JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 2, NO. 3, 2017

ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.05.003

EDITORIAL COMMENT

Reconsidering Renal Sympathetic Denervation for Heart Failure*

W.H. Wilson Tang, MD,[a,b] Mark E. Dunlap, MD[c]

It has long been established that sympathetic overactivation is associated with the development and progression of heart failure (HF), and emerging evidence suggests that it also contributes to the clinical presentations of cardiorenal dysfunction (1,2). Hence, effective renal sympathetic denervation (RSD), which reduces sympathetic activity to the kidney (and possibly to other organs), holds great promise as a targeted therapeutic intervention in the HF setting (3). Indeed, surgical sympathectomy can attenuate the exaggerated reduction in renal blood flow in animal HF models (4), with direct improvement in cardiac function (5–9). Over the past decade, novel percutaneous approaches to RSD have been developed to overcome the invasiveness of open surgical denervation. However, several promising human studies demonstrating the overall safety and striking efficacy of RSD in refractory hypertension (10,11) have been overshadowed by the disappointing results in the Symplicity-HTN3 (Renal Denervation in Patients With Uncontrolled Hypertension) study (12). In HF, early pilot data provided safety confirmation of 7 patients with chronic, stable HF with reduced left ventricular ejection fraction undergoing open-label RSD with follow-up up to 6 months. Despite some independent down-titration of medications, there were improvements in self-reported symptoms and 6-min walk distance following RSD (13). Similar findings were described recently in 2 Chinese cohorts of patients with chronic systolic HF receiving RSD using different RSD catheter systems, one of them in a randomized comparison with a control group (14,15). However, the follow-up Symplicity-HF study (Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment Clinical Trial) (NCT01392196) was terminated last year due to a "lack of a physiologic response despite no safety concerns up to 24 months." Another study looking at potential efficacy of RSD in patients with HF with preserved ejection fraction also showed no effects on macrovascular or microvascular function (16). Several clinical studies are still ongoing, albeit with limited sample sizes and study duration (**Table 1**).

SEE PAGE 270

It is in this context that Liao et al. (17) report in this issue of *JACC: Basic to Translational Science* the results of their large-animal HF model with successful bilateral RSD and showed both phenotypic and biochemical changes consistent with cardiorenal preservation in the setting of HF. First, the authors should be congratulated on their efforts to demonstrate the safety and efficacy of RSD in a large-animal model using a clinically tested percutaneous RSD system that has been shown to achieve consistent denervation (18,19) before testing in patients with HF. Their findings that the histological changes at the renal arteries, as well as the norepinephrine gradient across the kidneys and the heart, support both the safety and efficacy of the intervention. Second, individual data points reveal marked variability in neurohormonal activation and echocardiographic responses as expected. The investigators used a mixed cardiomyopathy swine model with the combination

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland, Ohio; [b]Center for Clinical Genomics, Cleveland Clinic, Cleveland, Ohio; and the [c]Heart & Vascular Center, MetroHealth Campus of Case Western Reserve University, Cleveland, Ohio. Both authors are supported by grants from the National Institutes of Health (U10HL110336).

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

TABLE 1 Major Ongoing Human Studies Evaluating the Safety and Efficacy of RSD in HF

Study	N	Inclusion Criteria	Duration	Endpoints	ClinicalTrials.gov Identifier
REACH (Renal Artery Denervation in Chronic Heart Failure Study)	76	HF, EF <40%, NYHA 2+, GDMT	12 months	KCCQ score, peak Vo_2, 6MWT distance, safety, chemoreflex sensitivity	NCT01639378
DIASTOLE (Denervation of the renAl sympathetIc nerveS in hearT Failure With nOrmal Lv Ejection Fraction)	60	HF, EF ≥50%, LVDD, eGFR >30 ml/min/1.73 m^2	12 months	Change from baseline E/E', safety	NCT01583881
RESPECT-HF (Renal Denervation in Heart Failure Patients With Preserved Ejection Fraction)	144	EF ≥50%, NYHA 2+, LVDD and/or BNP >220 pg/ml, eGFR >30 ml/min/1.73 m^2	6 months	Changes in LAVi and/or LVMi (MRI), pVo_2, 6MWT distance, biomarkers	NCT02041130

6MWT = 6-min walk test; BNP = B-type natriuretic peptide; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVi = left atrial volume index; LVDD = left ventricular diastolic dysfunction; LVMi = left ventricular mass index; MRI = magnetic resonance imaging; NYHA = New York Heart Association classification; RSD = renal sympathetic denervation; Vo_2 = oxygen consumption.

of both coronary ligation and rapid pacing procedures to study relatively chronic (rather than acute) cardiac remodeling with hemodynamic derangements. It should be noted that there were no experiments to demonstrate attenuated sympathetic responses with perturbations such as exercise or volume loading. Nevertheless, it was still reassuring that even with effective RSD, overall systemic blood pressures were largely sustained via lower heart rate and higher stroke work index even though the contractility data were more difficult to interpret due to variable loading conditions. Third, the study included pharmacological therapy in both the RSD and control groups, although less than fully "guideline-directed" according to medication doses and duration of treatment (only 10 weeks). Hence, long-term effects of RSD cannot be extrapolated from this otherwise elegant set of experiments that established direct proof-of-concept for future clinical research development using this RSD system in HF.

