The European Society of Cardiology Council on Hypertension

The European Society of Cardiology (ESC) Council on Hypertension was officially created on 2 September 2014 at the ESC General Assembly during the ESC Congress in Barcelona. Developed from the ESC Working Group on Hypertension and the Heart, the Council aims to establish itself as the leader in arterial hypertension within the ESC and in the cardiology community. Thereby, a historic aspiration of many members of our society has been fulfilled.

Similar to other ESC bodies, the Council on Hypertension comprises a nucleus of six officers, drawn from representative of different areas of hypertension and 502 voting members, mostly cardiologists, but also internists, nephrologists, endocrinologists, general practitioners, and basic scientists, interested in clinical aspects and/or in advanced research in hypertension and cardiovascular risk.

ESC HTN Council Nucleus members from (L) to (R)

Renata Cifkova, FESC Past-Chair;
Giovanni de Simone, FESC Secretary;
Bryan Williams, FESC Vice-Chair;
Antonio Coca, FESC Chair;
Michael Olsen, FESC Liaison Officer; and
Thomas Kahan

The ESC Council on Hypertension focuses on the cardiovascular aspects of hypertension and, in particular, on research, teaching, and education of ESC members.

Cardiovascular diseases (CVDs) remain the leading cause of deaths worldwide. Approximately 20 million people, 30% of all deaths, will have died from CVDs in 2015. Of these, an estimated 8 million are due to coronary heart disease and 7 million to stroke. It is projected that the number of deaths due to CVDs, mainly from coronary heart disease, heart failure, and stroke, will increase to ~23 million by 2030. Thus, in the coming decades, CVDs will remain the leading cause of death worldwide. Hypertension is recognized as one of the most important and prevalent cardiovascular risk factors related to cardiovascular morbidity and mortality, and current rates of blood pressure (BP) control in Europe are still far from desirable.

The current challenge for European physicians is to improve BP control and reduce the fatal and non-fatal consequences of high BP values. Scientific societies focused on CVDs, such as the ESC, have assumed the responsibility of educating doctors to achieve the best clinical practice in patients with hypertension, and to promote clinical and basic research on this subject. Improved knowledge of the pathophysiology of the haemodynamic impact of hypertension may lead to better treatment strategies to reduce mortality related to high BP.

The mission of the ESC Council on Hypertension is to promote, organize, and conduct educational programmes to improve the detection, clinical evaluation, diagnosis, global cardiovascular risk stratification, treatment, and follow-up of patients with hypertension by implementing current European guidelines and promoting new guidelines with the collaboration of the European Society of Hypertension and sister societies.

The ESC Council on Hypertension will encourage the participation of young cardiologists interested in the study and management of arterial hypertension, by creating a specific group for these professionals. We will reach out to both patient organizations and the scientific community and will develop firm links with cardiology societies and other societies operating in the field of hypertension, to develop joint initiatives. Effective management of hypertension requires a multidisciplinary approach, but the role of cardiologists...
is critical in addressing approaches and interventions, due to the intrinsic haemodynamic nature of raised BP, whatever the cause.

The ESC Council on Hypertension will involve various stakeholders: general practitioners who will care for most of the hypertensive patients; medical specialists from various fields, depending on the cause of increased BP and the difficulty posed by its treatment; specifically trained nurses who will follow patients during their lifetime; and pharmacists who handle physicians’ prescriptions and often have to deal directly with the patients’ problems and provide answers to their questions. In an ideal setting, all stakeholders will co-operate in a successful lifelong intervention against hypertension.

All members of the former Working Group on Hypertension and the Heart will automatically become members of the ESC Council of Hypertension unless they expressly state they do not wish to. The current nucleus officers hope that you will accompany us in this new journey towards obtaining greater influence and increased activity in our discipline. As the first Chairperson of the Council, I am proud to represent you in the ESC. Supported by a nucleus of renowned scientists and educators in this field, I look forward to a challenging but exciting mandate and a new era for hypertension.

The SPRINT trial results

Suzanne Oparil, a member of the SPRINT Study Research Group, discusses the findings of this important trial, which was discontinued early because of its pronounced beneficial effects

Observational studies show a progressive increase in the risk of cardiovascular disease and stroke associated with blood pressure (BP) >115/75 mmHg, and prior research has shown that reducing elevated systolic BP with medications lowers the risk. However, until recently, the optimal systolic BP to reduce BP-related adverse outcomes was unknown, and the benefit of treating to a level of systolic BP well below 140 mmHg had not been tested in a large clinical trial.

The Systolic Blood Pressure Intervention Trial (SPRINT) is a multicentre, randomized, controlled, open-label trial that tested the hypothesis that treating to a lower systolic BP target (<120 mmHg) would reduce clinical events more than treating to the standard target of <140 mmHg. Between 8 November 2010 and 15 March 2013, SPRINT recruited and randomized 9361 people at 102 clinics, including 3332 women, 2646 with chronic kidney disease [CKD; estimated glomerular filtration rate (eGFR) 20 to <60 mL/min/1.73 m²], 1877 with a history of cardiovascular disease, 3962 minorities, and 2636 ≥75 years of age. All participants were 50 years of age or older and had baseline systolic BP 130–180 mmHg depending on the intensity of antihypertensive treatment.

SPRINT excluded patients with diabetes, prior stroke, or polycystic kidney disease, as clinical trials previously sponsored (or initiated) by the US National Institutes of Health included those populations. Other important exclusions included heart failure, known secondary causes of hypertension, severe CKD (eGFR <20 mL/min/1.73 m²), or proteinuria.

