Review

Renal Denervation: Intractable Hypertension and Beyond

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Key Words

Renal denervation · Hypertension · Renal sympathetic nervous system

Abstract

Background: Hypertension continues to be a major burden of public health concern despite the recent advances and proven benefit of pharmacological therapy. A certain subset of patients has hypertension resistant to maximal medical therapy and appropriate lifestyle measures. A novel catheter-based technique for renal denervation (RDN) as a new therapeutic avenue has great promise for the treatment of refractory hypertension. **Summary:** This review included the physiology of the renal sympathetic nervous system and the renal nerve anatomy. Furthermore, the RDN procedure, technology systems, and RDN clinical trials as well as findings besides antihypertensive effects were discussed. Findings on safety and efficacy seem to suggest that renal sympathetic denervation could be of therapeutic benefit in refractory hypertensive patients. Despite the fast pace of development in RDN therapies, only initial and very limited clinical data are available. Large gaps in knowledge concerning the long-term effects and consequences of RDN still exist, and solid, randomized data are warranted.

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Hypertension: Epidemiology and Control

Hypertension has high and growing prevalence; in 2000, it affected approximately 1 in 4 adults (>20 years old) worldwide, and its prevalence is predicted to increase to 1 in 3 adults, to a total of 1,56 billion adults, in 2025 [1]. Hypertension is an independent major risk factor

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for cardiovascular events, stroke, heart attack, and heart failure or kidney failure. For every 20 mm Hg of systolic or 10 mm Hg diastolic increase in blood pressure (BP), there is a doubling of the 10-year cardiovascular mortality rate [2].

Resistant hypertension is defined [3–5] as persistence of BP levels above goal (systolic and diastolic BP values of <140 and 90 mm Hg, respectively) in spite of a therapeutic strategy that includes appropriate lifestyle measures plus concurrent use of three antihypertensive agents from different classes and in adequate doses, including a diuretic. These patients are at high risk for adverse cardiovascular events.

The Renal Sympathetic Nervous System and Hypertension

BP homeostasis is achieved by the coordinated action of several systems, and the sympathetic activity plays an important role among them. The increased sympathetic activity is correlated with all hypertensive phenotypes, and the central sympathetic drive, measured by muscle sympathetic nerve activities, is higher in the different degrees of hypertension than in normotensive patients [6]. Additionally, norepinephrine spillover, an index of the efferent renal sympathetic activity in hypertensive patients, augmented in parallel with an increased sympathetic outflow to the heart and the activity of the skeletal muscle sympathetic nervous system (SNS) [7–9].

The important role of the renal SNS (RSNS) in initiation and maintenance of hypertension has been demonstrated in animal experiments and experience in humans either by measuring its activity in hypertensive subjects or by monitoring BP changes after sympathetic manipulation [10, 11].

The sympathetic innervation of the kidneys is composed of efferent fibers that are directed from the central nervous system (CNS) to the kidneys and afferent fibers with opposite direction, from the kidneys to the CNS. The axons of the preganglionic neurons arising from T10 to L2 interact with the renal postganglionic nerves at the level of the pre- and paravertebral sympathetic ganglia. The renal postganglionic fibers run alongside the renal arteries, primarily lying around the adventitia, and finally enter into the kidney through the hilus to innervate the renal tubules, vasculature, and juxtaglomerular apparatus [12] (fig. 1). By enhancing the noradrenaline production, these efferent fibers transmit stimuli from the CNS to the kidney and contribute to volume and BP homeostasis by facilitating tubular sodium reabsorption and subsequent salt and water retention, renin secretion with subsequent renin-angiotensin-aldosterone system stimulation, and renal vasoconstriction with subsequent renal blood flow reduction [12–15].

Conversely, the kidneys transmit neural responses to the CNS via the afferent fibers, likewise located around the adventitia of the renal arteries [16–18]. The cell bodies are found in the ganglia root, whereas the fiber terminations are present in all parts of the kidneys, with a higher concentration in the renal pelvis. The fiber-ending network responds to two types of receptors: (1) mechanosensitive receptors which are linked to the hydrostatic renal pelvic, renal arterial, and venous pressure, and (2) chemosensitive receptors which are activated by renal ischemia, hypoxia and changes in the renal interstitial chemical concentration [17, 19]. The returning signal is transmitted to the autonomic center in the medulla oblongata and midbrain, where it is integrated with afferent signals originating from other districts to regulate the overall sympathetic tone, comprising that of kidneys by means of signals sent back through the efferent fibers.

