Reconsidering Renal Sympathetic Denervation for Heart Failure*

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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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Duration</th>
<th>Endpoints</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACH (Renal Artery Denervation in Chronic Heart Failure Study)</td>
<td>76</td>
<td>HF, EF &lt;40%, NYHA 2+, GDMT</td>
<td>12 months</td>
<td>KCCQ score, peak VO2, 6MWT distance, safety, chemoreflex sensitivity</td>
<td>NCT01639378</td>
</tr>
<tr>
<td>DIASTOLE (Denervation of the renal sympathetic nerves in heart failure with preserved systolic function)</td>
<td>60</td>
<td>HF, EF &gt;50%, LVDD, eGFR &gt;30 ml/min/1.73 m²</td>
<td>12 months</td>
<td>Change from baseline E/E', safety</td>
<td>NCT01583881</td>
</tr>
<tr>
<td>RESPECT-HF (Renal Denervation in Heart Failure Patients with preserved systolic function)</td>
<td>144</td>
<td>EF ≥50%, NYHA 2+, LVDD and/or BNP &gt;220 pg/ml, eGFR &gt;30 ml/min/1.73 m²</td>
<td>6 months</td>
<td>Changes in LAVI and/or LVMi (MRI), pVO2, 6MWT distance, biomarkers</td>
<td>NCT02041130</td>
</tr>
</tbody>
</table>

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; VO2 = oxygen consumption.

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.

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