The main finding of SPRINT, recently published in the New England Journal of Medicine, is that targeting systolic BP of <120 mmHg resulted in lower rates of a composite primary outcome of fatal and non-fatal major cardiovascular events (myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes). The benefits of intensive treatment on cardiovascular disease outcomes were so large that the BP intervention component of SPRINT was stopped early (after 3.26 years of a planned 5-year follow-up) by the director of the National Heart Lung and Blood Institute on the advice of the trial’s data and safety monitoring board.

The intensive intervention, which achieved a mean systolic BP of 121.4 mmHg at 1 year, reduced rates of the primary composite outcome by 25%, as well as all-cause mortality by 27%, compared with the standard intervention, which achieved a mean systolic BP of 136.2 mmHg (Figure 1). Separation between treatment groups was apparent at 1 year for the primary outcome (Figure 1A) and at 2 years for all-cause mortality (Figure 1B). Importantly, there was a 38% reduction in relative risk of heart failure and a 43% reduction in relative risk of death from cardiovascular causes in the intensive-treatment group. The number needed to treat with the intensive intervention over the 3.26-year follow-up period to prevent one primary outcome event was 61; to prevent one death from any cause was 90. The benefits of intensive treatment were consistent in all pre-specified subgroups, including those <75 or ≥75 years of age, with or without previous CKD or cardiovascular disease, black or non-black race, and in all three tertiles of baseline systolic BP (<132, >132 to <145, and ≥145 mmHg) (Figure 2).

Main secondary outcomes in the SPRINT protocol include decline in renal and cognitive function, conditions that are of major concern for the ageing hypertensive population. In participants
classified as possibly or definitely related to the intervention, including hypotension, electrolyte abnormalities, syncope, and acute kidney injury or acute renal failure, were uncommon, but occurred more frequently in the intensive-treatment group. Interestingly, injurious falls were not more common and orthostatic hypotension assessed at clinic visits was significantly less common in the intensive-treatment group. The pattern of adverse events in participants ≥75 years of age was similar to that in the study cohort as a whole.

SPRINT study results have been favourably reviewed and predicted to change practice by the lay press¹,4 and by commentaries and editorials in The New England Journal of Medicine.₅–₁₀ Decisions about applying the SPRINT results broadly will certainly have high impact, as a recent analysis using data from the National Health and Nutrition Examination Survey 2007–12 estimated that 20% of US adults with hypertension meet the SPRINT eligibility criteria and therefore may be candidates for a systolic BP goal of <120 mmHg.¹¹

However, important questions have been raised by both outside observers and SPRINT investigators. Issues that have been raised include the impracticality of achieving a target systolic BP of <120 mmHg in patients with very high (>180 mmHg) systolic BPs, the possible J-curve in diastolic BP, and the lack of strategies and resources in usual clinical practices to safely implement this potentially life-saving intervention. Further, questions about the generalizability of SPRINT results to important populations that were excluded from the trial, e.g. younger persons, those with lower cardiovascular disease risk, diabetes, or heart failure, have stimulated vigorous debate, but can be answered conclusively only by future trials.

The SPRINT investigators have emphasized the need for careful measurement of office BPs, as described in the SPRINT protocol, when applying the intensive BP-lowering treatment strategy.⁶ Multiple readings should be taken, preferably with an automated device, after 5 min of rest and with no conversation either during the rest period or during BP measurement to minimize the white coat effect.

Failure to take these precautions may cause either overestimation or underestimation of BP, leading to inappropriate treatment, higher rates of serious adverse effects, and unnecessary utilization of resources, including medications and provider time and effort. They further cautioned that this issue should be taken into account in the development of practice-based performance measures for antihypertensive treatment that are derived from SPRINT results.⁶

Even if BP is measured correctly, achieving lower BP targets using the SPRINT intensive treatment strategy will clearly require more frequent titration of medications and monitoring for adverse drug effects, greater use of drug combinations, and more frequent patient visits than is usual in real-world practice.¹⁰ Widespread implementation of the intensive BP-lowering strategies that have been so successful in SPRINT will likely require deployment of new resources, including use of treatment algorithms, electronic medical records for patient monitoring, and a variety of health care personnel, including nurse clinicians, physician assistants, and pharmacists.

As emphasized by Chobanian,¹⁰ an enhanced effort to slow age-related increases in BP and other cardiovascular risk factors by modifying the lifestyle of the population as a whole is even more important than intensive pharmacological treatment in achieving the goals of the SPRINT trial.
The use of devices to treat hypertension

Introduction

Blood pressure (BP) is sub-optimally controlled in many patients worldwide despite the availability of comprehensive guidelines that establish both BP targets for control and definitive treatment algorithms. Reasons for this include failure to persist with lifestyle modification and, alarmingly, poor rates of drug adherence to antihypertensives with higher rates of discontinuation of therapy accompanying increasingly complex multidrug regimens.\(^1\)\(^2\)

It is therefore timely to consider non-drug options to treat hypertension.

Device therapy for hypertension

The past several years have seen the introduction of a range of device therapies that target defined visceral afferents and/or the sympathetic nervous system regulating BP as well as a novel device, which targets mechanical aspects of the circulation. These are described in brief in what follows.

