Brief Review

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Changes in 24-Hour Patterns of Blood Pressure in Hypertension Following Renal Denervation Therapy

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The hypertension paradox was described over 10 years ago to stress the growing incidence of hypertension despite the availability of safe, effective, and inexpensive drug therapies.[1] Multiple factors contribute to the hypertension paradox, including lack of patient awareness and education, failure to adhere to prescribed lifestyle changes and prescribed drug regimens, aging societal demographics, and recent recommendations for lowered blood pressure goals. Hence, a rationale exists for procedural-based therapy options that could augment drug therapy regimens and help more patients achieve and sustain blood pressure goals.

Percutaneous renal denervation has gained continued scientific and clinical interest due to its proven impact on autonomic function, likely because of both efferent and afferent mechanisms affecting the renal nerves.[2] Clinical evidence suggests a strong association between renal denervation and reduced indices of sympathetic tone including muscle sympathetic nerve activity and renal norepinephrine spillover.[3] Historically, surgical sympathetic denervation was shown to improve mortality, independent of its effect on blood pressure.[4] In 2014, the randomized sham-controlled SYMPLICITY HTN-3 trial reported blood pressure drops in the renal denervation-treated group which were nearly matched by those in the sham control group.[5] More recently however, 3 new multicenter, international, prospective, randomized, sham-controlled clinical trials have demonstrated lower blood pressure after catheter-based renal denervation in uncontrolled hypertensive patients in both the presence and absence of concomitant drug therapy,[6–8] confirming the biological proof of principle. These trials have rekindled scientific and clinical interest in the procedure and have also revealed interesting new insights into the 24-hour profile of blood pressure reduction associated with the therapy. This review highlights the 24-hour circadian pattern of blood pressure lowering after renal denervation and hypothesize how these effects might complement drug therapy.

24-Hour Blood Pressure Monitoring: Toward Perfect Control

The advent of 24-hour ambulatory monitoring has allowed consideration of blood pressure as a continuous and dynamic circadian physiological signal, especially highlighting the unique blood pressure characteristics of the nighttime and early morning period. Thus, blood pressure control has been more meaningfully redefined relative to specific times of day[9] (Figure 1). Circadian blood pressure variability is a direct reflection of the relative integrity of the autonomic nervous system which modulates its behavior. Multiple clinical trials have demonstrated that elevated nighttime blood pressure is more strongly associated with cardiovascular risk than daytime or office blood pressure.[10,11] Furthermore, 24-hour blood pressure patterns distinguish between different hypertension phenotypes including white coat, masked and sustained hypertension as well as identifying abnormal nighttime dipping patterns. Recently, an analysis of the Spanish Ambulatory Blood Pressure registry with >60 000 patients enrolled, indicated that white-coat hypertension, defined by an out of office 24-hour ambulatory blood pressure lower than goal blood pressure and in-office blood pressure that was above goal in unmedicated patients, was associated with increased mortality, and that masked hypertension was associated with a greater risk of death than sustained hypertension.[12] Indeed, out of office ambulatory (ABPM) or home blood pressure measurement is now recommended to confirm the diagnosis of hypertension and, in the case of home blood pressure measurement, to monitor therapy efficacy in both the United States and European Hypertension Guidelines.[13–17] Despite these recommendations, ABPM monitoring is used relatively rarely in clinic to confirm the diagnosis of hypertension, even among patients treated by hypertension specialists. Likewise, only recently has ambulatory blood pressure become the focus end point for clinical trials.[18] Ideal blood pressure control includes 24-hour control, adequate circadian rhythm, and appropriate

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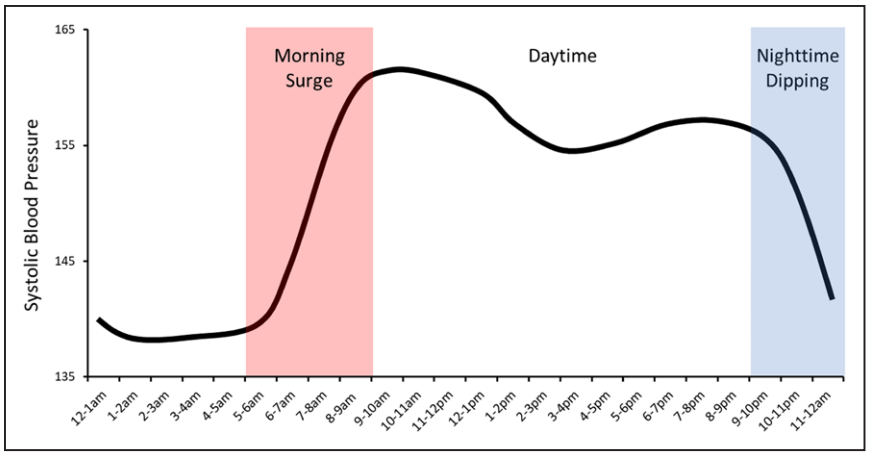