Therefore, this two ways communication system between the SNS and the kidney assumes a major role in regulating BP and in setting the overall sympathetic tone.

Fig. 1. Renal nerve anatomy: the renal postganglionic fibers run alongside the renal arteries, primarily lying around the adventitia.

Fig. 2. Point-by-point ablations: this ablation technique requires a series of pullback and rotation motions after each sequential ablation to create the desired helical ablation pattern in six different spots sequentially from distal to proximal. Reprinted with permission from Jacek Kadziela, Andrzej Januszewicz, Adam Witkowski: Evaluating renal denervation. Endovascular Today, 2012. www.evtoday.com.

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Renal Sympathectomy and Renal Denervation in the Treatment of Hypertension

Historically, surgical lumbar interruption of the SNS (sympathectomy) was used for reduction of resistant hypertension before effective antihypertensive medications were available. Dr. Reginald H. Smithwick was an early advocate of renal denervation (RDN), who reported splanchnicectomy in 1,266 cases with essential hypertension in 1953 [20]. Although effective when compared to conservative management available at that time, this procedure led to many adverse events, such as prolonged hospitalization, postural hypotension, syncope, impotence, difficulty in walking, and had a death rate of 10–30% and a nonresponse rate of 18–55% [21, 22]. The interest in this invasive surgical technique faded quite suddenly with the advent of the more effective antihypertensive drug therapy.

Advances in the knowledge of renal neural control provided a clearer connection between sympathetic renal nerves and BP, so that the idea that a localized endovascular approach to disrupt these nerves would theoretically result in BP reduction without the serious complications introduced by surgical sympathectomy was hinted.

Nowadays, a novel percutaneous catheter-based technique for selective renal sympathetic denervation may offer help for patients with resistant hypertension, in whom pharmacological therapy fails to control BP. This procedure is minimally invasive, characterized by short recovery times and absence of significant systematic side effects.

In resistant hypertensive patients, RDN therapy was proposed in a proof-of-concept trial called the Symplicity Hypertension (HTN)-1 trial [23], and its encouraging results were confirmed by the Symplicity HTN-2 trial [24]. Nowadays, a growing amount of data shows the benefits of renal sympathetic denervation in BP control, adding to previous literature evidence on the effect of surgical sympathectomy, improvement of renal function, cardiac size reduction and on the decreased incidence of headache, even if no comparison with pharmacological therapy was available at the time [12].

Renal Denervation Procedure and Technology Systems

The development of catheter-based radiofrequency ablation of the renal sympathetic nervous fiber (percutaneous transluminal radiofrequency sympathetic denervation) aims to disrupt neurogenic reflexes involved in BP control. This procedure is usually carried out using local anesthesia and conscious sedation that are required due to the intense pain experienced by patients during the ablation. Baseline aortogram is used to define anatomy, takeoff and angulation of renal arteries, vessel orientation and the presence of accessory polar arteries. Preliminary CT- or MR-based screening for suitable vascular anatomy is a useful strategy for patient selection. Catheterization is usually introduced via the femoral artery and advanced into each renal artery under fluoroscopic control. Alternatively, a radial or brachial approach can be used.

After cannulation of the renal artery, a selective angiography is performed and, when needed, the device size is determined. Then, the device is gently advanced and positioned in the main branch, proximal to the bifurcation. Once the ablation device is in place, radiofrequency energy is delivered to the vessel wall according to a predetermined controlled algorithm. Impedance estimation is used to determine the correct apposition of the catheter electrodes and is monitored throughout the procedure. The application of radiofrequency energy prompts thermal heat to penetrate through the artery wall into the adventitia layer and results in denervation of the target renal sympathetic nerves. Systemic heparinization is required throughout the procedure.

In general, the ablation device consists of a disposable catheter connected to a bedside console, which contains the control system, temperature and impedance monitoring and ancillary functions.