Renal sympathetic denervation

A wealth of evidence underpins an important role for both renal sensory and sympathetic activity in the initiation and perpetuation of hypertension in humans.\(^3\) By virtue that they are inter-twined, it is now possible to target selectively the renal afferent and sympathetic nerves via an endoluminal approach involving catheterization of the renal arteries and delivery of radiofrequency (RF) energy to cause heating of the renal artery at focal locations leading to destruction of renal sympathetic nerves lying in the adventitia. Initial reports of striking reductions in office BP using RF renal denervation (RDN) in the Symplicity HTN-1 and HTN-2 studies were criticized for not having a sham procedure or blinded endpoints such as 24 h ambulatory BP monitoring.\(^4\)\(^5\) Nonetheless,
this did not prevent the device industry from rushing into a headlong scramble to manufacture iterations of RDN catheters with RF or alternate platforms including ultrasound (US) therapy, microwave energy, cryotherapy, and chemical ablation using neurolytic agents such as alcohol delivered through micropuncture needles into the adventitia. One technology makes use of a per-urethral approach to denervate the renal pelvis where much of the renal afferent innervation exists.

Subsequently, the single-blind, randomized, sham-controlled Symplicity HTN-3 study (published early in 2014) has cast enormous doubt on the efficacy of RDN as there was no significant difference in BP reduction between the RDN and control groups. The study, however, had serious flaws including 40% of patients having medication changes in both groups during the study and RDN study, however, had serious flaws including 40% of patients having medication changes in both groups during the study and RDN only being delivered completely in 5% of patients. Despite the limitations of the HTN-3 trial, a number of device manufacturers terminated their RDN programmes. This resulted in increasing awareness from industry that any device therapy for the treatment of hypertension will be a more costly and complex endeavour than originally realized with no guarantee of success. Nonetheless, encouraging reports of the efficacy of RDN in the hands of experienced operators continue to lend support to the belief that the technology does have a future. In the Global Symplicity Registry, 6 months following RDN, the reductions in office and 24-h systolic BPs were −12 and −7 mmHg for all patients and −20 and −9 mmHg for those with severe hypertension, respectively (P < 0.001 for all responses). Renal denervation has been associated with low rates of adverse events in many studies although renovascular stenosis following RDN has been reported. Functional re-innervation has been demonstrated in sheep following RDN, but remains unsubstantiated in humans.

Somewhat remarkably, 5 years have elapsed following the first published report of RDN to treat human drug-resistant hypertension before there has been a formal description of human renal nerve anatomy. More recently, there has been growing appreciation of the complexity of human renal nerve signalling and that targeting of renal nerves is no simple matter. Techniques and platforms used commonly in the cardiac catheterization lab such as RF ablation and US ablation are not so easily transposed to the platforms used commonly in the cardiac catheterization lab such as RF ablation and US ablation are not so easily transposed to the renal artery where all matter of additional considerations come into play that can affect energy dispersal and thus impact upon efficacy. Future studies of RDN will focus on treating un-medicated patients and not solely drug-resistant hypertensives with concomitant arterial stiffening that may not respond well to sympathomodulation. There is also a need to identify potential ‘responders’ and develop on-table protocols confirming procedural success.

Baroreflex activation therapy

The carotid sinus has long been recognized to play a key role in the moment-to-moment regulation of BP and more recently its long-term regulation. It is possible to stimulate selectively the carotid sinus baroreflex bilaterally with a novel device (Rheos) that makes use of electrical field stimulation via implantable bipolar electrodes that are surgically attached to the carotid sinus (under general anaesthesia) and connected to a generator placed in the sub-clavicular pouch. An initial feasibility study with this device indicated promising results with substantial BP reductions, which appeared durable over a 2-year follow-up epoch. Subsequently, a larger double-blind, randomized, pivotal trial in 265 patients with resistant hypertension was undertaken in which patients were randomized in a 2:1 fashion to early (1-month post-implantation) or delayed (6-month post-implantation) device activation. Although this study failed to achieve its primary acute efficacy and acute safety endpoints (possibly due to methodological shortcomings), Rheos did, however, reduce BP during the controlled phase of the study with a 40% reduction in hospitalization for hypertensive emergencies and at 12 months, >50% of patients achieved a target BP of <140/90 mmHg. Subsequently, it has been shown that systolic BP lowering of 30 mmHg was sustained out to 53 months of follow-up.

A second-generation device with a unipolar unilateral lead for stimulating a carotid sinus (Barostim Neo TM), and miniaturized generator, is now available, which has a longer battery life and can be implanted under conscious sedation. There is, however, limited data to support the use of this device although there has been a recent report of an uncontrolled study in 30 patients with an encouraging safety and efficacy profile. Although this newer device is fully CE marked, at present the manufacturer is not planning further studies for the hypertension indication but focusing on patients with heart failure. Importantly, with costs of this therapy currently in excess of €20 000 per device, this will limit its market; and in the absence of compelling randomized controlled data, it may be hard to make a case for reimbursement of the therapy.

Carotid body ablation

Emerging evidence indicates that heightened activity of the carotid body (CB) chemoreceptor can lead to hypertension in both animal models and human patients and that (reversible) abrogation of CB signalling reduces sympathetic vasomotor tone in hypertensive humans. A proof of concept study of unilateral CB ablation for resistant hypertension has demonstrated significant and durable office BP reduction of 23/12 mmHg at 6 months post-operatively in 8 out of 15 patients who also had evidence of increased baseline CB tonicity. No serious adverse events were observed, and hypoxic ventilatory drive was not disrupted. Future studies will determine if BP reduction following CB ablation is durable and whether this is feasible via either an endovascular or pharmacological approach.

