Renal Denervation
Renal Denervation

A New Approach to Treatment of Resistant Hypertension
In the Western world, 30–40% of the adult population suffers from hypertension. The prevalence is expected to increase with the aging population. Sixty-five percent of patients over 60 years of age are affected by hypertension. It is thought to be the greatest risk factor for cardiovascular disease. Renal sympathetic efferent and afferent nerves are recognized as critical in the hypertensive disease process and represent an important therapeutic target. From the 1930s to 1950s, investigators performed surgical interruption of the sympathetic pathway and effectively lowered the pressure significantly in patients, but there were complications that precluded the continued application of this technique at the same time that effective drug regimens evolved.

Recently, renal denervation has been reborn as a catheter technique utilizing the proximity of the renal nerves to the renal arteries utilizing various forms of energy or injections. This technique has been effective in treating resistant hypertension in as many as 85% of patients. The ability to perform this transcatheter technique has the potential to cause a paradigm shift in cardiovascular care. Resistant hypertension is defined as blood pressure persistently above goal despite the use of antihypertensive medications from \( \geq 3 \) drug classes. These patients face worse cardiovascular outcomes and systemic hypertension-related complications, for which there is no viable treatment option. For example, poorly controlled hypertension can increase stroke rate by 50%.

The new percutaneous approach, based on the concept of an old surgical technique, may be a true game changer for treating patients with not only hypertension but also renal insufficiency, congestive heart failure, diabetes mellitus, obesity, sleep apnea, and glucose intolerance. Given the enormous market for this treatment approach and the rapidly compounded annual growth rate, an estimated 60 companies are pursuing technologies to achieve RDN with equivalent or superior approaches. This treatment is moving so quickly and has been thought effective enough in its early stages that the European Society of Cardiology (ESC) has issued a consensus statement describing patients that are appropriate to be screened for this therapy. The whole field of renal arterial based renal denervation dealt a serious blow with the publication of the Symplicity HTN-3 6-month data. This blinded trial did not show significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control (Funded by Medtronic: SYMPLICITY HTN-3 ClinicalTrials.gov, number, NCT01418261) [1]. After 6 months, office systolic blood pressure decreased from baseline to a similar extent in the renal-denervation and sham-procedure groups \((P<0.001)\) for both comparisons of the change from baseline); the difference in the change in blood pressure between the two groups was a paltry \(-2.39\) mmHg. In addition, a prespecified difference in 24-h ambulatory systolic pressure of only \(2\) mmHg was not met. Thus, in the SYMPLICITY HTN-3 STUDY, renal denervation had no significant effect on office or 24-h ambulatory systolic blood pressure, findings that contradict most published data on renal denervation. While renal denervation lowered blood pressure by an average of \(14.1\) mmHg, it was not statistically significant when compared to the sham treatment. Patients receiving no treatment may experience Hawthorne effect, believing they had received the treatment, resulting in an \(11.7\) mmHg reduction. The trial used the first-generation Medtronic Symplicity catheter, which uses a single electrode that must be maneuvered into specific positions for ablations that last about a minute each. The procedure is similar to cardiac
ablations to isolate arrhythmia-causing cardiac tissue. Electrophysiology ablations are sometimes difficult to perform or have mixed outcomes, depending on several factors, including catheter pressure applied, duration of the ablation and the ability of the operator to connect all the dots between ablation points to prevent the transmission of electrical signals across the scarred areas. Further studies in rigorously designed trials will be needed to confirm the results of the earlier trials. The 5-year results of this study will be fascinating and some groups had a near significant benefit compared to medical therapy. Results were maintained in prespecified subgroup analysis, although non–African Americans tended to benefit from renal denervation more so than African Americans ($P=0.09$). A number of limitations were identified by the study’s authors, and also reviewed by the discussion panel after the presentation. Blood levels of antihypertensive medications were not obtained, so drug adherence was not directly measured. The large and significant change over time in both groups may have been related to the placebo effect, or it may be that study participants in both arms achieved improved medication compliance after enrollment in the study. Further, there is no commonly accepted and easily obtained measure of denervation of the renal sympathetic system, so it is possible that renal denervation did not occur, although the study authors could confirm that the appropriate energy had been delivered by the device.

