012

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REACH

Assessment of the symptomatic benefit of renal denervation in chronic severe heart failure

PI's: Justin Davies & Darrel Francis, Imperial College London

Primary aim: Evaluation of symptomatic benefit of renal nerve denervation in chronic severe heart failure (6 min walk, Minnesota Heart Assoc. Questionnaire)

Secondary aims: Reduction in hospital admissions

Protocol: 100 patient, randomized, blinded, 3:2 (treatment : sham) study
Stable CHF, on maximum medical therapy +/- CRT +/- ICD
Bilateral denervation

Follow-up: 12 months

Study start: May 2012

Study-close: May 2013

Reports: August 2013

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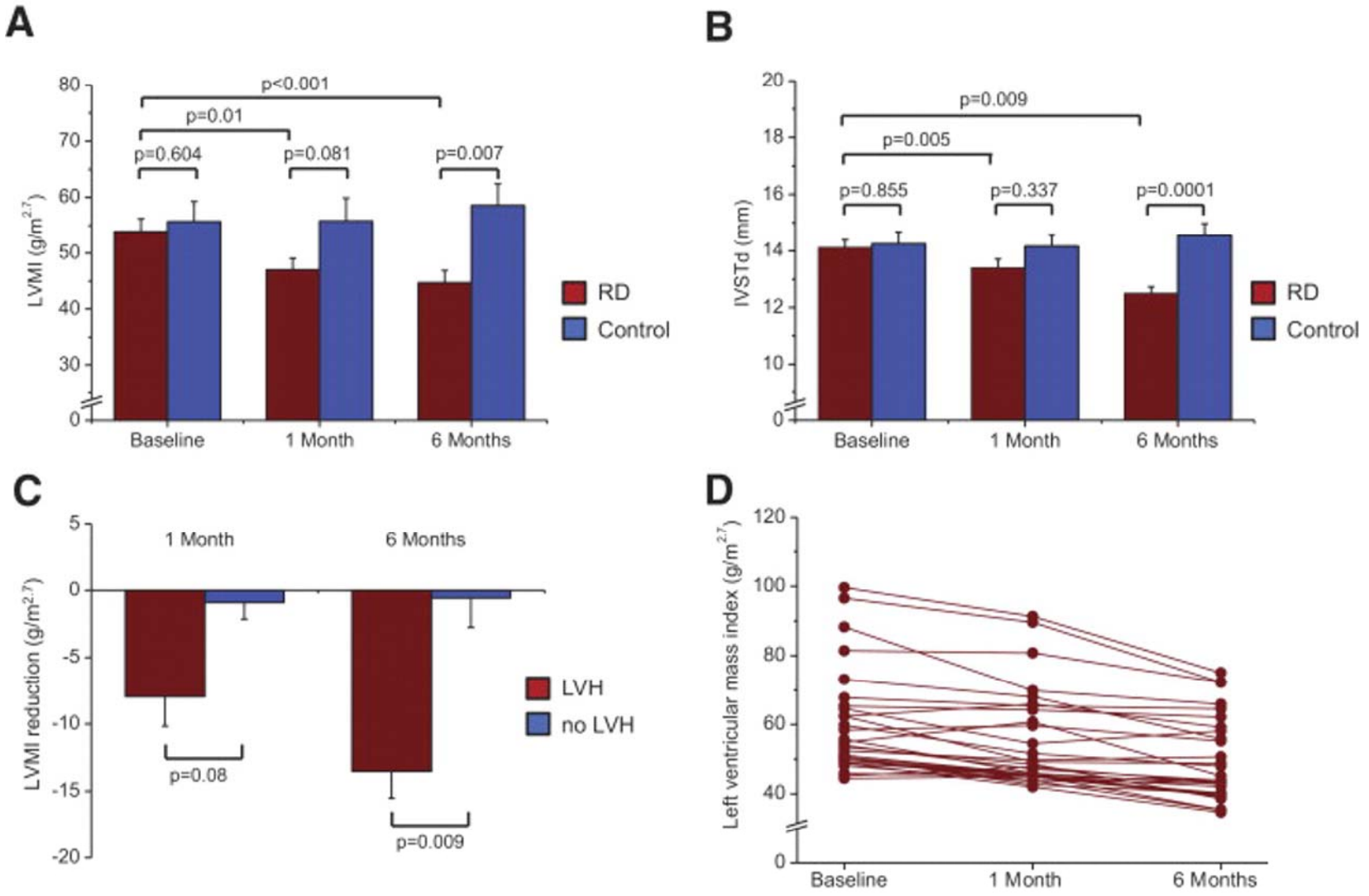
Influence of Renal Denervation on Regression of LVH and Improvement of Diastolic Function