Central iliac arteriovenous anastomosis

Originally developed as a therapy for chronic obstructive pulmonary disease (COPD), creation of a central iliac arteriovenous (AV) anastomosis using the ROX coupler device was found to lower BP and thereafter the device was repurposed for the hypertension indication after studies in the COPD population indicated only modest benefit for respiratory endpoints. In essence, the device creates a fixed calibre (4 mm) anastomosis between the external iliac vein and artery. The treatment is thought to work by restoring the Windkessel function of the circulation, which may make it a more suitable therapeutic option for patients with arterial stiffness unlike-
A randomized controlled trial comparing the coupler to usual medical care has demonstrated substantial office (27/20 mmHg) and ambulatory (14/14 mmHg) BP reduction at 6 months, which was highly significant. There was a 29% incidence of venous stenosis in the ipsilateral limb occurring at around 6 months’ post-therapy, which was successfully managed with venous stenting in all instances. Unlike RDN procedures, AV coupler implantation is fully verifiable and results in immediate BP reduction and is reversible using a covered stent. Currently, the device (which is CE marked) is being evaluated in a Pan-European registry study and a US IDE trial is in the pipeline.

Conclusion

Device-based therapy of hypertension is in its infancy, and on-going clinical trials with improved design that take into account the failings of earlier studies should determine whether or not any of the technologies merit a place in the armamentarium of antihypertensive therapies. As with pharmacological therapy of hypertension, it is clear that the different devices have heterogeneous effects and emphasizes the importance of extensively phenotyping patients and matching to the most appropriate intervention.

Whilst drugs are (relatively) inexpensive and generally have reversible side effects, device-based approaches are informing us of novel targets and mechanisms ripe for future pharmacological interrogation. The true adverse effect profile of device therapies remains equivocal at this time.

Conflict of interest: M.D.L. has received honoraria from Medtronic Inc., St Jude Medical, ROX Medical, and CardioSonic. J.F.R.P. is a consultant for Cibiem Inc.

References

Supplementary material is available at European Heart Journal online.

Dr Melvin Lobo, MBChB, PhD, FRCP, FBHS

A hypertension specialist, Melvin Lobo is Director of the Barts Blood Pressure Centre of Excellence in London and NHS Reader in Cardiovascular Medicine at Queen Mary University of London, UK

Dr Melvin Lobo is Consultant Cardiovascular Physician and Clinical Hypertension Specialist, Barts Health Trust in London and the Director of the internationally renowned Barts Blood Pressure Clinic, which has been recognized as a Hypertension Centre of Excellence by the European Society of Hypertension and receives referrals of complex hypertensive patients on a national and international basis. The clinic is allied to the world renowned William Harvey Research Institute and has participated in several landmark studies in hypertension. These include the ground-breaking ASCOT study that led to a change in UK Hypertension guidelines as well as the Symplicity HTN-2 study of renal denervation for treatment-resistant hypertension and most recently the ROX Control Hypertension Study of a novel central iliac arteriovenous anastomosis to treat uncontrolled hypertension. Melvin Lobo is also Reader in Cardiovascular Medicine, NIHR Barts CV BRU, William Harvey Research Institute, Queen Mary University London. His positions of responsibility include the following:

• Director, Barts Blood Pressure Centre of Excellence
• Section Editor—‘Hypertension’, Journal of the American College of Cardiology (from June 2015)
• Chief Investigator, EnligHTN II Study
• Chief Investigator, Wave VI Study and Co-CI Wave V Study (US & OUS)
• Chief Investigator, ROX Coupler Study and ROX Global Registry
• Principal Investigator, Symplicity HTN-2 Study and Wave IV Study
• Special Adviser to NICE: Renal Denervation/Baroreflex Activation
• ESH Working Group on Interventional Treatment of Hypertension
• Steering Group Lead, UK National Registry for resistant hypertension
• Chair of the Barts Health Trust Joint Prescribing Group

Since October 2011, he has co-hosted and chaired the annual UK Symposia on Renal Denervation at the Royal College of Physicians with a distinguished panel of international authorities in hypertension medicine and interventionists.

Dr Lobo is a member of the Joint UK Societies steering committee on renal denervation and author of the JUKS 2014 Consensus Statements on Renal Denervation. He has also participated in formulating international guidelines for renal denervation with the European Clinical Consensus Collaboration.
He has lectured and published extensively on hypertension and novel therapies of resistant hypertension.9,10

Dr Lobo has developed three major research themes in the Barts Blood Pressure Centre of Excellence:

(1) Device therapy of hypertension.
   As chief or principal investigator of numerous studies in the field of resistant hypertension, Dr Lobo continues to strive to bring new therapies to the hypertension clinic that are safe and effective.10–14
   (2) Phenotyping of complex hypertension
   Dr Lobo has set up an autonomic and cardiovascular haemodynamic laboratory to study the role of sympathetic nervous signalling in hypertension and circulatory regulation.15
   (3) Multi-drug intolerant patients
   A further major interest of his group is in the management of patients with multiple drug intolerances who are unable to take conventional antihypertensive medications and thus pose a real challenge to clinicians. Preliminary data from this cohort of patients indicate that a stratified medicine approach using fractional tablet dosing, liquid antihypertensives, and patch formulations of antihypertensive drugs can achieve significant blood pressure lowering in this high-risk patient group.16

Catheter-based renal denervation for hypertension treatment: update 2015

Hypertension is highly prevalent and one of the most frequent chronic diseases worldwide. More than 1 billion people worldwide have hypertension [systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg], and the numbers are increasing continuously. Despite the availability of many effective antihypertensive drugs, blood pressure (BP) control to target values still remains low.