Figure 1. Cartoon diagram of the sympathetically modulated 24-h circadian pattern of blood pressure changes including nighttime dipping and the pre and postawakening morning blood pressure surge.

blood pressure variability with the goal of eliminating cardiovascular events.

Prognostic Importance of Controlling Morning Blood Pressure

Hypertensive cardiovascular risk including myocardial infarction, stroke, and sudden death is the highest during the morning surge period between 6 AM and 10 AM[19,20] and the risk may be even higher than for nighttime hypertension.[21,22] Morning hypertension might be caused by overactivation of the sympathetic nervous system and can be modified by other sensory inputs and by posture.[23] Other factors, including arterial stiffness and endothelial function also may play a role. The recent J-HOP trial (Japan Morning Surge-Home Blood Pressure) of 4310 elderly patients with high cardiovascular risk showed a positive linear association between home morning systolic blood pressure (SBP) and cardiovascular events, especially stroke. However, such an association was not observed for either clinic SBP or home evening systolic pressure.[24] Likewise, the HONEST trial (Home Blood Pressure Measurement with Olmesartan Naive Patients to Establish Standard Target Blood Pressure) of over 21 000 hypertensive patients reported increased risk for a cardiovascular event among patients with home-measured morning SBP≥150 mm Hg as compared with the group with <125 mm Hg (HR, 5.03; 95% CI, 3.05–8.31).[25] Interestingly, even patients with normal office SBP were still at risk if the morning home blood pressure was uncontrolled (Figure 2). Furthermore, a pooled analysis of 5645 from the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome reported that morning surge SBP above the 90th percentile independently predicted cardiovascular outcomes.[11] Taken together, these and other trials highlight the importance of home blood pressure monitoring to effectively diagnose morning hypertension and titrate hypertensive therapy dosage and timing accordingly.

Effects of Percutaneous Renal Denervation Therapy on 24-Hour Blood Pressure Patterns

The renal denervation procedure has the potential to augment standard antihypertensive drug therapy regimens and may be especially useful if the drug regimen is suboptimal or not well adhered to by the patient. The proposed mechanism by which renal denervation lowers blood pressure may lend itself well to consistent 24-hour blood pressure control (Figure 3). Reducing efferent neural traffic from the brain to the kidney may particularly impact nighttime hypertension as increasing renal blood flow and sodium excretion may restore normal dipping patterns. Likewise, interrupting sensory afferent signals from the kidney to the brain may reduce central sympathetic nerve activity and increase baroreceptor sensor sensitivity, thereby attenuating the morning surge.

Reports of the impact of renal denervation on nocturnal blood pressure dipping patterns are mixed. Although some trials have reported improvements in nocturnal dipping status after renal denervation,[26,27] several nonrandomized[28–32] as well as randomized controlled studies[33–35] failed to show an impact