Brandt, M. C. et al. J Am Coll Cardiol 2012;59:901-909

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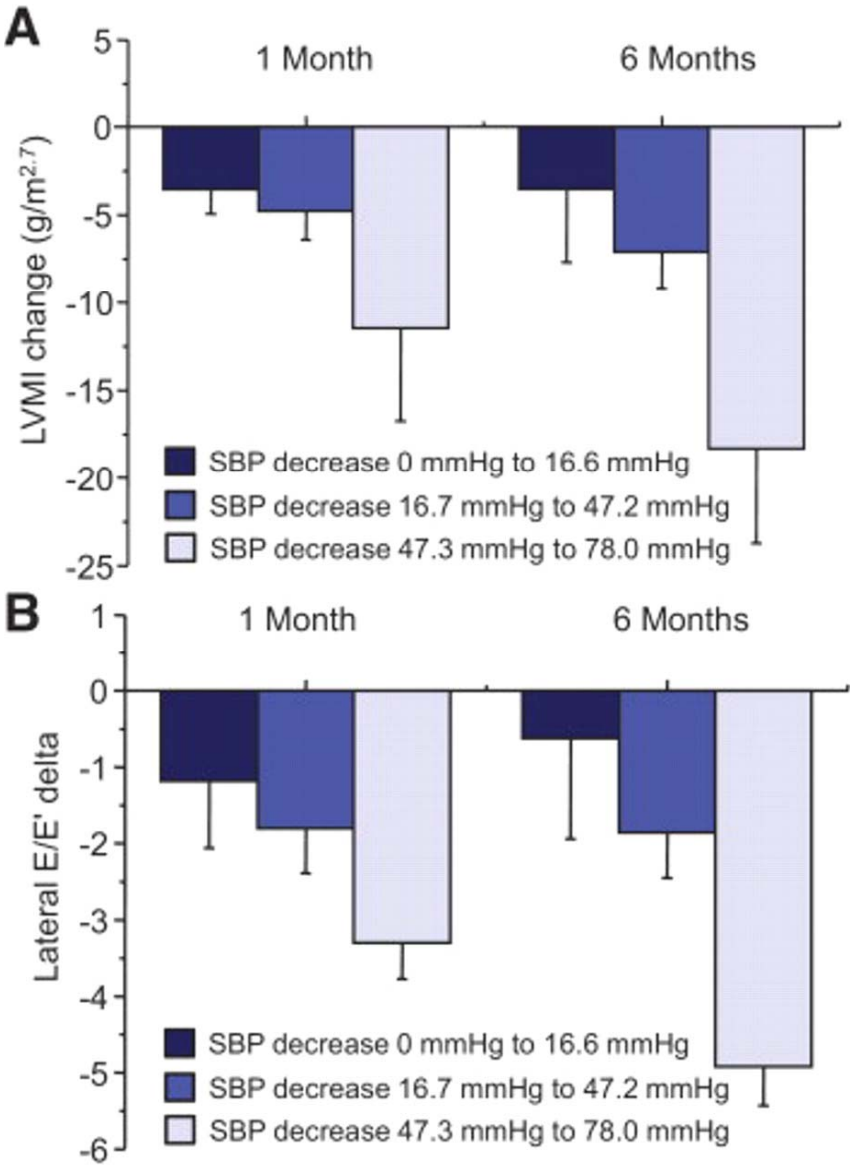
Regression of LVH and Improvement of Diastolic Function Relative to BP Reduction Achieved by Renal Denervation

Reduction in LV mass likely result of decreased LB workload and decreased sympathetic activity



Brandt, M. C. et al. J Am Coll Cardiol 2012

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How Might Renal Denervation Differ From Medical Therapy for Heart Failure?

- Most approved pharma dose are less than that needed to eliminate stimulation of beta and angiotensin II receptors
- RDN may reverse the effects of increased alpha adrenergic tone on renal blood flow, sodium excretion and systemic vasconstriction
- RDN should eliminate release of additional neurotransmitters (eg, neuropeptide Y) that contribute to sympathetically mediated vasconstriction