Experts have weighed in as to why this study showed different results than other studies, particularly in Europe. A large concern was operator’s inexperience with denervation (they were all experienced interventional cardiologists) another flaw in the trial design was that no method was used to monitor the efficacy of each denervation procedure, an easy decision because there is still no proven way to measure denervation efficacy during the procedure. In the first clinical study of renal denervation, in a series of 45 patients treated at five centers in Australia and Europe reported just 5 years ago (Lancet 2009;373:1275–81), Dr. Esler, a lead investigator for that study, and his associates carefully tested the efficacy of denervation in ten patients by measuring the direct effect of successful denervation and reduction of renal norepinephrine spillover. They reported that, in those ten patients, renal denervation cut norepinephrine spillover by an average of 47%, which correlated with an average reduction in systolic blood pressure of 22 mmHg after 6 months.

Because of the aging of the population and rising rates of obesity, hypertension is increasing in prevalence worldwide. Approximately 10% of patients with diagnosed hypertension have resistant hypertension, defined as a systolic blood pressure of 140 mmHg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, included a diuretic at an appropriate dose. The sympathetic nervous system – in particular, sympathetic cross-talk between the kidneys and the brain – appears to play an important role in resistant hypertension.

In spite of this recent published study, very limited data has been published on preclinical and clinical experiences with these new devices, and the future of this field is controversial. Other new approaches, including less invasive and outpatient-based therapies, may or may not be effective. Unfortunately, during the last 10 years, very few new antihypertensive agents have reached the market and no new therapeutic class has really emerged if one considers renin inhibitors as members of drugs inhibiting the renin-angiotensin system (RAS). Thus, the actual strategy to control blood pressure in hypertension relies on the use of three major classes of antihypertensive drugs, i.e., blockers of the RAS, calcium channel blockers (CCBs), and diuretics (D) as reported in the last 2013 hypertension guidelines of the European Society of Hypertension and European Society of Cardiology. One very important issue with any study of hypertensive patients, including HTN-3, is that there was no confirmation of medication adherence. More than 50% of patients with resistant hypertension are known to be nonadherent to medications. There was no direct measurement to confirm that the renal nerves were in fact denervated by the procedure, because there is no test that can be easily performed in a large trial. However, the Symplicity catheter system allowed confirmation of energy delivery, and the presence of angiographic notching indicated a biologic effect of energy delivery on the artery. Finally, the results of this trial are specific to the catheter tested and cannot necessarily
be generalized to other denervation systems. We shall await further data. This textbook is
aimed to provide an overview of the field, to describe the preclinical and clinical experiences
with the most prominent technologies in the pipeline, and to provide insights regarding the
possible directions this field may be heading.

I was pleased to have been introduced to Victoria John from Springer Publishing who
agreed with me that a textbook describing this new treatment would be a welcome addition.
My co-editors are two world renowned leaders in the field including Horst Sievert from
Germany and Markus Schlaich from Australia. We have attempted to pull together the experts
in the field in our textbook and are proud to say everyone we invited to contribute agreed to be
represented in the textbook. We have described most of the current devices and approaches,
and we hope to give the reader a snapshot of where things are available at this time.

I would like to thank Victoria and my co-editors Horst Sievert and Markus Schlaich, along
with our co-authors without which the textbook would not have been possible. As with other
textbooks I have edited, I will donate all my royalties to Johns Hopkins Hospital where I
trained. I also wish to dedicate this book to the Phoenix Heart Center, St. Luke’s Medical
Center and my daughter Alexandra and wife Shari. Special thanks to Peggy Layman for put-
ting up with everything she needs to deal with not only this publication, but everything involved
with interacting with me.