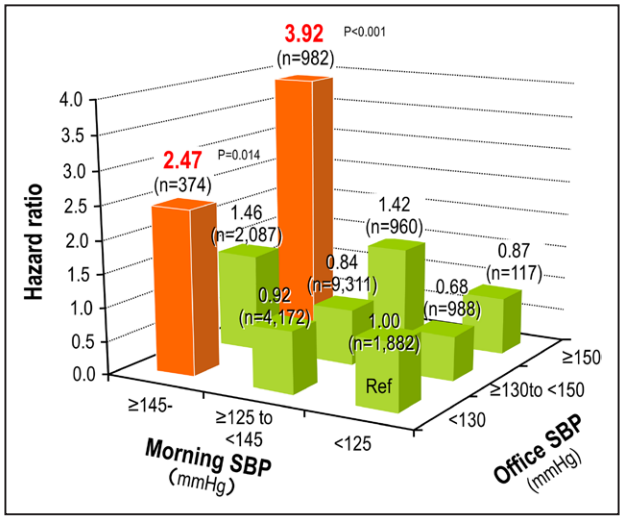

Figure 2. HONEST trial (Home Blood Pressure Measurement with Olmesartan Naive Patients to Establish Standard Target Blood Pressure) data indicating that low-office blood pressure may still be associated with high-morning blood pressure[25] and increased cardiovascular risk. Hazard ratios for the incidence of cardiovascular events was the highest in the patients with morning home systolic blood pressure (SBP) ≥145 mm Hg and office SBP ≥150 mm Hg followed by patients with morning home SBP ≥145 and office SBP <130 mm Hg. The subgroup with morning home SBP <125 and office SBP <130 mm Hg was defined as a reference. Orange highlighted bars emphasize statistical significance vs the reference group. Reprinted with permission from Kario K, Saito I, Kushiro T, Teramukai S, Ishikawa Y, Mori Y, Kobayashi F, and Shimada K. Home blood pressure and cardiovascular outcomes in patients during antihypertensive therapy: primary results of HONEST, a large-scale prospective, real-world observational study. *Hypertension*. 2014;64:989–996. Copyright ©2014, Wolters Kluwer Health, Inc.

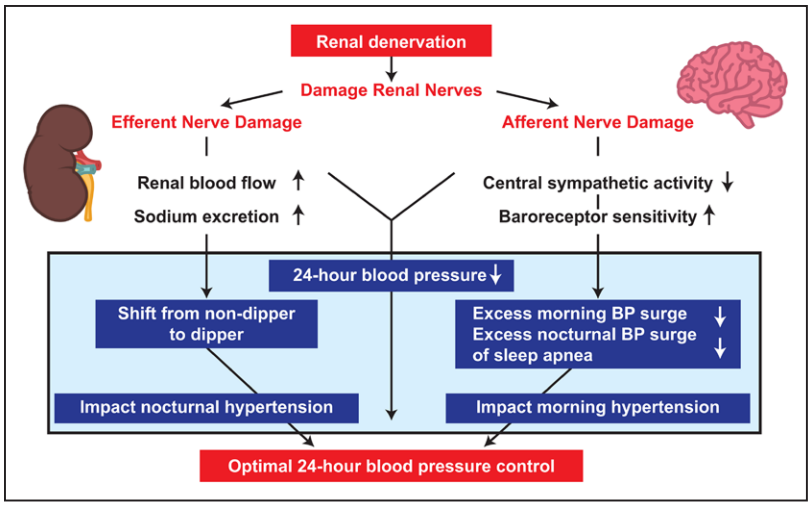

Figure 3. Proposed mechanism whereby both efferent and afferent mechanisms might affect 24-h blood pressure patterns after renal denervation. BP indicates blood pressure.

of renal denervation on nocturnal dipping patterns. However, these results may be due in part to nonspecific definitions and modest reproducibility of baseline dipping status.[36] Indeed, recently published analyses support the hypothesis that the effects of renal denervation are apparent throughout the 24-hour period including during the nighttime and morning surge period. Several single[30,37] and multicenter[28] analyses of patients with treatment-resistant hypertension showed that the amplitude of the morning blood surge decreased after renal denervation. Notably, the SYMPLICITY HTN-3 trial showed no significant difference between blood pressure reduction in the denervation versus sham groups over the nighttime period nor was there a difference in the slope of the morning blood pressure surge between the denervation and sham-controlled groups.[5] However, analysis of ambulatory SBP data from SYMPLICITY HTN-3 revealed that patients treated with renal denervation experienced a significantly greater change in morning (−7.3±19.8 mm Hg; $P<0.001$) and nighttime (defined from 1 AM to 6 AM; −6.1±18.2 versus −1.6±19.7 mm Hg; $P=0.02$) but not daytime SBP (−7.2±16.2 versus −6.4±18.6 mm Hg; $P=0.67$) as compared with control, and this finding was consistent when the SYMPLICITY HTN-3 results were pooled with the SYMPLICITY HTN-Japan study.[38] This observation is now corroborated by the results of both the SPYRAL HTN OFF and ON MED trials that also showed greater between group blood pressure drops during nighttime versus daytime.[6,7]