Recently, the SPRINT trial1 redefined BP target goals and challenged us to further improve BP management. SPRINT1 compared intensive treatment (target 120 mmHg) with standard treatment (target 140 mmHg) and documented a 25% lower relative risk of major cardiovascular events and a 27% lower relative risk of death from any cause in the intensive-treatment group. These results were consistent across all predefined subgroups and suggest that in non-diabetic adults 50 years and older at increased risk for heart disease or with kidney disease, a more stringent BP control translates into lower rates of acute coronary syndromes, stroke, heart failure, and death.

Treatment of uncontrolled hypertension requires a multimodal therapy concept, including polypharmacy, lifestyle modification, and a systematic identification of secondary causes of hypertension and/or pseudo-resistance. Increased activity of the sympathetic nervous system is a main contributor to the development and persistence of uncontrolled hypertension. Catheter-based renal denervation (RDN) has been introduced as a safe and minimally invasive treatment option for patients with uncontrolled hypertension. However, the clinical evidence in support of RDN as an effective interventional technique is conflicting.

What is known from clinical trials?

A number of observational studies,2 as well as several national and international registries,3 confirmed the BP-lowering results of the pivotal Symplicity HTN-1 and HTN-2 trials (Figure 1). However, the randomized, blinded, sham-controlled Symplicity HTN-3 trial4 failed to document the superiority of RDN compared with a sham procedure in reducing BP after 6 months. At 6-month follow-up, the average decrease in office and ambulatory SBP in the RDN group was 14 and 7 mmHg compared with a fall of 12 and 5 mmHg in the control group, respectively. Neither office nor ambulatory BP differences met the pre-specified criteria for superiority. The results were unexpected and truly challenged the field.

Several potential confounders, such as inadequate patient selection, low operator experience, and inadequate technical performance of the procedure, have been discussed extensively elsewhere.5,6 Kandzari et al.7 published in a subgroup analysis of Symplicity HTN-3 that a higher number of ablations and quadrantic ablation in all four quadrants of the arterial wall cross sections were associated with significant greater ambulatory BP reduction compared with the sham control group.

The randomized RSD-LEIPZIG8 included 71 patients with resistant hypertension but only mildly elevated BP and investigated the effect of RDN on BP compared with sham treatment. In the intention-to-treat analysis, no significant difference between the groups with respect to 24-h SBP at 6 months (primary endpoint) was observed. However, when analysed per protocol, which is a
better indicator of biological effectiveness of the procedure, RDN was found to be superior to sham treatment (−8.3 vs. −3.5 mmHg, \( P = 0.042 \)). These results underline the importance of procedural accuracy and performance.

The French, prospective, randomized, controlled, multicentre DENER-HTN study\(^9\) investigated the effect of single electrode Simplicity catheter-based RDN on BP in 121 patients with uncontrolled hypertension. All eligible patients received a standardized triple antihypertensive drug treatment of the main renal artery and branches or distal segment of the main renal artery. RDN was performed under general anesthesia, with a mean of 2.2±1.1 years elapsed from diagnosis of hypertension to the procedure. The optimal degree of wall contact and the depth, location, duration, and intensity of energy delivered to the renal artery wall to achieve the best procedural results are still being investigated. Renal sympathetic nerves are more abundant in the anterior area of the arterial ostium.\(^9\) However, recent studies have shown that in the proximal segments of renal artery these nerves are localized >5 mm from the lumen, a distance that may be beyond the ablation depth of at least the currently used radiofrequency-based catheters, which approximately achieve a depth of 3–4 mm.\(^9\) Targeted treatment of the renal artery branches or distal segment of the main renal artery in pigs resulted in markedly less variability of response and significantly greater reduction of both norepinephrine and axon density than conventional treatment of only the main renal artery. Clinical application of a combination treatment strategy employing treatment of the main renal artery and branches is currently being investigated in clinical trials (NCT02439749; NCT02439775), with emphasis on long-term efficacy and safety of this new optimized approach.


Where do we need to go from here?

To improve the efficacy of RDN, the procedure needs to be applied to a population with a high probability of BP response. This is complicated by (i) the complex pathophysiology of hypertension, (ii) the lack of clinically applicable measures of sympathetic activity, and (iii) the absence of predictors of the long-term BP response following RDN.\(^11\) Although the importance of renal nerve signalling in hypertension has been shown by a number of studies and clinical registries, there are many factors besides sympathetic nervous system activation that can drive increases in BP.

However, there is evidence indicating that younger patients tend to have greater sympathetic nervous system activation than older patients with hypertension.\(^12\) Isolated systolic hypertension (ISH), defined as office SBP \( \geq 140 \) mmHg and DBP \(<90 \) mmHg, is the predominant hypertensive subtype in elderly patients.\(^13\) Isolated systolic hypertension is characterized by an increased aortic stiffness, increased pressure wave reflections, and low pulse pressure amplification.\(^13\) Data indicate that ISH is associated with limited response to RDN,\(^14\) as expected from drug trials.\(^15\) Accordingly, increased central pulse pressure indicates that aortic stiffness is related to worse BP response after RDN.\(^16\) Lastly, the BP lowering after RDN appears to be associated with a reduction in total peripheral resistance\(^17\) and did not correlate with an improvement of antihypertensive drug intake at least 6 months after the procedure.\(^18\) Clearly, there is a need for more research on this topic and an urgent need to delineate the predictors of BP response following RDN.\(^11\)