We hope the reader will find this textbook a springboard for study and advancement of this
new, exciting field.

Phoenix, AZ, USA  Richard R. Heuser

Reference

## Contents

1. **Pathophysiology: The Target for Renal Denervation** .......................................................... 1  
   Michael Böhm, Dominik Linz, Christian Ukena, and Felix Mahfoud

2. **Physiological Rationale for Renal Denervation Therapy in Hypertension** .................. 9  
   C. Venkata S. Ram and A. Sreenivas Kumar

3. **Preclinical Model and Histopathology Translational Medicine and Renal Denervation** .......................................................... 15  
   Kenichi Sakakura, Elena Ladich, Fumiyuki Otsuka, Kazuyuki Yahagi,  
   Frank D. Kolodgie, Michael Joner, and Renu Virmani

4. **The Endpoint on Measuring the Clinical Effects of Renal Denervation: What Are the Best Surrogates** ................................................. 25  
   Paul A. Sobotka, David G. Harrison, and Marat Fudim

5. **Appraisal of the Clinical Trial Data on Renal Denervation for the Management of Resistant Hypertension** ............................................. 45  
   Aung Myat and Deepak L. Bhatt

6. **Catheter-Based Technology Alternatives for Renal Denervation: An Overview** ........ 59  
   Stefan C. Bertog and Horst Sievert

7. **Medtronic Ardian Symplicity™ Renal Denervation Devices** ........................................... 61  
   Krishna J. Rocha-Singh

8. **Sympathetic Renal Denervation Using the EnligHTN Multi-electrode Ablation System: The St Jude Experience** ........................................ 69  
   Costas Tsioufis, Michael Doumas, Charles Faselis, and Vasilios Papademetriou

9. **ReCor Medical Paradise® Renal Denervation System** ..................................................... 81  
   Marc Sapoval, Atul Pathak, Leslie A. Coleman, Austin R. Roth,  
   Helen L. Reeve, and Thomas Zeller

10. **Therapeutic Intra Vascular Ultrasound (TIVUS)** .......................................................... 91  
    Sharad V. Shetty and Sandeep Chopra

11. **The “OneShot” Irrigated Balloon-Mounted Spiral Electrode Renal Denervation Device** .......................................................... 97  
    William E.L. Ormiston and John A. Ormiston

12. **NOVOSTE: The Brachytherapy Approach to Renal Denervation** ................................. 101  
    Nevin C. Baker, Israel M. Barbash, and Ron Waksman
13 Perivascular Renal Denervation (PVRD™): Chemical Renal Denervation with Micro-Doses of Ethanol Using the Peregrine™ Renal Denervation Device ............................................. 107
   Tim A. Fischell, Félix Vega, and Vartan E. Ghazarossian

14 Vincristine Local Delivery for Renal Artery Denervation ...................... 117
   Konstantinos Toutouzas, Andreas Synetos, and Christodoulos Stefanadis

15 NephroBlate™ Renal Denervation System: Urologic-Nephrologic Based Approach to Resistant Hypertension .................................................. 125
   Richard R. Heuser, Terrence J. Buelna, Adam Gold, Rahul R. Rao,
   William G. Van Alstine, Randy I. Cooper, and Mihir Desai

16 Targeted Renal Nerve Deactivation by Neurotropic Agents ................. 135
   Mark H. Wholey, Emily Stein, Michael Evans, and K.T. Venkateswara Rao

17 Boston Scientific Vessix™ Renal Denervation System ....................... 145
   Stefan C. Bertog, Laura Vaskelyte, Ilona Hofmann,
   Sameer Gafoor, and Horst Sievert

18 Radiofrequency and Irrigated Ablation: Principles and Potential for Renal Artery Denervation (RDN) in the Treatment of Resistant Arterial Hypertension ........................................ 147
   Kenichi Sakakura, Elena Ladich, Kristine Fuimaono, Renu Virmani,
   and Michael Joner