What are the implications? Clearly, these findings are consistent with several other animal models using a wide variety of RSD systems (20–26), and point to a logical therapeutic target should the appropriate RSD techniques, ideal study population, and endpoints be identified. This breakthrough in our ability to selectively modulate the sympathetic system in the setting of HF is too important for investigators to abandon the pursuit even if our initial attempts have been challenged. The data presented by Liao et al. (17) serve as an important step to demonstrate the safety and efficacy of the RSD technique. It should also serve as a reminder that future studies should better identify those that are more vulnerable or who have greater neurohormonal activation (either at rest or upon perturbation), so that responders can be more precisely targeted to demonstrate the potential therapeutic benefits of RSD.

ADDRESS FOR CORRESPONDENCE: Dr. W.H. Wilson Tang, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J3-4, Cleveland, Ohio 44195. E-mail: tangw@ccf.org.

REFERENCES

1. Burchell AE, Sobotka PA, Hart EC, Nightingale AK, Dunlap ME. Chemohypersensitivity and autonomic modulation of venous capacitance in the pathophysiology of acute decompensated heart failure. Curr Heart Fail Rep 2013;10:139–46.

2. Mullens W, Verbrugge FH, Nijst P, Tang WH. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. Eur Heart J 2017 Feb 23 [E-pub ahead of print].

3. Sobotka PA, Krum H, Bohm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. Curr Cardiol Rep 2012; 14:285–92.

4. Volpe M, Tritto C, Mele AF, et al. Impairment of atrial natriuretic factor response to acute saline load in hypertensives with family history of cardiovascular accidents. J Hypertens Suppl 1991;9: S254–5.

5. Nozawa T, Igawa A, Fujii N, et al. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. Heart Vessels 2002;16:51–6.

6. Hu J, Li Y, Cheng W, et al. A comparison of the efficacy of surgical renal denervation and pharmacologic therapies in post-myocardial infarction heart failure. PLoS One 2014;9:e96996.

7. Hu J, Yan Y, Zhou Q, et al. Effects of renal denervation on the development of post-myocardial infarction heart failure and cardiac autonomic nervous system in rats. Int J Cardiol 2014;172:e414–6.

8. Li ZZ, Jiang H, Chen D, et al. Renal sympathetic denervation improves cardiac dysfunction in rats with chronic pressure overload. Physiol Res 2015; 64:653–62.

9. Liu Q, Zhang Q, Wang K, et al. Renal denervation findings on cardiac and renal fibrosis in rats with isoproterenol induced cardiomyopathy. Sci Rep 2015;5:18582.

10. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Lancet 2010;376:1903–9.

11. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–81.

12. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370:1393–401.

13. Davies JE, Manisty CH, Petraco R, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. Int J Cardiol 2013;162:189–92.

14. Gao JQ, Xie Y, Yang W, Zheng JP, Liu ZJ. Effects of percutaneous renal sympathetic denervation on cardiac function and exercise tolerance in patients with chronic heart failure. Revista portuguesa de cardiologia 2017;36:45–51.

15. Chen W, Ling Z, Xu Y, et al. Preliminary effects of renal denervation with saline irrigated catheter on cardiac systolic function in patients with heart failure: a prospective, randomized, controlled, pilot study. Catheter Cardiovasc Interv 2017;89:E153–61.

16. Patel HC, Hayward C, Keegan J, et al. Effects of renal denervation on vascular remodelling in patients with heart failure and preserved ejection fraction: a randomised control trial. JRSM Cardiovasc Dis 2017;6. 2048004017690988.

17. Liao S-Y, Zhen Z, Liu Y, et al. Improvement of myocardial function following catheter-based renal denervation in heart failure. J Am Coll Cardiol Basic Trans Science 2017;2:270–81.

18. Al Raisi SI, Pouliopoulos J, Barry MT, et al. Evaluation of lesion and thermodynamic characteristics of Symplicity and EnligHTN renal denervation systems in a phantom renal artery model. EuroIntervention 2014;10:277–84.

19. Tsioufis CP, Papademetriou V, Dimitriadis KS, et al. Catheter-based renal denervation for resistant hypertension: twenty-four month results of the EnligHTN I first-in-human study using a multi-electrode ablation system. Int J Cardiol 2015;201:345–50.

20. Dai Z, Yu S, Zhao Q, et al. Renal sympathetic denervation suppresses ventricular substrate remodelling in a canine high-rate pacing model. EuroIntervention 2014;10:392–9.

21. Hu W, Zhao QY, Yu SB, et al. Renal sympathetic denervation inhibits the development of left ventricular mechanical dyssynchrony during the progression of heart failure in dogs. Cardiovasc Ultrasound 2014;12:47.

22. Zhao Q, Huang H, Wang X, et al. Changes of serum neurohormone after renal sympathetic denervation in dogs with pacing-induced heart failure. Int J Clin Exp Med 2014;7:4024–30.

23. Guo J, Zhou Z, Li Z, Liu Q, Zhu G, Shan Q. Effects of renal sympathetic denervation on cardiac systolic function after myocardial infarction in rats. J Biomed Res 2016;30:373–9.

24. Patel KP, Xu B, Liu X, Sharma NM, Zheng H. Renal denervation improves exaggerated sympathoexcitation in rats with heart failure: a role for neuronal nitric oxide synthase in the paraventricular nucleus. Hypertension 2016;68:175–84.

25. Polhemus DJ, Gao J, Scarborough AL, et al. Radiofrequency renal denervation protects the ischemic heart via inhibition of GRK2 and increased nitric oxide signaling. Circ Res 2016;119:470–80.

26. Pinkham MI, Loftus MT, Amirapu S, et al. Renal denervation in male rats with heart failure improves ventricular sympathetic nerve innervation and function. Am J Physiol Regul Integr Comp Physiol 2017;312:R368–79.

KEY WORDS heart failure, norepinephrine, renal sympathetic denervation