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COMMENT

Renal denervation in patients with chronic kidney disease: an approach using CO_2 angiography

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Renal denervation (RDN) has evolved through several pivotal randomized controlled trials (RCTs) to its clinical application as an adjunctive therapy for patients with uncontrolled, treatment-resistant hypertension [1]. While the previous RCTs have excluded patients with severe chronic kidney disease, animal studies and some human studies have shown that RDN is effective in lowering blood pressure in chronic kidney disease (CKD) [2, 3]. However, patients with CKD are at high risk for contrast-induced nephropathy following RDN procedures with contrast. Therefore, if RDN procedures can be performed without contrast or with only minimal amounts of contrast, CKD patients may benefit from RDN.

The present study by Lo et al. showed the feasibility, efficacy, and safety of the RDN procedure using CO_2 angiography in patients with severe CKD [4]. The authors conducted an observational study of 10 patients who had an eGFR of less than 45 mL/min/1.73 m^2 without dialysis (mean eGFR at baseline: 31.7 ± 12.5 mL/min/1.73 m^2) and had been diagnosed with hypertension treated with at least three different antihypertensive drug classes. The RDN procedure using the "Symplicity Spyral^{TM} RDN System" was performed via the radial artery approach, with the assistance of CO_2 angiography. As an efficacy outcome, systolic blood pressure in 24-h ambulatory blood pressure monitoring was significantly reduced at 6 months compared to baseline (124.6 ± 12.7 vs. 138.8 ± 19.4 mmHg). As safety outcomes, serum creatinine and eGFR levels did not change significantly from baseline at 1 week or 6 months. Notably, in the two patients initially diagnosed with CKD stage 5, no progression to dialysis was observed after the RDN, even at 6 months. Although their study had some limitations, such as an observational study without a sham control group, a small number of patients, and a short follow-up period, it suggests the possibility of providing a treatment option for RDN in patients with pre-dialysis severe CKD who have difficulty using contrast media.

Recent guidelines on contrast media indicate that intra-arterial contrast injection with first pass renal exposure (e.g., injection into the left heart, thoracic and suprarenal abdominal aorta, or the renal arteries) is associated with a higher risk of contrast-induced acute kidney injury compared with intravenous injection or intra-arterial injection with second pass renal exposure (after dilution either in the pulmonary or peripheral circulation, e.g., injection into the right heart, pulmonary artery, carotid, subclavian, coronary, mesenteric, or infrarenal arteries) [5, 6]. In particular, contrast injection into the renal arteries, categorized as intra-arterial injection with first pass renal exposure, is a risk factor for contrast-induced acute kidney injury in patients with eGFR less than 45 mL/min/1.73 m^2 [5]. Therefore, as discussed in the report by Lo et al, a significantly lower use of contrast media with the assistance of CO_2 angiography may contribute to the renal safety outcome. The amount of contrast media used during the RDN in their study was 9.5 ± 10.7 mL, which was much lower than in RCTs using the same RDN catheter system, such as the SPYRAL HTN-OFF MED study (251.0 ± 99.4 mL) and the SPYRAL HTN-ON MED study (204.2 ± 81.4 mL) [7, 8].

In addition to the advantage of CO_2 angiography in reducing the use of contrast media, its disadvantages should also be recognized. Compared to contrast angiography, CO_2 angiography can cause an underestimation or over-stimulation of vessel caliber and has greater inter-observer variability in determining vessel caliber [9]. To compensate for this disadvantage, intravascular ultrasound and magnetic resonance angiography may be useful for assessing renal artery dimensions without the use of contrast media [10].

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Furthermore, this paper will address not only the procedural advantages and disadvantages of CO_2 angiography in patients with CKD, but also whether CKD patients can benefit from RDN. The sympathetic nervous system plays a critical role in cardiovascular and blood pressure regulation. RDN may impact not only the kidneys, which regulate sodium/water retention and renin–angiotensin system activity, but also the brain, which determines sympathetic outflow. The renal nerves consist of sympathetic efferent and sensory afferent fibers [2]. Previous studies have demonstrated that activation of renal afferent nerves increases sympathetic nerve activity by stimulating pre-sympathetic neurons in the brain, and renal damage can activate renal afferent nerves. Therefore, RDN may be effective in lowering blood pressure under pathophysiological conditions involving chronic renal damage and subsequent renal afferent activation and central sympathoexcitation, such as in CKD. In animal models of CKD, such as two-kidney-one-clip mice/rats, 5/ 6 nephrectomized rats, and deoxycorticosterone acetate-salt rats, selective afferent renal denervation with preservation of efferent renal nerves showed the antihypertensive and sympathoinhibitory effects [2, 11–14]. In contrast, selective afferent renal denervation did not attenuate the increase in blood pressure in young stroke-prone spontaneously hypertensive rats without significant renal damage [15]. In the Global SYMPLICITY Registry, the largest dataset of patients treated with RDN ($n = 1742$), there was an insignificant difference in 24-hour ambulatory blood pressure reduction between patients with and without CKD [16]. A meta-analysis also showed the efficacy and safety of RDN for hypertension in patients with CKD [3]. These findings support the notion that RDN could be an effective antihypertensive treatment option for patients with CKD.

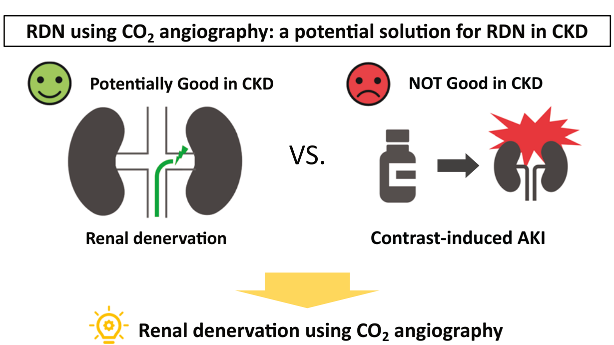

Fig. 1 RDN using CO_2 angiography: a potential solution for RDN in CKD. Patients with severe CKD may benefit from RDN, although these patients were excluded from the pivotal RCTs of RDN. However, CKD patients are at high risk for contrast-induced nephropathy following RDN procedures with contrast. Further clinical research is urgently needed to elucidate the efficacy and safety of RDN and to establish the RDN procedure, such as a renal protective strategy including CO_2 angiography, in CKD patients

Patients with severe CKD may benefit from RDN, although these patients were excluded from the pivotal RCTs of RDN. Further clinical research is urgently needed to elucidate the efficacy and safety of RDN and to establish the RDN procedure, such as a renal protective strategy including CO_2 angiography, in CKD patients (Fig. 1).

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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