Current Renal Denervation Systems

The first device was a single electrode manually controlled device. Actually, the new devices are developed mounting the electrode on a modified balloon system or inserting different terminals on a specially designed basket-like self-expandable frame, causing a shift from an electrophysiologically based approach (i.e. ablation catheter) to a coronary interventional approach (i.e. balloon based) and making the procedure more appealing to the vascular

Table 1. Technical features of available renal ablation radiofrequency devices

	Medtronic Symplicity™	St. Jude Medical EnligHTN	Covidien OneShot™	Boston Scientific Vessix™
CE marking	2008/02	2011/12	2012/02	2012/04
Size	6 Fr, one size fits all	8 Fr, large and small baskets	7–8 Fr, balloon diameter 5, 6, 7 mm	8 Fr, balloon length 25 mm, balloon diameter 4, 5, 6, 7 mm
Renal artery treatment range	≥4 mm	4–8 mm	4–7 mm	3–7 mm
Treatment time	2 min/ablation, recommended minimum 4 ablations/artery	90 s/ablation, 8 ablations/artery	One single, 2 min ablations/artery	30 s/ablation, 1–2 ablations/artery
Over-the-wire system	no	no	yes	yes
Cooling features	no	no	yes	no
Total energy delivery	max. 8 W	max. 6 W	max. 25 W	max. 2 W
Maximum temperature	75° C	75° C	60° C	68° C
Catheter length	90 cm	115 cm	74 cm	90 cm

interventionist. Additionally, the possibility to obtain multiple contact sites during a single application has the effect of shortening the procedure time and ensures a circumferential coverage of the vessel wall.

There are four devices for RDN with radiofrequency, which are currently being approved for clinical use in Europe: Medtronic Symplicity™, St. Jude Medical EnligHTN, Boston Scientific Vessix™ and Covidien OneShot™. Their characteristics are described below and summarized in table 1 [25–28].

Moreover, novel treatment modalities for RDN are under development based on ultrasound energy, cryoablation techniques, radiation, and local drug delivery.

The Medtronic Symplicity Renal Denervation System

The Medtronic Symplicity is the first system that has been used for RDN with radiofrequency. The currently used second-generation system consists of a single unipolar electrode on the flexible tip of the catheter, with a non-over-the-wire system. It reaches a temperature up to 75° C, with an approximate energy delivery of 5–8 W in 2 min/ablation.

The catheter is directed to the vessel surface using a manipulating handle, which allows flexion and rotation to direct the catheter tip to the vessel wall. An average procedure consists of radiofrequency energy delivered for 2 min in ideally four to six different spots in a circumferential manner sequentially from distal to proximal, at least 5 mm apart, on each side (fig. 2). The procedure time is influenced by the operator's experience and the renal anatomy because in tortuous vessels it may be difficult to obtain an adequate vessel wall contact at all required sites [29–31].

The St. Jude Medical EnligHTN Renal Denervation System

The St. Jude Medical EnligHTN consists of a catheter with a non-occluding nitinol basket on the tip, with four unipolar electrodes on it. There are two basket sizes of 16 mm (for 4–6 mm diameter vessels) and 18 mm (for 5–8 mm diameter vessels), respectively. Once the tip of the catheter is positioned, without the use of a guidewire, the nitinol basket is expanded. Once the electrodes' apposition is confirmed, it is possible to start a simultaneous, multi-electrode ablation for 90 s, using a target temperature of 75°C that needs a maximum of 6 W of switch on power, and then a lower maintenance power. After a first distal round into the renal artery, the catheter is retracted and rotated to perform another round of ablation in proximal segments or the vessel (on average, eight ablations/artery are required).

The Boston Scientific Vessix Renal Denervation System

The Boston Scientific Vessix is a balloon-based technology consisting of a low-pressure (3 atm/304 kPa), noncompliant, over-the-wire balloon available in different sizes (4, 5, 6 and 7 mm in diameter) and a radiofrequency generator. On the balloon surface, there is a helical array of four, six or eight radiopaque bipolar electrodes, depending on the balloon size, that have independent temperature sensing and control features. Only vessel-apposed electrodes are activated by the generator when the balloon is inflated reaching a temperature of 68°C, making the procedure effective within 30 s, with a total amount of energy delivery of 1 W.