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**Table 1 Enrolling randomized trials for renal denervation in hypertension**

<table>
<thead>
<tr>
<th>Name</th>
<th>Identification number</th>
<th>Randomization device</th>
<th>Number of patients</th>
<th>Inclusion criteria</th>
<th>Primary outcome</th>
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<tr>
<td>REDUCE-HTN: REINFORCE</td>
<td>NCT02392351</td>
<td>Renal denervation vs. sham control</td>
<td>Vessix Reduce™</td>
<td>100</td>
<td>Off-treatment office SBP ≥ 150 and ≤ 180 mmHg</td>
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<td>Average 24-h ambulatory SBP ≥ 135 and ≤ 170 mmHg</td>
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<tr>
<td>SPYRAL HTN-ON MED Study</td>
<td>NCT02439775</td>
<td>Renal denervation vs. sham control</td>
<td>Medtronic Symplicity Spyral™</td>
<td>100</td>
<td>Office SBP ≥ 150 and &lt; 180 mmHg and DBP ≥ 90 mmHg as well as 24-h ambulatory BP monitoring average SBP ≥ 140 and &lt; 170 mmHg despite the intake of three antihypertensive agents</td>
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<td>Change in SBP as measured by 24-h ambulatory BP monitoring</td>
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<td>Patient is willing to discontinue current antihypertensive drugs or is drug naive</td>
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<td>Stable (for at least 1 month and with no planned changes for the next 6 months) antihypertensive therapy with at least three antihypertensive drugs, including a diuretic</td>
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<td>Treatment-resistant hypertension in patients taking a stable drug regimen for at least 4 weeks consisting of three or more antihypertensive medications from different classes, including a diuretic</td>
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<td>Under maximal therapy, office BP should be ≥ 140/90 mmHg and the 24-h ambulatory BP should be 130 mmHg systolic or 80 mmHg diastolic or higher</td>
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<td>Average office SBP ≥ 160 mmHg and average daytime SBP ≥ 135 mmHg in 24-h ambulatory BP</td>
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<td>No medication changes for a minimum of 1 month prior to screening</td>
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*Just the main parts were extracted in the list. The total trial designs are available at www.clinicaltrials.gov.*
Upcoming clinical trials

Table 1 provides an overview of the ongoing trials in RDN. The multicentre, prospective, single-blind, randomized, placebo-controlled REDUCE-HTN: REINFORCE study (NCT02392351) is currently enrolling patients in the USA who are not on antihypertensive medication, and will focus primarily on the mean reduction in 24-h ambulatory SBP at 8-week post-randomization. Further, the multicentre, prospective, single-blind, randomized, sham-controlled SPYRAL HTN-OFF MED (NCT02439749) and SPYRAL HTN-ON MED (NCT02439775) studies started enrolling up to 120 and 100 patients with moderate-to-severe uncontrolled hypertension, respectively. These studies will be conducted at ~20 centres in Europe, the USA, Japan, and Australia, using a multi-electrode catheter, designed to enable circumferential four-quadrant ablation of the main renal artery and the more distally positioned segmental and accessory arteries. The SPYRAL HTN-OFF MED study is designed to investigate the specific effect of RDN on BP in patients not receiving any antihypertensive medication. Separately, the SPYRAL HTN-ON MED study will evaluate the effect of RDN on BP in patients with uncontrolled BP despite the intake of three commonly used antihypertensive agents. Adherence will be closely monitored using toxicological analyses to ensure consistency between both arms of the on- and off-medication studies.

External body delivery of focused ultrasound energy to the renal arteries is a novel, non-invasive approach to achieve RDN. The Kona Medical Surround Sound System delivers externally focused ultrasound to the renal nerves using Doppler-based ultrasound image guidance to track and correct for renal artery motion during treatment. This approach has shown promising results in early trials and animal studies. This technology may offer the advantages of shorter procedure times and less patient discomfort. The randomized, sham-controlled, double-blinded WAVE IV study (NCT02029885) evaluates the safety and efficacy of the Surround Sound system in 132 patients with resistant hypertension at sites in Europe, New Zealand, Australia, and South America. Interestingly, the trial includes a treatment arm for those patients who have failed other forms of RDN.

Conclusion

In conclusion, a number of observational studies and four randomized, controlled trials (Symplicity HTN-2, Prague-15, RSD-LEIPZIG, and DENER-HTN) support both the safety and efficacy of RDN, but some smaller studies and the large, single-blind, randomized, sham-controlled Symplicity HTN-3 trial failed to show superiority of RDN when compared with medical therapy alone. New RDN studies will provide important information on the role of RDN in the treatment of drug-naïve hypertensives and patients with uncontrolled hypertension on a triple antihypertensive therapy.

Noise pollution and arterial hypertension

Münzel et al. discuss causative effects of noise on the cardiovascular system

Introduction

The health burden of environmental noise has recently been quantified in a report of the World Health organization (WHO) in terms of disability-adjusted life years (i.e. the number of years lost because of disability or death, a measure that combines both morbidity and mortality). The WHO estimates that—in western Europeans—annually 45 000 years are lost due to noise-induced cognitive impairment in children, 903 000 due to noise-induced sleep disturbance, 61 000 due to noise-induced cardiovascular disease, and 22 000
due to tinnitus. Additionally, while not being a disease per se, noise-induced annoyance decreases quality of life and thus also causes disability, quantified in 587,000 disability-adjusted life years lost in the western European population.¹

The present report focuses on the effects of noise pollution on the cardiovascular system, in particular, on non-auditory effects such as noise-induced arterial hypertension.