Additional insight to the mechanism of the 24-hour effects of renal denervation on blood pressure may be derived by examining hourly blood pressure changes (Figure 4). Unique patterns of 24-hour blood pressure reduction were recently reported in the randomized sham-controlled SPYRAL HTN-OFF MED trial at 3 months[39] and the SPYRAL HTN-ON MED trial at 6 months.[7] The observed reductions in 24-hour blood pressure were not present in the sham control group. Likewise, the recent RADIANCE HTN-SOLO clinical trial of renal denervation using an ultrasound-based catheter in uncontrolled hypertensive patients not taking antihypertensive medications reported similar patterns of blood 24-hour blood presssure reduction after 2 months,[40] and these reductions were maintained out to 6 months after titration of drug therapy in those patients not initially achieving blood presssure control.[41] In addition, a recent analysis of the long-term results of the SYMPLICITY HTN-Japan trial showed a shift in the 24-hour SBP curve versus baseline in the combined renal denervation and crossover group at 6 months as compared with the original untreated control group[42] (Figure 4). The results in aggregate support the concept that denervation therapy is always on, providing cardiovascular protection throughout the day and the nighttime including the high-risk morning surge period. This action may result in consistently lower BP levels throughout the day and and night and may thus partially compensate for the relative peaks and troughs of plasma drug concentrations because of pharmacokinetics and variable dosing times as well as drug nonadherence. More consistent 24-hour blood pressure control could have a critical positive impact on long-term clinical outcome.

Interestingly, the impact of denervation may also extend to 24-hour patterns of heart rate, another index of cardiovascular risk.[43] A recently published analysis of the SPYRAL HTN OFF-MED trial showed that renal denervation lowered heart rate compared with sham, and these reductions were more apparent in the morning than during the day. The complex relationship between denervation therapy and the patterns of blood pressure and heart rate require additional investigation.

Summary and Conclusions

Ambulatory blood pressure is a better predictor of cardiovascular risk compared with office blood pressure, especially during nighttime and early morning periods, and is recommended to confirm hypertension diagnosis. Currently prescribed drug regimens make it challenging to achieve optimal 24-hour blood pressure control, especially in less adherent patients. New evidence on the 24-hour blood pressure reductions associated with renal denervation, coupled with the limitations of daily oral drug dosing, may improve blood pressure control when multiple therapy strategies, including procedures, drugs, and lifestyle changes are combined. Multiple independent trials demonstrate that renal denervation provides 24-hour blood pressure lowering including during the early morning high-risk period. Whether the documented blood pressure-lowering effects are persistent through long-term follow-up and lead to improved cardiovascular end points must be investigated in future clinical studies. Currently, several larger-scale randomized sham-controlled clinical trials of renal denervation in both