The Covidien OneShot Renal Denervation System

The Covidien OneShot is a low-pressure balloon-based system delivered over a standard 0.014" guidewire. There are three different balloon diameter sizes (5, 6 or 7 mm) to treat vessels ranging from 4 to 7 mm of diameter, and they have a spiral silver unipolar electrode with an electrode ablation length of 20 mm and two radiopaque markers. The integrated low-pressure irrigation system allows continuous cooling of the artery during ablation, through eight tiny irrigation holes.

One single 2-min ablation/artery is sufficient and delivers 25 W of radiofrequency energy and a maximum temperature of 60°C.

Preclinical Data in Renal Denervation

In an extensive research study of over 300 swine, a significant ($p < 0.0001$) reduction in renal tissue norepinephrine was observed between the untreated controls ($n = 24$) and those animals receiving catheter denervation ($n = 33$) models. The safety of the procedure was verified through angiography, gross pathology, histopathology and clinical pathology at 7, 30, 60, and 180 days. Intact endothelium was found at 7 days and the arteries were well healed (no inflammatory cells were found). At 30, 60, and 180 days after treatment, the sites were considered stable and no stenosis or vessel alterations was seen in any treated artery through 180 days [32].

Clinical Trials in Renal Denervation

The clinical effectiveness of the RDN procedure for the treatment of resistant hypertension has been mainly investigated with the Symplicity Clinical Trial Program that consists in a set of clinical studies that include the Symplicity HTN-1 [31] with extended follow-up [23], the Symplicity HTN-2 [24] with extended follow-up [33], both completed, and the ongoing Symplicity HTN-3 [34]. These trials are making use of Medtronic devices. The newest devices have preliminary results from first-in-man trials (the EnligHTN-1 trial for the St. Jude Medical EnligHTN device [35, 36], the RHAS trial [37] for the Covidien OneShot device, and the ReduceHTN study for the Boston Scientific Vessix device), confirming the efficacy of the RDN in patients enrolled, and are awaiting results from larger ongoing trials.

The Symplicity HTN-1 Study and Extended Follow-Up

This first-in-man study was not a prospective controlled clinical trial, but an open label, nonrandomized study focused on safety and proof-of-concept of therapeutic RDN in patients with severe resistant hypertension (systolic BP of ≥ 160 mm Hg). A total of 50 patients at five Australian and European centers were enrolled between June 2007 and November 2008. Baseline mean office BP was 177/101 mm Hg, with a mean of five antihypertensive medications. Office BP after procedure was progressively reduced by 14/10 mm Hg at 1 month to 27/17 mm Hg at 12 months. Renal noradrenaline spillover was evaluated in a small subset of patients, showing a mean reduction of 47%.

To evaluate the long-term safety and the durability of reduction in BP following the denervation procedure, the Symplicity HTN-1 investigators enrolled a larger group of similar patients (153 patients of which 45 already belonging to the initial Symplicity HTN-1 cohort) treated with RDN in a nonrandomized manner at 19 investigation sites in Australia, Europe, and the US between June 2007 and May 2010.

Postprocedural office BP was progressively reduced by 20/10 mm Hg at 1 month, 23/11 mm Hg at 12 months and 32/14 mm Hg at 24 months. The magnitude of BP reduction at 24 months after the procedure is no less than that observed at 12 months. In this larger cohort of patients, a longer period of postprocedure follow-up demonstrated the ongoing safety, showing no complications in 97% of the patients. Only four acute procedural complications were reported (a renal artery dissection and three femoral artery pseudoaneurysms) which were all managed without sequelae.

However, Gu et al. [38] objected to these findings because they indicated that the percentage of patients in the Symplicity HTN-1 registry with a follow-up of 1 and 2 years was only 41.8 and 11.7% for BP, respectively.

The Symplicity HTN-2 Trial

A prospective, open-label, randomized control study was conducted at 24 centers in Europe, Australia, and New Zealand from June 2009 to January 2010 recruiting similar patients to the HTN-1 trial. One-hundred and six (56%) of 190 screened patients were eligible for study inclusion and were randomized to RDN plus antihypertensive medications ($n = 52$) or to the control medication-only group ($n = 54$). Follow-up duration was 6 months. Office-based BP measurements in the RDN group were reduced by 32/12 mm Hg, whereas in the control group measurements did not vary from baseline. Similarly, 24-hour ambulatory blood-pressure monitoring (ABPM) showed a mean decrease of 11/7 mm Hg, while home-

based BP measurements decreased by 20/12 mm Hg at 6 months. The Difference in BP between groups was of 33/11 mm Hg. A total of 84% of the RDN patients had a reduction in systolic BP of at least 10 mm Hg compared with 35% of the controls. No serious complications related to the device or procedure were reported.