Pathophysiology of noise-induced increases in blood pressure

Noise exposure modifies the function of multiple organs and systems. Acute noise exposure, both in laboratory settings where traffic noise was simulated and in real-life working environments, can cause increases in blood pressure, heart rate, and cardiac output.

According to the noise reaction scheme by Babisch, noise may induce damage through a direct pathway, e.g. by causing hearing loss, and indirect pathways, reflecting disturbances of sleep, communication, and daily activities, with or without noise-induced annoyance.² Chronic annoyance causes stress characterized by increased levels of stress hormones such as cortisone and catecholamines. Chronic stress in turn will cause a number of pathophysiological adaptations such as increased blood pressure, increases in heart rate and cardiac output, and increases in blood lipids (cholesterol, triglycerides, free fatty acids, phosphatides) and carbohydrates (glucose), as well as an activation of blood coagulation³ ultimately leading to manifest cardiovascular diseases such as arterial hypertension, coronary artery disease, and stroke (Figure 1).

Noise affects vascular function

In two recently published field studies, nocturnal aircraft noise exposure played-back with loudspeakers in the subjects’ bedrooms was shown to dose-dependently affect parameters of vascular (endothelial) function in healthy subjects and in patients with established coronary artery disease including endothelial function as measured by flow-dependent dilation of the brachial artery.⁴,⁵ Although these studies were limited to single-night exposures, a priming effect of noise was detected, i.e. the adverse effects of noise on vascular function were clearly more pronounced if the subject had previously been exposed to noise.⁵ Thus, in response to repeated exposure, the vessel appears to be unable to develop a form of accommodation, and is rather sensitized to noise-induced vascular damage.⁵ As expected, the deterioration in endothelial function was paralleled by increased catecholamine production and impaired sleep quality.⁷ In subjects with established coronary artery disease, there was also a significant increase in blood pressure.⁴ Interestingly, in these studies with patients and coronary artery disease, there was no correlation between annoyance reactions and the degree of deterioration of vascular function in response to noise, suggesting that noise per se adversely affects vascular function, whether one is getting angry or not.⁵

Many epidemiological studies indicate that nocturnal noise exposure may be more relevant for cardiovascular health than daytime noise exposure (for a detailed discussion of epidemiological studies and both daytime and night-time noise exposure see the following sections). For aircraft noise, the HYENA study (‘Hypertension and Exposure to Noise near Airports’) found no significant association for daytime noise, but a significant increase in blood pressure with increases in night noise.⁶ Compatible with this evidence, it has been demonstrated that road traffic noise exposure has a larger impact on those who sleep with open windows or whose bedroom faces the road.⁷ A sustained decrease in blood pressure during the night (so-called dipping) seems to be important for resetting the cardiovascular system and for long-term cardiovascular health.⁸ Repeated nocturnal autonomic arousals may prevent blood pressure dipping and contribute to the risk for developing hypertension in those exposed to relevant levels of environmental noise for prolonged periods of time.⁹,¹⁰ In line with this, it was found that the risk to develop hypertension was higher in subjects sleeping with open windows during the night, but it was lower in those with sound insulation or where the bedroom was not facing the main road.¹¹ A recent Swiss study showed an adverse effect of railway noise on blood

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**Figure 1** Noise reaction scheme explaining the development of cardiovascular diseases, e.g. hypertension in response to noise-induced stress reactions (modified from Munzel et al.²).
pressure, that was more strongly associated with night-time exposure.12

The Night Noise Guidelines for Europe were published by the WHO in 2009 and constitute an expert consensus correlating four noise exposure ranges to negative health outcomes ranging from ‘no substantial biological effects’ to ‘increased risk of cardiovascular disease’.13 The WHO considers average nocturnal noise levels of L_{Aeq, outside} 55 dB as an interim goal when the recommended guideline value of 40 dB is not feasible in the short term for the prevention of noise-induced health effects.

In sum, nocturnal noise has been shown to affect both autonomic regulation (via increases in heart rate mediated by sympathetic activation and/or parasympathetic withdrawal14–16 and with increases in blood pressure17) and, directly, vascular function through the induction of endothelial dysfunction. Importantly, both endothelial dysfunction and reduced heart rate variability have been demonstrated to have prognostic value in patients with peripheral artery disease, arterial hypertension, and patients with an acute coronary syndrome or chronic stable coronary artery disease.18–20 Taken together, these observations appear to be compatible with the observation of an increased incidence of arterial hypertension and subsequent myocardial infarction and stroke in subjects with long-term exposure to relevant noise levels.