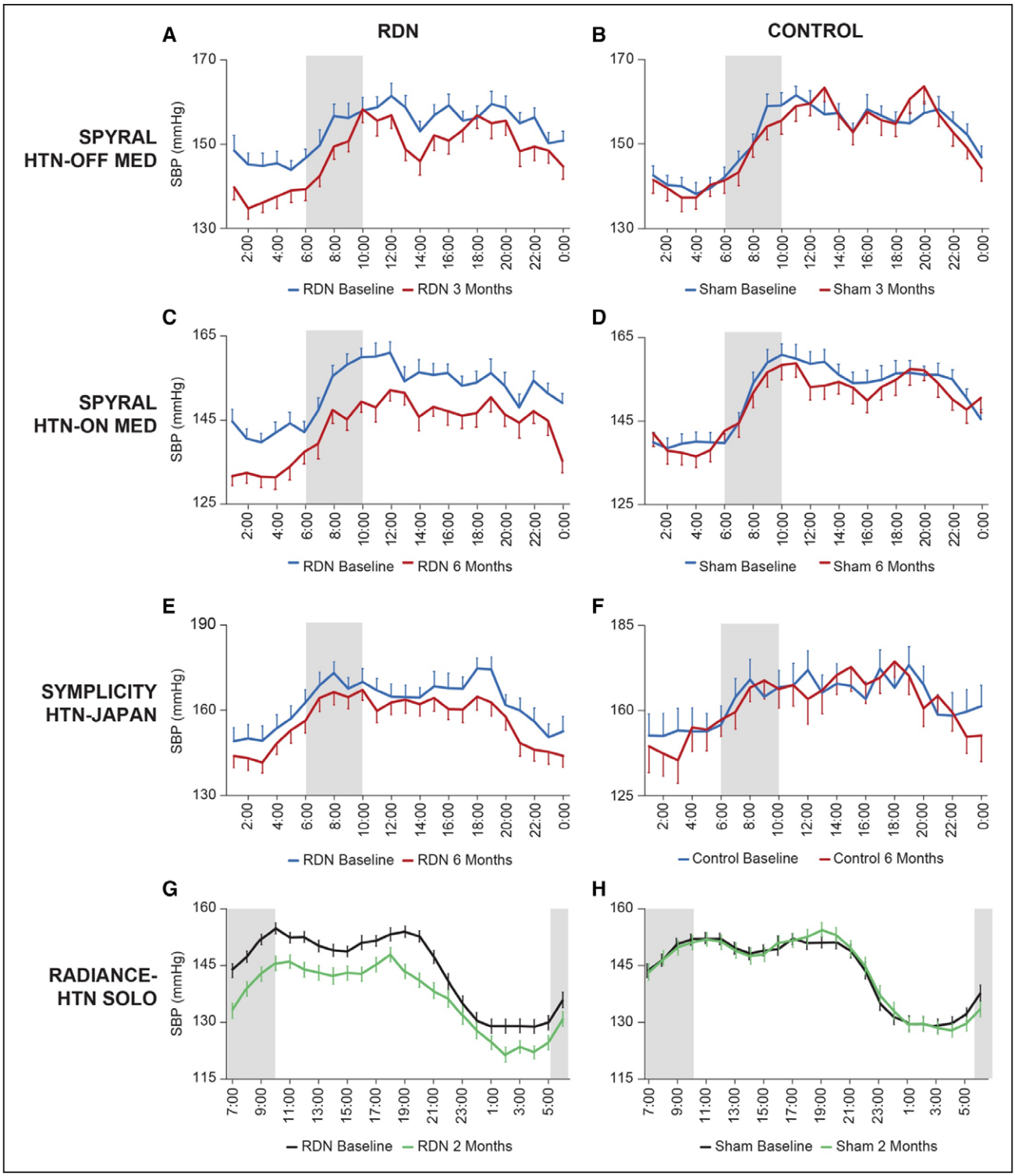

Figure 4. Twenty four-h blood pressure changes derived from 4 recent prospective randomized controlled trials at baseline and follow-up showing changes in systolic blood pressure throughout the day and night and during the morning surge period. Data are adapted from the Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications (SPYRAL HTN-OFF MED) (3-mo follow-up, N=80; **A**,**B**),[39] SPYRAL HTN-ON MED[7] (6-mo follow-up, N=80; **C**,**D**), SYMPLICITY HTN-Japan[42] (6-mo follow-up; N=22; **E**,**F**), and Study of the ReCor Medical Paradise System in Clinical Hypertension[41] (2-mo follow-up; N=122; intention to treat subgroup; **G**,**H**) trials. Figure clock starting times differ between trials, as originally reported. Shaded regions indicate morning surge period. The renal denervation group for the SYMPLICITY HTN-Japan trial includes control group patients that crossed over to renal denervation (RDN) after the primary end point. Error bars indicate Standard Error. Data derived from Kandzari et al,[7] Kario et al,[39] Azizi et al,[41] and Kario et al.[42]

the presence and absence of antihypertensive medications are underway that will further enhance our understanding of the patterns of 24-hour blood pressure reduction associated with this novel therapy option. These studies should help define new care pathways that integrate drug and device-based strategies in this era of the hypertension paradox.

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K. Kario has received research/consultant fees from Medtronic and Omron Healthcare; M.A. Weber has received research/consultant fees from Medtronic, Boston Scientific, ReCor Medical, and Ablative Solutions. R.E. Schmieder has received research funding, consultant fees, and travel support from ReCor Medical, Ablative Solutions, Pythagorus Medtronic, and ROX Medical; D.E. Kandzari has received research/grant support and consulting honoraria from Medtronic; F. Mahfoud has received speaker honoraria and consultancy fees from St. Jude Medical, Medtronic, and ReCor Medical; A.J. Kirtane has received grant support to Columbia University and Cardiovascular Research Foundation from ReCor Medical, Medtronic, Abbott Vascular, Boston Scientific, Abiomed, CathWorks, Siemens, and Philips. M. Böhm has received honoraria for lectures and scientific advice from Medtronic; R.R. Townsend has received research support and consultant fees from Medtronic; D.A. Hettrick is a full-time employee of Medtronic; K.P. Tsioufis has received research support from Pythagorous Medical and research support, consultant fees and travel support from Medtronic.

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