In a study with a longer follow-up [33], after 6 months from recruitment, RDN was permitted in control patients, resulting in a crossover arm of the study. One-year results of the original RDN group (n = 47) and 6-month postprocedure results of the crossover group (n = 35) were reported. A total of 78.7% of the patients in the original RDN group experienced a reduction in systolic BP of 10 mm Hg or more at 12 months, with a similar outcome of 62.9% patients in the delayed RDN group at 6 months. The crossover group had a significant drop in BP at 6 months (mean reduction was 23.7/8.4 mm Hg vs. preprocedure), similar to that observed in original RDN patients at 12 months (decrease in office BP was 28.1/9.7 mm Hg).

The Symplicity HTN-3 Trial

The Symplicity HTN-3 trial is ongoing in the US; it is designed as a prospective, randomized, masked procedure, single-blind trial, in which 24-hour BP change is an important and powered secondary end point, patients will be blinded to randomization assignment, and a sham RDN procedure is incorporated into the study design [34].

Safety of Renal Denervation

In the Symplicity trials, the RDN was performed without major complications in 98% of the cases. Theoretical adverse events include renal artery dissection and perforation, late stenosis or promotion of atheroma in the renal artery in the long term, sodium depletion and hypotension.

Available data on treated patients obtained in the follow-up have not shown major adverse consequences on the vascular wall such as stenosis or aneurysm. However, vessel spasm is common during energy applications and can be reversed with nitroglycerin or verapamil.

In animal studies, transient local de-endothelialization, acute cellular swelling, connective tissue coagulation, and thrombus formation were reported [39]. In humans, edema and thrombus formation in the sites of RDN have been described by optical coherence tomography although not visible on angiography [40]. These observations suggest that the use of antiplatelet therapy during and after the procedure might be advisable, but controlled data are missing [41].

Open Questions and Future Horizons of Renal Denervation

Safety and effectiveness of BP lowering have been established in catheter-based RDN. The effect of RDN therapy on clinical outcomes, especially on cardiovascular mortality, has not been proven until today. The importance of destruction of renal nerves, beyond its anti-hypertensive effect, needs to be further elucidated in patients with substantial cardiovascular risk.

Renal reinnervation is only described in rats after RDN [42] and after kidney transplantation [43]. Whether the use of the prevalent RDN technique can permanently interrupt renal sympathetic nerve activity in humans is still to be proven, further follow-up is required

beyond this time point to ascertain the longevity of the BP-lowering effect over a longer time period as well as implications regarding the need for repeat procedure.

In the HTN-1 trial, 13% of the RDN patients had little BP reduction. Among the baseline parameters, only elevated BP and use of central sympatholytic were predictors in the 24-months results. A key issue in the clinical application of the procedure is how to predict which patients may be good responder and achieve BP reduction.

Further studies are also needed to elucidate how this procedure lowers BP and to define its clinical role in the management of hypertension and associated disorders in which the renal sympathetic outflow is activated. Hypertension may indicate the start of RDN [14, 44], which could be of therapeutic value in conditions associated with sodium retention or systemic sympathetic hyperactivity.

With the increasing use of RDN, complications such as renal artery stenosis might occur more often [45]. Safety issues will still be a subject for further investigation in a broader registration database for long-time follow-up. Further limitations of RDN also include its higher costs (EUR 3,000 vs. EUR 5,000) compared to medical treatment. Additional evaluation of its therapeutic economics is needed.