19 Renal Denervation: Potential Future Implications
   Beyond Resistant Hypertension ............................................ 155
   Markus P. Schlaich

20 Renal Denervation for Congestive Heart Failure ............................ 163
   Claire E. Raphael and Justin E. Davies

21 Great Myths of Blood Pressure Effect Size in Renal Denervation ........ 175
   James P. Howard, Matthew J. Shun-Shin, and Darrel P. Francis

22 The Potential Role of Catheter-Based Renal Sympathetic Denervation in Chronic and End-Stage Kidney Disease ........................................ 181
   Markus P. Schlaich and Yusuke Sata

23 Diabetes and Metabolic Syndrome ........................................... 191
   Felix Mahfoud, Sebastian Ewen, and Michael Böhm

24 Obstructive Sleep Apnea ................................................... 197
   Adam Witkowski and Jacek Kądziela
Contributors

Nevin C. Baker, DO  Department of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, USA

Israel M. Barbash, MD  Department of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, USA
Interventional Cardiology Department, Sheba Medical Center, Tel Aviv University, Ramat Gan, Israel

Stefan C. Bertog, MD, FACC, FScaI  CardioVascular Center Frankfurt, Frankfurt, Germany

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC  Interventional Cardiovascular Programs, Brigham and Women’s Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA

Michael Böhm, MD  Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

Terrence J. Buelna  Verve Medical Inc., Peoria, AZ, USA

Sandeep Chopra, MBBS, MD, DM  Department of Cardiology, Royal Perth Hospital, Perth, WA, Australia

Leslie A. Coleman, DVM, MS  ReCor Medical Inc., Palo Alto, CA, USA

Randy I. Cooper, MD  Department of Nephrology, Southwest Vascular Center/Southwest Kidney Institute, Tempe, AZ, USA

Justin E. Davies, MBBS, BSc, MRCP, PhD  Department of Cardiology, Hammersmith Hospital, Imperial College London, London, UK

Mihir Desai, MD  Department of Urology, University of Southern California, USC Institute of Urology, Los Angeles, CA, USA

Michalis Doumas, MD  Aristotle University, Thessaloniki, Greece
Department of Cardiology/Hypertension, Department of Veterans Affairs Medical Center, Washington, DC, USA

Michael Evans, BS  Palo Alto, CA, USA
Northwind Medical, San Jose, CA, USA

Sebastian Ewen, MD  Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany
Charles Faselis, MD  Veteran Affairs Medical Centre and George Washington University, Washington, DC, USA
Department of Internal Medicine/Hypertension, Department of Veterans Affairs Medical Center, Washington, DC, USA

Tim A. Fischell, MD, FACC  Heart Institute at Borgess Medical Center, Kalamazoo, MI, USA
Ablative Solutions, Inc., Kalamazoo/Menlo Park, MI/CA, USA

Darrel P. Francis, MA, MB BChir, FRCP  International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK

Marat Fudim, MD  Internal Medicine, Vanderbilt Medical Center, Nashville, TN, USA

Kristine Fuimaono, BS  Cordis Corporation/Biosense Webster, Inc., Diamond Bar, CA, USA

Sameer Gafoor, MD  CardioVascular Center Frankfurt, Frankfurt, Germany

Vartan E. Ghazarossian, PhD  Ablative Solutions Inc., Kalamazoo/Menlo Park, MI/CA, USA

Adam Gold, MSME  Verve Medical, Inc., Peoria, AZ, USA

David G. Harrison, MD  Medicine and Pharmacology, Vanderbilt Medical Center, Nashville, TN, USA

Richard R. Heuser, MD  Department of Cardiology, St Lukes Medical Center, Phoenix, AZ, USA

Ilona Hofmann, MD  CardioVascular Center Frankfurt, Frankfurt, Germany

James P. Howard, MA, MB BChir, MRCP  International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK

Michael Joner, MD  CVPath Institute, Inc., Gaithersburg, MD, USA

Jacek Kądzielia, MD, PhD  Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

Frank D. Kolodgie, PhD  CVPath Institute, Inc., Gaithersburg, MD, USA

A. Srinivasa Kumar  Cardiology Department, Continental Hospitals, Hyderabad, AP, India

Elena Ladich, MD  CVPath Institute, Inc., Gaithersburg, MD, USA

Dominik Linz, MD, PhD  Department of Cardiology, University Hospital of Saarland, Homburg/Saar, Germany

Felix Mahfoud, MD  Department of Internal Medicine, University Hospital of Saarland, Homburg/Saar, Germany

Aung Myat, BSc (Hons), MBBS, MRCP  The Rayne Institute, British Heart Foundation of Research Excellence, St Thomas’ Hospital, King’s College London, London, UK

William E.L. Ormiston, MBChB  Department of Radiology, Auckland City Hospital, Auckland, New Zealand

John A. Ormiston, MBChB, FRACP, FRACR  Department of Mercy Angiography, Mercy Hospital, Auckland, New Zealand
University of Auckland School of Medicine, Auckland, New Zealand
Cardiology, Auckland City Hospital, Auckland, New Zealand

Fumiyuki Otsuka, MD  CVPath Institute, Inc., Gaithersburg, MD, USA
Vasilios Papademetriou, MD Veteran Affairs Medical Center and Georgetown University, Washington, DC, USA
Department of Interventional Cardiology/Hypertension, Department of Veterans Affairs Medical Center, Washington, DC, USA

Atul Pathak, MD, PhD, DACLAM Clinical Pharmacology and Cardiovascular Medicine, University Hospital and Faculty of Medicine, Toulouse, France

C. Venkata S. Ram, MD, MA, CP, FACC Apollo Institute for Blood Pressure Management, Apollo Blood Pressure Clinics, Apollo Hospitals, Hyderabad, AP, India
Texas Blood Pressure Institute, Medical School, University of Texas Southwestern, Dallas, TX, USA

Rahul R. Rao, P.E., BSc Verve Medical, Inc., Peoria, AZ, USA

Claire E. Raphael, MA, BSc, MRCP Department of Cardiology, Royal Brompton and Harefield NHS Foundation Trust, London, UK

Helen L. Reeve, PhD ReCor Medical BV, Herengracht 124-128, 1015 BT Amsterdam, The Netherlands

Krishna J. Rocha-Singh, MD Department of Cardiology, Prairie Heart Institute at St. John’s Hospital, Springfield, IL, USA

Austin R. Roth, BS, MS ReCor Medical, Palo Alto, CA, USA

Kenichi Sakakura, MD CVPath Institute, Inc., Gaithersburg, MD, USA

Marc Sapoval, MD, PhD Interventional Radiology, Hopital Européen Georges Pompidou, Paris, France

Yusuke Sata, MD Neurovascular Hypertension and Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Markus P. Schlaich, MD, PhD Neurovascular Hypertension and Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Sharad V. Shetty, MBBS, MD, FRACP Department of Cardiology, Royal Perth Hospital, Perth, WA, Australia

Matthew J. Shun-Shin, MA, MB BChir, MRCP International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK

Horst Sievert, MD, FESC, FACC, FSCAI CardioVascular Center Frankfurt, Frankfurt, Germany

Paul A. Sobotka, MD Division of Cardiology, Department of Medicine, The Ohio State University, West St. Paul, MN, USA

Christodoulos Stefanadis, MD, FESC, FACC First Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Emily Stein, PhD San Leandro, CA, USA
Northwind Medical, San Jose, CA, USA

Andreas Synetos, MD, FACC First Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Konstantinos Toutouzas, MD First Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Costa Tsioufis, MD Kapodistrian University, Athens, Greece