Epidemiological studies: noise and arterial hypertension

Studies on chronic exposure to road traffic and/or railway or aircraft noise have reported a relationship with elevated blood pressure, arterial hypertension, or the use of antihypertensive medications. These studies demonstrate that environmental noise carries a considerable health burden that has important medical and economic implications: e.g. in the UK, daytime noise levels ≥55 dB have been estimated to cause an additional 542 cases of hypertension-related myocardial infarction, 788 cases of stroke, and 1169 cases of dementia, with a cost valued at around £1.09 billion annually.21

Road traffic noise, blood pressure, and hypertension

A meta-analysis of 24 cross-sectional studies on the relationship between road traffic noise and the prevalence of hypertension reported an odds ratio (OR) of 1.07 (95% confidence interval (CI) = 1.02–1.12) per 10 dB increase of the 16-h daytime average road traffic noise level (L_{Aeq,16h}) in the range <50 to >75 dB. A certain degree of heterogeneity among studies was detected with respect to age, gender, the way the exposure was assessed, the noise reference level used, and the duration of the exposure. For example, in the HYENA study, road traffic noise was linked to hypertension in men but not in women,6 and in the Groningen study and the PREVENT cohort road traffic noise was significantly associated with hypertension only in people aged 45–55 years.23 Similarly, a significant higher systolic blood pressure per 10 dB increase of the road traffic noise level was found in middle-aged subjects participating in a large Danish cohort study, with stronger and significant associations in men and older subjects.24 In this study, road traffic noise was not associated with diastolic blood pressure or self-reported hypertension. Co-morbidity was also found to be an effect modifier of the association between road traffic noise and blood pressure readings. For example, in the SAPALDIA 2 study, this association was found only in diabetics.25

Aircraft noise and arterial hypertension

An increased prevalence of arterial hypertension in the vicinity of Stockholm airport was reported in 2001.26 With respect to the early stages of hypertension, time-series study in the area surrounding the Frankfurt airport showed that even in the physiological blood pressure range, a relationship exists between aircraft noise and early-morning blood pressure.27 Two groups were followed over a period of 3 months; they were exposed to night-time outdoor aircraft noise of 50 dB: the ‘Western Group’ for 75% of the time, and the ‘Eastern Group’ for 25% of the time. The evaluation of a total of 8266 blood pressure measurements from 53 individuals yielded a statistically significant higher blood pressure level of 10/8 mmHg in the Western Group above that of the Eastern Group.

Similarly, a dose–response relationship has been shown in the HYENA study with respect to night-time noise.5 A 14% increase in OR (95% CI = 1.01–1.29; P = 0.031) for arterial hypertension was in this study associated with every 10 dB increase in L_{night}; in contrast, no effect was found for daytime aircraft noise exposure (L_{Aeq}; OR = 0.93, 95% CI = 0.83–1.04; P = 0.19). Data from the European Union-funded RANCH (Road Traffic and Aircraft Noise Exposure and Children’s Cognition and Health) study reported an association between both daytime and nocturnal noise exposure at home and blood pressure values in 9- to 10-year-old children living near Schiphol (Amsterdam) and Heathrow (London)28 airports. A meta-analysis of four cross-sectional and one cohort study on the relationship between aircraft traffic noise and the prevalence of hypertension reported an OR of 1.13 (95% CI = 1.00–1.28; P < 0.001) per 10 dB increase of the day–night weighted noise level (L_{DEN}) in the range <55 to >65 dB.29

Studies carried out repeatedly in the area neighbouring Amsterdam’s Schiphol airport reported a higher prevalence of prescriptions for cardiovascular medications (OR ranging between 1.2 and 1.4 between high- and low-noise groups).30 Likewise, a cross-sectional study data from the Cologne airport region in Germany demonstrated higher individual rates of cardiovascular medicine prescriptions in residents exposed to high aircraft noise levels, particularly during the night and the early-morning hours (3–5 h).31 Higher risks were found for subjects for whom the average noise level during the late night period exceeded 40 dB. Results from the HYENA study also suggest an effect of aircraft noise on the use of antihypertensive medication, but this effect did not hold for all participating study centres.32 Results were more consistent across centres for the increased use of anxiolytics in relation to aircraft noise.32

Thus, taken together, based on the existing literature, a causal relation between exposure to noise and blood pressure elevation appears to be scientifically confirmed. The consequence is that noise per se, as an environmental stressor, should be considered as a novel cardiovascular risk factor, a risk factor that cannot be influenced by patients or by doctors but rather by policymakers with anti-noise laws that protect people living close to airports rather than protecting people who operate the airport.
Rene Laennec lecture on clinical cardiology, at European Society of Cardiology Congress 2015

George Sutherland proposes a new theory to explain sudden cardiac death

‘Before retiring I wanted to investigate whether acute blood pressure changes alone, or in combination with a substrate, could act as a trigger for sudden death,’ says Sutherland, who in Rene Laennec’s Clinical Cardiology lecture proposed a possible new paradigm for sudden clinical death (SCD) linking everyday changes in blood pressure to electromechanical changes within the heart that are pro-arrhythmic.

On the subject of his lecture, Sutherland and his colleagues, Piet Claus and Peter Hamers, in a series of studies at the University of Leuven, Belgium, simulated everyday short-lived physiological blood pressure using short-lived aortic balloon inflations with descending pressures in a pig model.

They found that a balloon inflation for 5/10 beats inducing a 30 mmHg pressure change in the aorta led to marked shape changes in the left ventricle and caused a striking dissociation of mechanical and electrical events within the left ventricle. This challenge opened a ‘window’ of electrical instability, which frequently resulted in the production of premature ventricular beats. ‘Interestingly, it was acute pressure fall which was related per beat to the induction of the arrhythmia and not pressure rise,’ says Sutherland.

The potential mechanisms underlying this phenomenon were discussed during the lecture and Sutherland postulated that the acute induced ventricular premature beats, which are a result of the release of stretch within the left ventricular myocardium, act as a ‘trigger’, which interacts with a subclinical/clinical substrate within either right or left ventricle to produce a fatal ventricular arrhythmia. Such a mechanism, he suggested, could underlie the relatively large cohort of SCD, which is currently unexplained.

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