Eligibility Criteria for Renal Denervation

Based on evidence gathered from available clinical studies, the European Society of Hypertension (ESH) has recently suggested a set of recommendations on the utilization of RDN for the treatment of resistant hypertension [46]. The ESH identified three steps for the eligibility criteria for RDN. The first step is to exclude patients with false resistant hypertension (pseudo-resistance) by using 24-hour ABPM and home BP monitoring, patients with secondary arterial hypertension or finally patients having high BP values due to other causes (e.g. obstructive sleep apnea, high salt intake, BP-raising drugs, or severe obesity). The second step consists in optimizing antihypertensive treatment with at least three (or better four) tolerated drugs, including a diuretic and an antialdosterone drug, when clinically possible, and then check for effective BP control using ABPM before giving the indication for RDN. The third and last step to check the eligibility for RDN consists in considering anatomic contraindications due to unresolved safety issues (avoid RDN in case of multiple renal arteries, main renal artery diameter of less than 4 mm or main renal artery length less than 20 mm, significant renal artery stenosis, previous angioplasty or stenting of renal artery), and in ensuring that eGFR is >45 ml/min/1.73 m².

Overall, the ESH recommends to perform the procedure in very experienced hospital centers, such as hypertension excellence centers, and to use the devices that have demonstrated efficacy and safety in clinical studies.

Outcomes of Renal Denervation besides Antihypertensive Effects

Chronic activation of the SNS is also common in chronic kidney disease [47]. As resistant hypertension is associated to end organ damage, the effect of RDN on kidneys was investigated. The percentage of patients for Symplicity HTN-1 registry with a follow-up of 1 and 2 years was, respectively, 41.8 and 6.5% for estimated glomerular filtration rate (eGFR). During the first year of follow-up, eGFR remained stable, while changing by -16.0 ml/min/1.73 m² at 24 months after the procedure in patients that received spironolactone or another diuretic, which was added after the first year of follow-up. Compared to patients without newly added spironolactone or another diuretic, eGFR changed by -7.8 ml/min/1.73 m², with an annu-

alized change of -3.9 ml/min/ 1.73 m². In the Symplicity HTN-2 study, no changes were reported in measured renal function with RDN, suggesting that the procedure itself and associated hemodynamic changes have no adverse effects on the kidneys even in patients with mild-to-moderately impaired renal function [13].

In a recent study ($n = 100$ patients) [48] aiming at evaluating renal function and hemodynamics after RDN, RDN reduced BP, renal resistive index, and incidence of albuminuria without adversely affecting glomerular filtration rate or renal artery structure within 6 months.

Schlaich et al. [49] showed that in 15 patients with stage 3–4 chronic kidney disease, RDN caused no alterations in kidney function after a 12-month follow-up. They also performed RDN in 12 end-stage renal disease patients with uncontrolled hypertension, obtaining a significant reduction of office systolic BP at 3, 6, and 12 months.

RDN was shown to have potential effects on improving glucose metabolism, insulin sensitivity and sleep apnea severity but with potential limitations, including a small number of patients and interference with drug effects on insulin sensitivity, such as beta-blockers, diuretics and ACE inhibitors [29, 50]. It was shown that RDN decreased angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure, and in diabetic hypertensive rats it reduced heart rate variability [51, 52]. In the extended investigation of the Symplicity HTN-2 trial, 37 patients underwent bilateral RDN and 9 patients were assigned to the control group, heart rate at rest decreased and heart rate recovery improved after the RDN procedure [53]. In another study [54], 7 patients with chronic systolic heart failure (mean BP on referral 112/65 mm Hg) on maximal tolerated heart failure therapy were followed up for 6 months, and no procedural or postprocedural complications after RDN were found. The results suggested improvement in both symptoms and exercise capacity. Moreover, in another study with 46 patients who underwent bilateral RDN and 18 controls, the authors showed for the first time that RDN significantly reduced left ventricle mass and improved diastolic function [55].

Conclusion

Based on the results of the initial and small clinical experience, catheter-based RDN therapy has great promise for the treatment of refractory hypertension. Safety and efficacy findings seem to suggest that renal sympathetic denervation could be of therapeutic benefit in this patient population. Despite the fast pace of development in RDN therapies, significant gaps in knowledge still exist, especially with regards to possible nerve or vessel injury and long-term consequences. Further larger studies and solid randomized clinical trials are required to assess duration of BP control, quality of life, hard cardiovascular outcome, long-term safety and cost-effectiveness analysis. Other potential indications are subject of active research and ongoing studies.

Disclosure Statement

The authors declared no competing interests.

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